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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/822,612	02/03/2015	8945621	POZN.P0027US	6136

108197 7590 01/14/2015

Parker Highlander PLLC
1120 South Capital of Texas Highway
Bldg. 1, Suite 200
Austin, TX 78746

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 480 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Brian Ault, Wilmington, DE;
Clara Hwang, Wilmington, DE;
Everardus Orlemans, Chapel Hill, NC;
John R. Plachetka, Chapel Hill, NC;
Mark Sostek, Wilmington, DE;

Allowable Subject Matter

The following is an examiner's statement of reasons for allowance: Applicants have demonstrated the unexpected result that patients taking low dose aspirin who were administered the instantly recited dosage form (PN400) showed a lower incidence of gastric ulcers than non-aspirin using patients administered PN400 (see instant tables 3 and 5).

Any comments considered necessary by Applicants must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Examiners Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to Applicants, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Steven Highlander on 9/16/2014.

Change(s) applied to document, /A.C./ 10/22/2014

The application has been amended as follows:

Claim 1. At line 19, please delete the word **[[and]]**. At line ~~22~~ 21 immediately before the period, please insert the phrase **---<u>and wherein administration of the unit dose form is more effective at reducing the incidence of the NSAID-associated ulcers in</u>**

Change(s) applied to document, /D.H.T./ 11/16/2014

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12822612
Filing Date	2010-06-24
First Named Inventor	Ault
Art Unit	1614
Examiner Name	
Attorney Docket Number	103786-US-NP/NS

	36	20090074863		2009-03-19	Taneja	
	37	20100062064		2010-03-11	Ault et al.	
	38	20100172983		2010-07-08	Plachetka	
	39	20100178334		2010-07-15	Johansson et al.	
	40	20120064156		2012-03-15	Plachetka	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1	2139653	CA		1994-12			☐
	2	19801811	DE		2004-12-23	Stada Arzneimittel AG		☒
	3	4035455	DE		1992-05-14	Byk Gulden Lomberg Chemische Fabrik GmbH		☐
	4	0005129	EP		1981-04-29	Aktiebolaget Hassle Fack		☐

/Adam Milligan/ 09/09/2012

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

Form PTO-1449 (modified)	Atty. Docket No.: PZAZ.P0002US	Serial No.: 12/822,612
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	Applicant: Brian AULT *et al.*	
	Filing Date: June 24, 2010	Group: 1612

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page2*	*See Pages 2-4*

U.S. Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name	Class	Sub Class	Filing Date of App.
	A1	2001-0036473	11/01/01	Scott *et al.*	424	463	04/17/01
	A2	2001-0044410	11/22/01	Gelber *et al.*	514	27	01/05/01
	A3	2002-0111370	08/15/02	Bergman *et al.*	514	338	12/20/01
	A4	2002-0155153	~~12/24/02~~ October 24, 2002	Depui *et al.*	424	452	03/04/02
	A5	2002-0160046	10/31/02	Robinson *et al.*	424	469	11/21/01
	A6	2003-0040537	02/27/03	Plachetka *et al.*	514	406	09/26/02
	A7	2003-0129235	07/10/03	Chen *et al.*	424	470	10/28/02
	A8	2003-0232876	12/18/03	Plachetka	514	419	04/16/03
	A9	2004-0022846	02/05/04	Depui *et al.*	424	452	07/17/03
	A10	2004-0180089	09/16/04	Plachetka *et al.*	424	4	12/22/03
	A11	2005-0249811	11/10/05	Plachetka	424	472	05/16/05
	A12	2006-0177504	08/10/06	Sudharadas	424	488	02/08/06
	A13	2007-0207200	09/06/07	Plachetka *et al.*	424	451	03/02/07
	A14	2009-0297594	12/03/09	Depui *et al.*	424	451	02/09/09
	A15	5,690,960	11/25/97	Bengtsson *et al.*	424	480	09/27/94
	A16	5,872,145	02/16/99	Plachetka	514	415	08/14/97
	A17	6,060,499	05/09/00	Plachetka	514	415	09/11/98
	A18	6,126,816	10/03/00	Ruiz Jr.	210	95	07/14/99
	A19	7,030,162	04/18/06	Plachetka *et al.*	514	619	09/26/02
	A20	7,060,694	06/13/06	Plachetka *et al.*	514	177	10/29/02
	A21	7,332,183	02/19/08	Plachetka *et al.*	424	472	12/22/03

Change(s) applied to document, /D.H.P./ 11/13/2014

{00044203}

EXAMINER:	/Adam Milligan/	DATE CONSIDERED:	07/10/2013

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

108197 7590 09/25/2014
Parker Highlander PLLC
1120 South Capital of Texas Highway
Bldg. 1, Suite 200
Austin, TX 78746

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

Steven L. Highlander	(Depositor's name)
/Steven L. Highlander/	(Signature)
December 16, 2014	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/822,612	06/24/2010	Brian Ault	POZN.P00270S	6136

TITLE OF INVENTION: Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	12/26/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
MILLIGAN, ADAM C	1612	424-472000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Parker Highlander PLLC
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE	(B) RESIDENCE: (CITY and STATE OR COUNTRY)
POZEN INC.	Chapel Hill, NC
HORIZON PHARMA USA, INC.	Deerfield, IL

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☐ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies .....

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☒ Payment by credit card. ~~Form PTO-2038 is attached.~~ Via EFS-Web
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number 50-5902 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
☐ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☐ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Steven L. Highlander/ Date December 16, 2014
Typed or printed name Steven L. Highlander Registration No. Attorney - Reg. No. 32,165

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Electronic Patent Application Fee Transmittal

Application Number:	12822612
Filing Date:	24-Jun-2010
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Filer:	Steven Lee Highlander/Richard Ortiz
Attorney Docket Number:	POZN.P0027US

Filed as Large Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	960	960

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**960**

Electronic Acknowledgement Receipt

EFS ID:	20978176
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	108197
Filer:	Steven Lee Highlander/Richard Ortiz
Filer Authorized By:	Steven Lee Highlander
Attorney Docket Number:	POZN.P0027US
Receipt Date:	16-DEC-2014
Filing Date:	24-JUN-2010
Time Stamp:	15:45:07
Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	yes
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1	Post Allowance Communication - Incoming	POZNP0027US_Applicants-Response.pdf	33335 a44e8299a3bd1fe29eb9351c6f297ac0bd8666c6	no	2
Warnings:					
Information:					
2	Issue Fee Payment (PTO-85B)	POZNP0027US_Issue-Fee.pdf	1589905 49ccc0d47afc0fa278b2d1fee2ae97d91eda79b8	no	1
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	30641 19b94298c038a05f940d767de1b81574f49df22b	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1653881		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brian AULT *et al.*	Group Art Unit: 1612
Serial No.: 12/822,612	Examiner: Adam C. Milligan
Filing Date: June 24, 2010	Attorney Docket No.: POZN.P0027US
Title: METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER	Confirmation No.: 6136

CERTIFICATE OF ELECTRONIC TRANSMISSION

I hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:

December 16, 2014 /Steven L. Highlander/
Date Steven L. Highlander

APPLICANT'S RESPONSE TO EXAMINER'S STATEMENT OF REASONS FOR ALLOWANCE

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Commissioner:

This submission is in response to the examiner's statement of reasons for allowance ("Statement"), mailed on September 25, 2014, regarding the captioned application. According to the Statement, "Applicants have demonstrated the unexpected result that patients taking low dose aspirin who were administered the instantly recited dosage form (PN400) showed a lower incidence of gastric ulcers than non-aspirin using patients administered PN400 (see instant tables 3 and 5)." Applicants are unclear as to the scope of this comment, and thus cannot agree with the Statement, for example because Applicants have demonstrated many different unexpected results

in the present disclosure related to the administration of the claimed pharmaceutical composition in unit dosage form to patients taking low dose aspirin (LDA). While the Examiner has pointed to a single unexpected result, the claims are indeed supported by other unexpected results as well, which are not necessarily explicitly recited in the claims. That said, Applicants can agree that unexpected results have been demonstrated for the claimed methods of reducing the incidence of NSAID-associated gastric ulcers in patients taking LDA who are at risk of developing such ulcers.

Respectfully submitted,

/Steven L. Highlander/

Steven L. Highlander
Reg. No. 37,642
Attorney for Applicants

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1120 S. Capital of Texas Highway
Building One, Suite 200
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512-334-2900 (Telephone)
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Date: December 16, 2014

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/822,612	06/24/2010	Brian Ault	POZN.P0027US	6136

108197 7590 10/14/2014

Parker Highlander PLLC
1120 South Capital of Texas Highway
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Austin, TX 78746

EXAMINER	
MILLIGAN, ADAM C	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
10/14/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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APPLICATION NO./ CONTROL NO.	FILING DATE	FIRST NAMED INVENTOR / PATENT IN REEXAMINATION	ATTORNEY DOCKET NO.
12/822,612	24 June, 2010	AULT ET AL.	POZN.P0027US

		EXAMINER	
Parker Highlander PLLC 1120 South Capital of Texas Highway Bldg. 1, Suite 200 Austin, TX 78746		ADAM C. MILLIGAN	
		ART UNIT	PAPER
		1612	20141008

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner for Patents

Applicant's representitive informed examiner that there was an error in the consideration of an IDS submitted 8/28/2012. Specifically, the last two pages of the IDS were deleted. Accordingly, Examiner has now considered the IDS in full and attached the considered IDS hereto.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12822612
	Filing Date	2010-06-24
	First Named Inventor	Ault
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	103786-US-NP/NS

	1	Panara et al., "Effects of the novel anti-inflammatory compounds, N-[2-(cyclohexyloxy)-4-nitrophenyl] methanesulphonamide (NS-398) and 5-methanesulphonamido-6-(2,4-difluorothio-phenyl)-1-inda none (L-745,337), on the cyclo-oxygenase activity of human blood prostaglandin endoperoxide synthases," British Journal of Pharmacology, 116, pp. 2429-2434 (1995)	☐
	2	Pang et al., "Modeling of intestinal drug absorption: roles of transporters and metabolic enzymes (for the Gillette review series)" Drug Metabolism and Disposition, 31(12), pp. 1507-1519 (2003)	☐
	3	Patrono, et al., "Low-Dose Aspirin for the Prevention of Atherothrombosis," New Eng. J. Med., 353, pp. 2373-2383 (2005)	☐
	4	Petersen, "Doubts are raised on the safety of 2 popular arthritis drugs," NY Times, p. C1 (May 22, 2001)	☐
	5	Pilbrant et al., "Development of an Oral Formulation of Omeprazole," Scand. J. Gastroenterol., 20, Supp. 108, pp. 113-120 (1985)	☐
	6	Pirmohamed et al., "Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients," Br. Med. J., 329, pp. 15-19 (2004)	☐
	7	Porter S.C., "Coating of Pharmaceutical Dosage Forms," in: A. Gennaro (Ed.), Remington: the Science and Practice of Pharmacy, 19th ed., pp. 1650-1651 (1995)	☐
	8	Qureshi, et al., "Pharmacokinetics of Two Enteric-Coated Ketoprofen Products in Humans with or Coadministration of Omeprazole and Comparison with Dissolution Findings," Pharmaceutical Research, 11(11), pp. 1669-1672 (1994)	☐
	9	Raskin, et al., "Misoprostol Dosage in the Prevention of Nonsteroidal Anti-Inflammatory Drug-Induced Gastric and Duodenal Ulcers: A Comparison of Three Regimens," Ann. Intern. Med., 123(5), pp. 344-350 (Sep. 1995)	☐
	10	Richardson et al., "Proton pump inhibitors, pharmacology and rationale for use in gastrointestinal disorders," Drugs, 56 (3), pp. 307-335 (1998)	☐
	11	Robinson, et al., "Effects of Ranitidine Gastroduodenal Mucosal Damage Induced by Nonsteroidal Anti-inflammatory Drugs," Dig. Dis. Sci., 34(3), pp. 424-428 (Mar. 1989) /Adam Milligan/ 10/08/2014	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12822612
	Filing Date	2010-06-24
	First Named Inventor	Ault
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	103786-US-NP/NS

	12	Roth, et al., "Cimetidine Therapy in Nonsteroidal Anti-inflammatory Drug Gastropathy: Double-blind Long-term Evaluation," Arch. Intern. Med., 147, pp. 1798-1801 (1987)	☐
	13	Rubinstein, "Gastrointestinal anatomy physiology and permeation pathways," Enhancement in Drug Discovery, CRC Press, pp. 3-35 (2007)	☐
	14	Sangiah et al., "Effects of misoprostol and omeprazole on basal gastric pH and free acid content in horses," Res. Vet. Sci., 47(3), pp. 350-354 (1989)	☐
	15	Savarino et al., "Effect of one-month treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) on gastric pH of rheumatoid arthritis patients," Digestive Diseases and Sciences, 43, pp. 459-463 (1998)	☐
	16	Scarpignato et al., Gastroenterology International; Pages 186-215 (1999)	☐
	17	Scheiman et al., "NSAID-induced peptic ulcer disease: a critical review of pathogenesis and management," Dig. Dis., 12, pp. 210-222 (1994)	☐
	18	Scheiman et al., "Omeprazole ameliorates aspirin-induced gastroduondenal injury," Digestive Diseases and Sciences, 39(1), pp. 97-103 (1994)	☐
	19	Scheiman, Seminars in Arthritis and Rheumatism, pp. 201-210 (1992)	☐
	20	Scott and Sundell, "Inhibition of H+K+ ATPase by SCH 28080 and SCH 32651," European Journal of Pharmacology, 112, pp. 268-270 (1985)	☐
	21	Seitz et al., "Tablet coating," in The theory and practice of industrial pharmacy, Lachman et al. eds., Lea and Febiger, pp. 346-373 (1986)	☐
	22	Selway et al., "Potential hazards of long-term acid suppression," Scand. J. Gastroenterol., 25, Supp. 178, pp. 85-92 (1990) /Adam Milligan/ 10/08/2014	☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12822612
	Filing Date	2010-06-24
	First Named Inventor	Ault
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	103786-US-NP/NS

	23	Sharma et al., "Comparison of 24-hour intragastric pH using four liquid formulations of lansoprazole and omeprazole," Am. J. Health-Syst. Pharm., 56, Supp. 4, pp. S18-S21 (1999)	☐
	24	Silverman, The Organic Chemistry of Drug Design and Drug Action, 2nd Edition, Academic Press, pp. 102 & 527 (2004)	☐
	25	Silverstein et al., "Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis; the CLASS study: A randomized controlled trial," JAMA, 284, pp. 1247-1255 (2000)	☐
	26	Silverstein, et al., "Misoprostol Reduces Serious Gastrointestinal Complications in Patients with Rheumatoid Arthritis Receiving Nonsteroidal Anti-Inflammatory Drugs," Ann. Intern. Med., 123(4), pp. 241-249 (1995)	☐
	27	Simon English translation ---- Simon, et al., "Schutzwirkung von Omeprazol gegenuber niedrig dosierter Acetylsalicylsaure," Arzneimittel Forschung, 45, pp.701-703 (1995)	☐
	28	Simon, et al., "Schutzwirkung von Omeprazol gegenuber niedrig dosierter Acetylsalicylsaure," Arzneimittel Forschung, 45, pp. 701-703 (1995)	☐
	29	Sung, "Management of nonsteroidal anti-imflammatory drug-related peptic ulcer bleeding," Am. J. Med., 110(1A), pp. 29S-32S (2001)	☐
	30	Tronstad et al., "Gastroscopic findings after treatment with enteric-coated and plain naproxen tablets in healthy subjects," Scand. J. Gastroenterol., 20, pp. 239-242 (1985)	☐
	31	Vane, et al., "The future of NSAID therapy: selective COX-2 inhibitors," IJCP, 54(1), pp.7-9 (Jan./Feb. 2000)	☐
	32	Vimovo Press Release (Oct 16, 2009)	☐
	33	von Unge et al., "Stereochemical assignment of the enantiomers of omeprazole from X-ray anaylysis of a fenchyloxymethyl derivative of (+)-(R)- omeprazole," Tetrahedron, 8(12), pp. 1967-1970 (1997)	☐

/Adam Milligan/ 10/08/2014

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12822612
	Filing Date	2010-06-24
	First Named Inventor	Ault
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	103786-US-NP/NS

	34	Wagner et al., "Effects of nonsteroidal anti-inflammatory drugs on ulcerogenesis and gastric secretion in pylorus-ligated rat," Digestive Diseases and Sciences, Vol. 40, pgs. 134-140 (1995)	☐
	35	Wakitani et al., "Profile of JTE-522 as a human cyclooxygenase-2 inhibitor," Jpn. J. Pharmacol., 78, pp. 365-371 (1998)	☐
	36	Wallmark et al., "The relationship between gastric acid secretion and gastric H.sup.+, K.sup.+-ATPase activity," J. Biol. Chem., 260(25), pp. 13681-13684 (1985)	☐
	37	Warner, et al., "Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human gastrointestinal toxicity: A full in vitro analysis," Proc. Natl. Acad. Sci. USA, 96, pp. 7563-7568 (Jun. 1999)	☐
	38	Weil et al., "Prophylactic aspirin and risk of peptic ulcer bleeding," Br. Med. J., 310, pp. 827-830 (1995)	☐
	39	Wolfe et al., "Gastrointestinal toxicity of nonsteroidal anti-inflammatory drugs," N. Engl. J. Med., 340, pp. 1888-1899 (1999)	☐
	40	WOLFE, et al., "Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress Related Erosive Syndrome," Gastroenterology, 118(2), pp. S9-S31 (2000)	☐
	41	Yeomans et al., "A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal anti-inflammatory drugs," N. Engl. J. Med., 338, pp. 719-726 (1998)	☐
	42	Yeomans et al., "New data on healing of nonsteroidal anti-inflammatory drug-associated ulcers and erosions," Am. J. Med., 104, pp. 56S-61S (1998)	☐

If you wish to add additional non-patent literature document citation information please click the Add button **Add**

EXAMINER SIGNATURE

Examiner Signature	/Adam Milligan/	Date Considered	10/08/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

108197 7590 09/25/2014

Parker Highlander PLLC
1120 South Capital of Texas Highway
Bldg. 1, Suite 200
Austin, TX 78746

EXAMINER
MILLIGAN, ADAM C

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 09/25/2014

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/822,612	06/24/2010	Brian Ault	POZN.P0027US	6136

TITLE OF INVENTION: Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	12/26/2014

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

108197 7590 09/25/2014
Parker Highlander PLLC
1120 South Capital of Texas Highway
Bldg. 1, Suite 200
Austin, TX 78746

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/822,612	06/24/2010	Brian Ault	POZN.P0027US	6136

TITLE OF INVENTION: Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	$960	$0	$0	$960	12/26/2014

EXAMINER	ART UNIT	CLASS-SUBCLASS
MILLIGAN, ADAM C	1612	424-472000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ❑ Applicant certifying micro entity status. See 37 CFR 1.29
  NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
- ❑ Applicant asserting small entity status. See 37 CFR 1.27
  NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
- ❑ Applicant changing to regular undiscounted fee status.
  NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/822,612	06/24/2010	Brian Ault	POZN.P0027US	6136

108197 7590 09/25/2014

Parker Highlander PLLC
1120 South Capital of Texas Highway
Bldg. 1, Suite 200
Austin, TX 78746

EXAMINER	
MILLIGAN, ADAM C	

ART UNIT	PAPER NUMBER
1612	

DATE MAILED: 09/25/2014

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	12/822,612	AULT ET AL.	
	Examiner	Art Unit	
	ADAM C. MILLIGAN	1612	

All participants (applicant, applicant's representative, PTO personnel):

(1) *ADAM MILLIGAN*. (3)_____.

(2) *STEVE HIGHLANDER*. (4)_____.

Date of Interview: *16 September 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1-4,18-20,25,26,31,46 and 47*.

Identification of prior art discussed: *N/A*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Examiner and Applicants representive discussed claim amendments which would render the claims commensurate in scope with the demonstrated unexpected results. An agreement was reached which is reflected in the attached Examiners Amendment.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/ADAM C MILLIGAN/ Primary Examiner, Art Unit 1612	

Notice of Allowability	Application No. 12/822,612	Applicant(s) AULT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *5/30/2014*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-4, 18-20,25,26,31,38,46-48,64 and 65*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 1pg(5/30/2014)
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *20140904* .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☒ Other *bib.data sheet*.

/ADAM C MILLIGAN/
Primary Examiner, Art Unit 1612

Allowable Subject Matter

The following is an examiner's statement of reasons for allowance: Applicants have demonstrated the unexpected result that patients taking low dose aspirin who were administered the instantly recited dosage form (PN400) showed a lower incidence of gastric ulcers than non-aspirin using patients administered PN400 (see instant tables 3 and 5).

Any comments considered necessary by Applicants must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Examiners Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to Applicants, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Steven Highlander on 9/16/2014.

The application has been amended as follows:

Claim 1. At line 19, please delete the word **[[and]]**. At line 22 immediately before the period, please insert the phrase **---<u>and wherein administration of the unit dose form is more effective at reducing the incidence of the NSAID-associated ulcers in</u>**

patients taking LDA than in patients not taking LDA who are administered the unit dose form---.

Claim 3. At line 1 immediately following the word "said", please insert the phrase **---patient is treated for a---**. At line 2, please delete the word **[[is]].**

Claim 4. At line 1 immediately following the word "said", please insert the phrase **---patient is treated for a---**. At line 2, please delete the word **[[is]].**

Claim 25. At line 16, please delete the word **[[and]]**. At line 18 immediately before the period, please insert the phrase **---and wherein administration of the unit dose form is more effective at reducing the incidence of the NSAID-associated ulcers in patients taking LDA than in patients not taking LDA who are administered the unit dose form---.**

Claim 64. At line 2, please insert the term **---(LDA)---** immediately before the word "who". At line 4, please insert the term **---comprising---** immediately before the semicolon. At line 17, please delete the clause **[[wherein said pharmaceutical composition in unit dose form reduces the incidence of NSAID-associated gastric ulcers in said patient taking LDA as compared to patients taking low dose aspirin who are administered twice a day for 1 month enteric coated naproxen, or a pharmaceutically acceptable salt thereof]]** and insert the clause **---wherein administration of the unit dose form is more effective at reducing the incidence of the NSAID-associated gastric ulcers in patients taking LDA than in patients not taking LDA who are administered the unit dose form---.**

Claim 65. At line 2, please insert the term **---(LDA)---** immediately before the word "who". At line 4, please insert the term **---comprising---** immediately before the semicolon. At line 20, please delete the clause **[[wherein said pharmaceutical composition in unit dose form reduces the incidence of NSAID-associated gastric ulcers in said patient taking LDA as compared to patients taking low dose aspirin who are administered twice a day for 1 month enteric coated naproxen, or a pharmaceutically acceptable salt thereof]]** and insert the clause **---wherein administration of the unit dose form is more effective at reducing the incidence of said ulcers in patients taking LDA than in patients not taking LDA who are administered the unit dose form---.**

Any inquiry concerning this communication should be directed to ADAM C. MILLIGAN at telephone number (571)270-7674.

/ADAM C MILLIGAN/

Primary Examiner, Art Unit 1612

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	12/822,612	AULT ET AL.	
	Examiner	Art Unit	
	ADAM C. MILLIGAN	1612	

All participants (applicant, applicant's representative, PTO personnel):

(1) *ADAM MILLIGAN*. (3)_____.

(2) *STEVE HIGHLANDER*. (4)_____.

Date of Interview: *16 September 2014*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1-4,18-20,25,26,31,46 and 47*.

Identification of prior art discussed: *N/A*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Examiner and Applicants representive discussed claim amendments which would render the claims commensurate in scope with the demonstrated unexpected results. An agreement was reached which is reflected in the attached Examiners Amendment.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/ADAM C MILLIGAN/ Primary Examiner, Art Unit 1612	

Form PTO-1449 (modified)	Atty. Docket No.: POZN.P0027US	Serial No.: 12/822,612
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	Applicant(s): Brian AULT *et al.*	
	Filing Date: June 24, 2010	Group: 1612

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1*	*See Page 1*

U.S. Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name

Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C34	U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, "Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation," available online at http://www.fda.gov/downloads/Drugs/Guidances/UCM070640.pdf , September 1997.
	C35	World Health Organization, "Revision of Monograph on Tablets. Final text for addition to *The International Pharmacopoeia*," available online at http://www.who.int/medicines/publications/pharmacopoeia/Tabs-GeneralMono-rev-FINAL_31032011.pdf, March 2011.

{00147610}

EXAMINER: /Adam Milligan/	DATE CONSIDERED: 09/16/2014

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12822612	AULT ET AL.
	Examiner	**Art Unit**
	ADAM C MILLIGAN	1612

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	09/17/2014								
1	1	=								
2	2	=								
3	3	=								
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CLAIM		DATE								
Final	Original	09/17/2014								
	37	-								
11	38	=								
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16	65	=								

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12822612	AULT ET AL.
	Examiner	Art Unit
	ADAM C MILLIGAN	1612

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
424	472	9/10/2010	AM

SEARCH NOTES		
Search Notes	Date	Examiner
PALM Inventor Search	9/9/2012	AM
EAST Search - see attached search history	9/9/2012	AM
STN Search - caplus - esomeprazole, naproxen, NSAID induced GI ulcer, enteric coating	9/9/2012	AM
Updated EAST and STN searches	3/20/2014	AM
Updated EAST and STN searches	9/17/20140	AM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
424	472	9/10/2014	AM

UNITED STATES PATENT AND TRADEMARK OFFICE

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BIB DATA SHEET

CONFIRMATION NO. 6136

SERIAL NUMBER	FILING or 371(c) DATE RULE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/822,612	06/24/2010	424	1612	POZN.P0027US

APPLICANTS

INVENTORS

Brian Ault, Wilmington, DE;
Clara Hwang, Wilmington, DE;
Everardus Orlemans, Chapel Hill, NC;
John R. Plachetka, Chapel Hill, NC;
Mark Sostek, Wilmington, DE;

**** CONTINUING DATA ***************************

This appln claims benefit of 61/220,420 06/25/2009
and claims benefit of 61/225,970 07/16/2009
and claims benefit of 61/310,525 03/04/2010

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ****

07/01/2010

Foreign Priority claimed	❑ Yes ☑ No	❑ Met after Allowance	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
35 USC 119(a-d) conditions met	❑ Yes ☑ No					
Verified and Acknowledged	/ADAM C MILLIGAN/ Examiner's Signature	Initials	DE	0	62	4

ADDRESS

Parker Highlander PLLC
1120 South Capital of Texas Highway
Bldg. 1, Suite 200
Austin, TX 78746
UNITED STATES

TITLE

Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer

FILING FEE RECEIVED		
4326	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ All Fees ❑ 1.16 Fees (Filing) ❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12822612	AULT ET AL.
	Examiner	**Art Unit**
	ADAM C MILLIGAN	1612

CPC								
Symbol							**Type**	**Version**
A61K		31	/	192			F	2013-01-01
A61K		9	/	209			I	2013-01-01
A61K		31	/	4439			I	2013-01-01
A61K		45	/	06			I	2013-01-01
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CPC Combination Sets									
Symbol							**Type**	**Set**	**Ranking**	**Version**
A61K		31	/	192			I	1	1	2013-01-01
A61K		2300	/	00			A	1	2	2013-01-01
A61K		31	/	4439			I	2	1	2013-01-01
A61K		2300	/	00			A	2	2	2013-01-01

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	16	
/ADAM C MILLIGAN/ Primary Examiner.Art Unit 1612	09/17/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12822612	AULT ET AL.
	Examiner	**Art Unit**
	ADAM C MILLIGAN	1612

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
424	472	A	6	1	K	9 / 24 (2006.01.01)						

CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				

NONE		Total Claims Allowed:	
(Assistant Examiner)	(Date)	16	
/ADAM C MILLIGAN/ Primary Examiner.Art Unit 1612	09/17/2014	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	**Art Unit**
	ADAM C MILLIGAN	1612

☒ **Claims renumbered in the same order as presented by applicant** ☐ **CPA** ☐ **T.D.** ☐ **R.1.47**

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1		17		33		49	16	65						
2	2	5	18		34		50								
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	14		30	12	46		62								
	15	10	31	13	47		63								
	16		32	14	48	15	64								

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 16	
/ADAM C MILLIGAN/ Primary Examiner.Art Unit 1612 (Primary Examiner)	09/17/2014 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure None

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brian AULT *et al.*	Group Art Unit: 1612
Serial No. 12/822,612	Examiner: Adam C. Milligan
Filed: June 24, 2010	Atty. Dkt. No.: POZN.P0027US
For: METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER	Confirmation No.: 6136

CERTIFICATE OF ELECTRONIC TRANSMISSION
37 C.F.R. § 1.8

I hereby certify that this response is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:

May 30, 2014	/Steven L. Highlander/
Date	Steven L. Highlander

AMENDMENT AND REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.111

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Dear Sir:

This is in response to the Office Action ("the Action") mailed on April 2, 2014, to which a response is due on July 2, 2014. No fees are believed to be due in connection with the filing of this response; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be deemed necessary for any reason relating to these materials, the Commissioner is authorized to deduct the appropriate fees from Parker Highlander PLLC Deposit Account No.: 50-5902/POZN.P0027US/SLH.

Amendments to the Claim begin on page 2 of this response; **Remarks** begin on page 7.

AMENDMENTS TO THE CLAIMS

Listing of Claims

The following listing of claims replaces all previous listings or versions thereof:

1. (Currently amended) A method of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, wherein the method comprises administering to said patient in need thereof a pharmaceutical composition in unit dose form comprising:

(a) 20 mg of esomeprazole, or pharmaceutically acceptable salt thereof, in a form and route sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and

(b) ~~375 mg or~~ 500 mg of naproxen, or pharmaceutically acceptable salt thereof;

wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen,

wherein ~~such that: (i)~~ at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium, ~~; and~~

~~(ii) at least a portion of said naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher; and~~

wherein the unit dosage form releases less than 10% of the naproxen or a pharmaceutically acceptable salt thereof after 2 hours when tested using the USP Paddle Method in 1000 ml of 0.1N HCl at 75 rpm at 37° C +/-0.5° C, and

wherein said pharmaceutical composition in unit dose form reduces the incidence of NSAID-associated ulcers in said patient.

2. (Previously presented) The method according to claim 1, wherein the risk is associated with chronic NSAID treatment.

3. (Previously presented) The method according to claim 1, wherein said disease or disorder is selected from pain and inflammation.

4. (Previously presented) The method according to claim 1, wherein said disease or disorder is selected from osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and a combination thereof.

5-17. (Canceled)

18. (Currently amended) The method according to claim [[13]] 1, wherein said unit dose form ~~multi-layer tablet~~ is at least about 95% free of sodium bicarbonate.

19. (Currently amended) The method according to claim [[13]] 1, wherein said unit dose form ~~first layer~~ begins to release said ~~at least a portion of said~~ naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 4.0 or greater.

20. (Currently amended) The method according to claim [[13]] 1, wherein said unit dose form ~~first layer~~ begins to release said ~~at least a portion of said~~ naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 4.5 or greater.

21.-24. (Canceled)

25. (Currently amended) A method of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, wherein the method comprises administering to the patient a pharmaceutical composition in unit dosage form suitable for oral administration comprising:

(a) 20 mg of esomeprazole or a pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms, and

(b) ~~375 mg or~~ 500 mg of naproxen or pharmaceutically acceptable salt thereof, ~~wherein at least a portion of said naproxen or a pharmaceutically acceptable salt thereof,~~ wherein the unit dosage form releases less than 10% of the naproxen or a pharmaceutically acceptable salt thereof after 2 hours when tested using the USP Paddle

Method in 1000 ml of 0.1N HCl at 75 rpm at 37° C +/-0.5° C; ~~is surrounded by a coating that is substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of about 37° C~~;

and

wherein said pharmaceutical composition in unit dose form reduces the incidence of NSAID-related ulcers in said patient.

26. (Original) The method of claim 25, wherein the risk is associated with chronic NSAID treatment.

27-30. (Canceled)

31. (Previously presented) The method of claim 25, wherein the patient is treated for a disease or disorder selected from pain, inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and combinations thereof.

32-37. (Canceled)

38. (Previously presented) The method of claim 25, wherein the pharmaceutical composition is formulated to be administered to a patient twice daily.

39-45. (Canceled)

46. (Currently amended) The method according to claim [[44]] 25, wherein the unit dosage form further comprises a pharmacologically inert, water soluble coating or film ~~surrounding the outermost layer of the unit dosage form~~.

47. (Previously presented) The method of claim 46, wherein the inert coating or film comprises a water soluble sugar.

48. (Previously presented) The method of claim 25, wherein administration of the unit dosage form is more effective at reducing the risk of ulcer than treatment with enteric coated naproxen or a pharmaceutically acceptable salt thereof.

49-63. (Canceled)

64. (Currently amended) A method of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, wherein the method comprises administering to said patient in need thereof twice a day for 1 month a pharmaceutical composition in unit dose form:

(a) 20 mg of esomeprazole, or pharmaceutically acceptable salt thereof, in a form and route sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and

(b) ~~375 mg or~~ 500 mg of naproxen, or pharmaceutically acceptable salt thereof; wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen,

wherein ~~such that: (i)~~ at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium, ~~; and~~

wherein the unit dosage form releases less than 10% of the naproxen or a pharmaceutically acceptable salt thereof after 2 hours when tested using the USP Paddle Method in 1000 ml of 0.1N HCl at 75 rpm at 37° C +/-0.5° C, and

wherein said pharmaceutical composition in unit dose form reduces the incidence of NSAID-associated gastric ulcers in said patient as compared to patients taking low dose aspirin who are administered twice a day for 1 month enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

65. (Currently amended) A method of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, wherein the method comprises administering to said patient in need thereof twice a day for 3 months a pharmaceutical composition in unit dose form:

(a) 20 mg of esomeprazole, or pharmaceutically acceptable salt thereof, in a form and route sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and

(b) ~~375 mg or~~ 500 mg of naproxen, or pharmaceutically acceptable salt thereof; wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen such that:

wherein ~~such that:~~ ~~(i)~~ at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium, ~~; and~~

~~(ii) at least a portion of said naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher; and~~

wherein the unit dosage form releases less than 10% of the naproxen or a pharmaceutically acceptable salt thereof after 2 hours when tested using the USP Paddle Method in 1000 ml of 0.1N HCl at 75 rpm at 37° C +/-0.5° C, and

wherein said pharmaceutical composition in unit dose form reduces the incidence of NSAID-associated gastric ulcers in said patient as compared to patients taking low dose aspirin who are administered twice a day for 3 months enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

66-67. (Canceled)

REMARKS

I. Status of the Claims

Claims 1, 18-20, 25, 46, 64, and 65 have been amended herein. Claims 13-15, 22, 23, 36, 37, 42-45, 66, and 67 have been cancelled without prejudice or disclaimer. With entry of this amendment, claims 1-4, 18-20, 25, 26, 31, 38, 46-48, 64, and 65 are pending in the application and stand rejected, variously, under 35 U.S.C. §103 and for alleged obviousness-type double-patenting. The specific grounds for rejection, and Applicants' response thereto, are set forth in detail below.

II. Interview

Applicants wish to thank Examiner Milligan for the courtesy of an interview held on April 14, 2014. While agreement was not reached, it is believed that the interview was helpful in clarifying the remaining issues. As requested, Applicants provide with this response a copy of the materials provided to the Examiner at the interview.

III. Rejection Under 35 U.S.C. §103

Claims 1-4, 13-15, 17-20, 22, 23, 25, 26, 31, 36-38, 42-48, and 64-67 remain rejected as obvious over U.S. Patent 6,926,907 ("the '907 patent"), optionally taken with Phillips (U.S. 20004/0048896). Applicants traverse the rejection presented in this Action that the '907 patent creates a *prima facie* case of obviousness for the claims presented in the January 17, 2014 submission. Regardless, as explained below, the present claims are supported by a surprising and unexpected result that would overcome even a valid *prima facie* case.

In the previous response, Applicants amended claims 1 and 25 to recite methods of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, based on surprising clinical data in this subset of patients (data presented in Angiolillo *et al.*, *J Thromb Thrombolysis* (published online: December 25, 2013 ("Angiolillo"). As set forth in the present application, while NSAIDs are a key therapy for pain and inflammation, there is a substantial risk of gastric ulcers associated with such treatment, particularly in subsets of patients with certain risk factors. One such risk factor associated with NSAID patients developing gastric ulcers is concomitant use of low-dose aspirin ("LDA"). As such, one of skill in the art understood that patients receiving NSAIDs and concomitant LDA are at an increased risk of upper gastrointestinal complications and ulcers.

In the Action, the Office argues that while ***the data from Angiolillo are indeed unexpected***, the instant specification does not support such results. As explained during the interview on April 14, 2014, support for the data underlying the surprising result in the subset of patients taking LDA and NAP/ESO can indeed be found in the specification as-filed. NAP/ESO as referenced by Angiolillo is the same unit dosage form referred to as PN400 in the specification. As set forth in the specification, in patients taking both LDA and naproxen, higher incidences of gastric ulcers occurred as compared to patients taking naproxen but not LDA (at 6 months, 28.4% versus 22.2%, respectively). In contrast, in patients taking both LDA and PN400 (a.k.a. NAP/ESO), a lower incidence of gastric ulcers occurred (again, despite the expectation that these patients would be at an increased risk for developing such ulcers based on the concomitant use of LDA) as compared to patients taking PN400 but not LDA (at 6 months, 3% versus 6.4%, respectively). Thus, the data in the specification show this unexpected and surprising trend in the subset of patients taking LDA and PN400. The relevant portions of the

specification are reproduced below (with the data discussed above underlined) for the examiner's ease of reference:

> Baseline demographics were similar between Study A and Study B groups. Approximately 82% of patients had OA and 6% had RA. The cumulative observed incidence of GUs over 6 mos was significantly lower in the PN400 groups versus the EC-naproxen groups (P<0.001 for both studies) (See Table 2). Of the 854 subjects in Study A + Study B, 201 were concomitant LDA users; the incidence of GUs in concomitant LDA users was lower in the PN400 group versus the EC-naproxen group [3.0% vs 28.4%, respectively, P<0.001] (See Table 3). Of the 201 concomitant LDA users out of the 854 total subjects in Study A + Study B, the incidence of GDUs in concomitant LDA users was lower in the PN400 group versus the EC-naproxen group [4.0% vs 32.4%, respectively, P<0.001] (See Table 4). The incidence of GUs in non-LDA users (n=653) across Study A + Study B subjects (n=854) was lower in the PN400 group versus the EC-naproxen group [6.4% vs 22.2%, P<0.001] (See Table 5). A pooled analysis of Study A and Study B demonstrated PN400 was associated with a significantly lower incidence of GU versus EC-naproxen regardless of age. (See Table 6). The relative risk reduction (RRR) for GUs in patients treated with PN400 was 64.9% (95% confidence interval [CI] 39.0, 79.8) in patients aged 50-59 yrs and 89.2% (95% CI 75.6, 95.3) in patients aged ≥ 60 yrs.

Pages 24-25 of the specification as filed (paragraph [0155] of the published application). This result is also supported in Tables 3 and 5 of the specification as filed, as shown below (with the data discussed herein boxed for emphasis):

TABLE 3

Cumulative Observed Incidence of GUs for LDA Users at 1, 3 and 6 Months in ITT Population

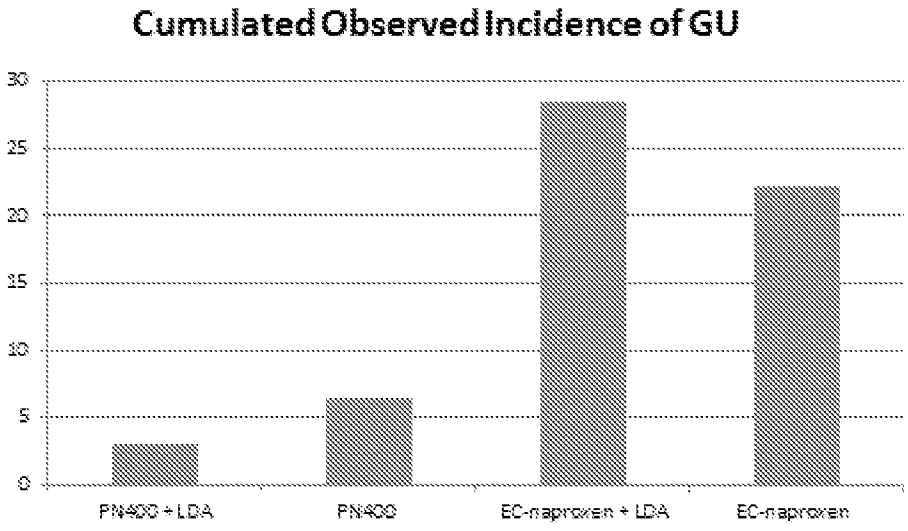
		GUs	
		No. (%) (95% CI)	p-value
Study A 0-1 month	PN400 (n=53)	0 (0.0-6.7)	--
	EC-naproxen (n=51)	6 (11.8) (4.4-23.9)	
Study A 0-3 months	PN400 (n=53)	0 (0.0-6.7)	--
	EC-naproxen (n=51)	10 (19.6) (9.8-33.1)	
Study A 0-6 months	PN400 (n=53)	1 (1.9) (0.0-10.1)	--
	EC-naproxen (n=51)	12 (23.5) (12.8-37.5)	
Study B 0-1 month	PN400 (n=46)	0 (0.0-7.7)	--
	EC-naproxen (n=51)	10 (19.6) (9.8-33.1)	
Study B 0-3 months	PN400 (n=46)	0 (0.0-7.7)	--
	EC-naproxen (n=51)	14 (27.5) (15.9-41.7)	
Study B 0-6 months	PN400 (n=46)	2 (4.3) (0.5-14.8)	--
	EC-naproxen (n=51)	17 (33.3) (20.8-47.9)	
Study A + Study B 0-6 months	PN400 (n=99)	3 (3.0) (0.6-8.6)	P<0.001
	EC-naproxen (n=102)	29 (28.4) (19.9-38.2)	

TABLE 5

Incidence of GUs for Non-LDA Users at 1, 3 and 6 Months in ITT Population

		GUs	
		No. (%) (95% CI)	p-value
Study A 0-1 month	PN400 (n=165)	3 (1.8) (0.4-5.2)	--
	EC-naproxen (n=165)	22 (13.3) (8.5-19.5)	
Study A 0-3 months	PN400 (n=165)	4 (2.4) (0.7-6.1)	--
	EC-naproxen (n=165)	32 (19.4) (13.7-26.3)	
Study A 0-6 months	PN400 (n=165)	8 (4.8) (2.1-9.3)	--
	EC-naproxen (n=165)	38 (23.0) (16.8-30.2)	
Study B 0-1 month	PN400 (n=164)	4 (2.4) (0.7-6.1)	--
	EC-naproxen (n=159)	11 (6.9) (3.5-12.0)	
Study B 0-3 months	PN400 (n=164)	10 (6.1) (3.0-10.9)	--
	EC-naproxen (n=159)	23 (14.5) (9.4-20.9)	
Study B 0-6 months	PN400 (n=164)	13 (7.9) (4.3-13.2)	--
	EC-naproxen (n=159)	34 (21.4) (15.3-28.6)	
Study A + Study B 0-6 months	PN400 (n=329)	21 (6.4) (4.0-9.6)	<0.001
	EC-naproxen (n=324)	72 (22.2) (17.8-27.7)	

These results have been summarized in a graphic form for the examiner's convenience and are presented below:



Based on these data, which the examiner acknowledged "does appear to be unexpected" (*see* Action, p. 7), the claims are patentable over the '907 patent, as there is nothing in the specification of the cited patent that could suggest such an outcome. Thus, given these observations, the rejection is believed to be overcome.

Beyond the question of support, the Office has raised another concern, namely, whether the claims are commensurate in scope with the provided data. In that regard, the Office notes that the data were generated with the PN400 formulation composition comprising 500 mg, whereas the claims recite both 375 mg and 500 mg in the alternative. While Applicants strongly disagree with the Office's position for at least the reasons discussed in the interview, solely to expedite prosecution, Applicants have amended the claims herein to focus on the embodiment having 500 mg of naproxen.

In addition, the Office maintains that PN400 contains naproxen "all of which is enterically coated" (*see* Action, p. 8), whereas the present claims only require "a portion of the naproxen to be surrounded by a coating that is substantially insoluble at a pH of below 3.5." *Id.* Again, Applicants strongly disagree with the Office's concerns for at least the reasons discussed

in the interview. In addition, Applicants note that the independent claims prior to the Action were silent as to enteric coating. Rather, they recited that "at least a portion of said naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher." The present application makes clear that coordinated delivery of the naproxen, or pharmaceutically acceptable salt thereof, and the esomeprazole, or pharmaceutically acceptable salt thereof, can be accomplished, for example, via the use of one or more pH-dependent delayed release coatings and/or time release coatings with respect to the naproxen.

Nevertheless, solely to expedite prosecution and given the examiner's concern that the claims are commensurate in scope with the evidence offered to support the claims, Applicants have amended the claims herein to include parameters that PN400 (a.k.a. NAP/ESO) would meet, namely, that the unit dosage form releases less than 10% of the naproxen or a pharmaceutically acceptable salt thereof after 2 hours when tested using the USP Paddle Method in 1000 ml of 0.1N HCl at 75 rpm at 37° C +/-0.5° C.[1] As set forth in the appended Declaration under 37 C.F.R. §1.132 from Brian Downey ("Downey Declaration"), at paragraph 4, these parameters, in combination with the unit dosage form releasing the esomeprazole or a pharmaceutically acceptable salt thereof as set forth in the claims, reflect the coordinated delivery of the claimed unit dosage form as disclosed in the present application, and would be commensurate in scope with the coordinated delivery of "NAP/ESO" described in Angiolillo. *Id.* The newly added parameters are also standard in the field for determining the performance of delayed release dosage forms (see Downey Declaration at paragraph 5), and consistent with the definition set

[1] Support for those amendments can be found in the application as filed, *e.g.*, at page 4.

forth by the World Health Organization with respect to enteric coated tablets, *i.e.*, disintegration testing in 0.1 N HCl for 2 hours.[2]

Applicants respectfully request that the rejection be withdrawn.

IV. Rejection for Obviousness-Type Double-Patenting

Claims 1-4, 13-15, 17-20, 22, 23, 25, 26, 31, 36-38, 42-48, and 64-67 are provisionally rejected over claims 1-20 of copending application U.S. Serial No. 12/823,082 in view of the '907 patent. Although the rejection is provisional in nature, Applicants traverse the rejection as follows.

The claims as presented here now all recite methods of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, based on surprising clinical data in this subset of patients. The detailed discussion presented in Part III above will not be repeated here, but is incorporated by reference. Thus, in light of similar considerations, it is believed that this rejection also is overcome. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

[2] See, http://www.who.int/medicines/publications/pharmacopoeia/Tabs-GeneralMono-rev-FINAL_31032011.pdf, copy attached. See, also, FDA's Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (September 1997).

V. Conclusion

In light of the foregoing, Applicants respectfully submit that all claims are in condition for allowance, and an early notification to the effect is earnestly solicited. The Examiner is invited to contact the undersigned representative with any questions or concerns regarding this submission or the application.

Respectfully submitted,

/Steven L. Highlander/

Steven L. Highlander
Reg. No. 37,642

Date: May 30, 2014

PARKER HIGHLANDER PLLC
1120 S. Capital of Texas Hwy.
Bldg. One, Suite 200
Austin TX 78746

Direct: 512-334-2901
General: 512-334-2900
Fax: 512-334-2999

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brian AULT *et al.*	Group Art Unit: 1612
Serial No. 12/822,612	Examiner: Adam C. Milligan
Filed: June 24, 2010	Atty. Dkt. No.: POZN.P0027US
For: METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER	Confirmation No.: 6136

CERTIFICATE OF ELECTRONIC TRANSMISSION
37 C.F.R. § 1.8

I hereby certify that this response is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:

May 30, 2014 /Steven L. Highlander/
Date Steven L. Highlander

DECLARATION UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

I, Brian Downey, do declare that:

1. I am a United States citizen residing in Raleigh, North Carolina. I am currently employed by the assignee of the above-captioned application, Pozen Inc. A copy of my *curriculum vitae* is attached hereto as Exhibit A.

2. I am a pharmaceutical industry professional with experience in the management of external contract manufacturing and testing organizations, including planning and reviewing of analytical methods development, validation, and stability studies, and assessing in-process and release testing, for both drug substance and drug products. I am familiar with GLPs, GMPs, USP, ICH, and FDA regulatory requirements and have experience in performing quality assurance audits for analytical and bioanalytical laboratories and API and drug product manufacturing facilities. I am knowledgeable in bioanalytical method validation, clinical plasma sample analyses, and basic pharmacokinetic evaluation using the appropriate statistical software, and am familiar with drug product manufacturing processes including granulation, tablet compression, tablet film coating, packaging, and labeling. I am an active participant in FDA teleconferences relating to analytical issues.

3. I am familiar with the development and validation of the analytical testing methods used for the analysis of PN400 tablets (fixed-dose combination of enteric coated (EC) naproxen 500 mg and immediate release (IR) esomeprazole magnesium 20 mg), which specifically include an acid stage dissolution test for delayed release dosage forms, which is applicable to this enteric coated tablet.

4. Based on my experience with PN400, described above, I am confident that this unit dosage form releases less than 10% of the naproxen or a pharmaceutically acceptable salt thereof after 2 hours when tested using the USP Paddle Method in 1000 ml of 0.1N HCl at 75 rpm at 37 °C +/-0.5 °C. Therefore, in my opinion, NAP/ESO as referenced in Angiolillo *et al., J. Thromb. Thrombolysis* (published online: December 25, 2013) is a unit dosage form that would meet the parameters of releasing less than 10% of the naproxen or a pharmaceutically acceptable

thereof after 2 hours when tested using the USP Paddle Method in 1000 ml of 0.1N HCl at 75 rpm at 37 °C +/-0.5 °C.

5. Furthermore, I note that the dissolution profile cited above is a standard in the field for determining the performance of delayed release dosage forms. It is set forth in the US Pharmacopeia <711> Dissolution for just this purpose.

6. I hereby declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

May 28, 2014
Date

Brian Downey

BRIAN DOWNEY, MS
Pharmaceutical Development Professional

CONTACT INFORMATION
4812 Wood Valley Dr., Raleigh, NC 27613
Phone: (919) 607-4562
briandowney@nc.rr.com

CAREER SUMMARY AND SKILLS
Pharmaceutical industry experience in performing, contracting, and reviewing analytical methods development, validation, stability, and project management for drug substance and drug product dosage forms including tablets, soft gel capsules, oral liquids, aerosols, and injectables. Experienced in performing quality assurance audits for API manufacturing facilities, and analytical and bioanalytical laboratories. Knowledgeable in bioanalytical method validation, pre-clinical and clinical plasma sample analyses, and basic pharmacokinetic evaluation using WinNonLin. Familiar with GLPs, GMPs, USP, ICH, and FDA regulatory requirements.

PROFESSIONAL EXPERIENCE
26 years of professional experience in the pharmaceutical industry.

POZEN® Inc., Chapel Hill, NC, Apr 2000 - present

Director, Analytical/Pharmaceutical Development, Jan 2006 – present
Associate Director, Pharmaceutical Development, Apr 2000 – Jan 2006

- Design and manage pharmaceutical development plans for analytical activities needed to support different phases of clinical studies (Phase 1, 2, 3), and regulatory filings.
- Contract analytical method development, method validation, and stability studies to appropriate facilities for drug product and drug substance.
    - Conduct audits at contract lab facilities
    - Manage analytical method development & validation and provide problem-solving strategies
    - Review all study reports and provide expert feedback
- Review and scientifically assess reports and specifications, including validation and stability data;
- Author and review regulatory filings including INDs, CTAs and NDAs.
    - Author analytical sections for five 505(b)(2) NDAs including MT100, MT300, Treximet®, Vimovo®, and PA32540.
    - Conduct comprehensive editing and review of pharmaceutical development sections of NDAs and INDs and provide expert guidance
- Secure facilities for API production and drug product manufacturing
    - API for pre-clinical studies; review and audit production of drug substance at contract facilities.
    - Secure manufacturing and analytical laboratories for manufacture and testing of drug products.
- Expertise in Bioanalytical Development, including:
    - Contracting, reviewing and assessing dose solution checks
    - Overseeing bioanalytical method development, method validation, and plasma analysis to support pre-clinical and clinical studies.
    - Conduct Audits and Assess capabilities of bioanalytical facilities.
    - Proficient in Phoenix WinNonlin to provide clinical colleagues with an early evaluation of plasma data from bioavailability and bioequivalence studies
    - Knowledgeable of statistical analysis and interpretation of study results
- Ability to effectively manage numerous drug product development plans simultaneously in various stages of development

Glaxo Wellcome Inc., Research Triangle Park, NC, Jun 1987 – Apr 2000

Research Investigator I, Chemical Analysis Department, Jul 1997 – Apr 2000
Senior Scientist, Analytical Sciences Department, Jun 1994 – Jun 1997
Research Scientist, Structural Chemistry Department, Nov 1990 – May 1994
Associate Scientist, Analytical Chemistry Department, Jun 1987 – Oct 1990

- Supervised staff of four BS, MS, and Ph.D. chemists in the Chemical Analysis Laboratory.
- Pioneered introduction of bench-top LC/MS technology (Hewlett Packard HPLC/MSD) to the laboratory and trained 12 chromatographers in instrument operation and data interpretation.
- Analytical sciences project leader for multiple new chemical entity projects.
- CMC team leader for a new chemical entity which required coordinating and writing regulatory documentation including INDs and NDAs, representing Pharmaceutical Development on the international project team, and testing and release of clinical supplies.
- Analytical Sciences Project Team Representative for three Zantac® line extension projects including a combo tablet, chewable tablet, and oral liquid.
- Planned and completed the development and validation of analytical methods for a dry powder inhaler.
- US representative to Zantac® Impurities International Working Group tasked with standardizing ranitidine methods across Glaxo Worldwide sites.
- Performed several LC/MS techniques including thermospray, electrospray and particle beam LC/MS. Elucidated structure for impurities and degradation products in drug products and drug substances using mass spectrometry.
- Chairman of Promotion Review Committee.

Baxter Travenol Laboratories, Morton Grove, IL

Research Assistant, Analytical Methods Development Laboratory, Jan 1986 – May 1987

United States Air Force, Colorado Springs, CO, Sep 1978 – Aug 1982

EDUCATION

Master of Science in Analytical Chemistry
University of North Carolina at Chapel Hill. Jan 1988 – Dec 1992
Completed graduate work for Master of Science while working full time at Glaxo Welcome Inc.

Bachelor of Science in Chemistry, Minor in Mathematics
Illinois State University, Normal, IL. Aug 1982 – Dec 1985
Undergraduate teaching assistant.

Undergraduate Coursework (30 hours)
University of Colorado at Colorado Springs. Aug 1979 – May 1982
Completed undergraduate course work towards Bachelor of Science while serving full time in the USAF.

INTERESTS

Regularly participate in running races including 5K, 10K, and marathons. Active in mountain hiking, mountain biking, and water skiing.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brian AULT *et al.*	Group Art Unit: 1612
Serial No.: 12/822,612	Examiner: Adam C. Milligan
Filing Date: June 24, 2010	Attorney Docket No.: POZN.P0027US
Title: METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER	Confirmation No.: 6136

CERTIFICATE OF ELECTRONIC TRANSMISSION

I hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:

May 30, 2014 /Steven L. Highlander/
Date Steven L. Highlander

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Commissioner:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56, it is respectfully requested that this Supplemental Information Disclosure Statement be entered and the documents listed on attached Form PTO-1449 be considered by the Examiner and made of record. Copies of the listed documents required by 37 C.F.R. § 1.98(a)(2) are attached for the convenience of the Examiner.

In accordance with 37 C.F.R. §§ 1.97(g) and (h), this Supplemental Information Disclosure Statement is not to be construed as a representation that a

search has been made, and is not to be construed to be an admission that the information cited is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

A fee as set forth in 37 C.F.R. § 1.17(p) in the amount of $180.00 is being paid via credit card concurrently herewith via EFS-Web. If an appropriate payment has not been enclosed, or if it is insufficient, the Commissioner is authorized to deduct the appropriate fee from Parker Highlander PLLC Deposit Account No. 50-5902/POZN.P0027US.

Applicants respectfully request that the listed documents be made of record in the present application. The examiner is invited to contact the undersigned attorney with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

/Steven L. Highlander/

Steven L. Highlander
Reg. No. 37,642
Attorney for Applicants

Parker Highlander PLLC
1120 S. Capital of Texas Highway
Building One, Suite 200
Austin, Texas 78746
512-334-2900 (Telephone)
512-334-2999 (Fax)

Date: May 30, 2014

Form PTO-1449 (modified)	Atty. Docket No.: POZN.P0027US	Serial No.: 12/822,612
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT	Applicant(s): Brian AULT *et al.*	
(Use several sheets if necessary)	Filing Date: June 24, 2010	Group: 1612

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1*	*See Page 1*

U.S. Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name

Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C34	U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, "Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation," available online at http://www.fda.gov/downloads/Drugs/Guidances/UCM070640.pdf , September 1997.
	C35	World Health Organization, "Revision of Monograph on Tablets. Final text for addition to *The International Pharmacopoeia*," available online at http://www.who.int/medicines/publications/pharmacopoeia/Tabs-GeneralMono-rev-FINAL_31032011.pdf, March 2011.

EXAMINER:	DATE CONSIDERED:

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

Electronic Patent Application Fee Transmittal

Application Number:	12822612
Filing Date:	24-Jun-2010
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Filer:	Steven Lee Highlander/Christopher Jackson
Attorney Docket Number:	POZN.P0027US

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	19174772
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	108197
Filer:	Steven Lee Highlander/Christopher Jackson
Filer Authorized By:	Steven Lee Highlander
Attorney Docket Number:	POZN.P0027US
Receipt Date:	30-MAY-2014
Filing Date:	24-JUN-2010
Time Stamp:	16:51:22
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	3819
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		POZNP0027US_AMEND.pdf	280387 71b7e9c5b69ae4c69456263aae29508d6f7ebe46	yes	15

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	6
	Applicant Arguments/Remarks Made in an Amendment	7	15

Warnings:

Information:

2	Oath or Declaration filed	POZNP0027US_DECEXCV.pdf	1505284 0fb23830d46cd4bdb960972ce82a553fcc064f36	no	5

Warnings:

Information:

3	Transmittal Letter	POZNP0027US_SUPPLIDS.pdf	33773 1c8addf9777d1d716a2d27d7e49316811f9082a8	no	2

Warnings:

Information:

4	Information Disclosure Statement (IDS) Form (SB08)	POZNP0027US_PTO1449.pdf	34735 08fc07df9afe009b2e13303bfeeadb10b0716223	no	1

Warnings:

Information:

This is not an USPTO supplied IDS fillable form

5	Other Reference-Patent/App/Search documents	POZNP0027US_C34.pdf	3794519 2394b4bc83fd7eaee5830fb8c15ae7d0453d4922	no	52

Warnings:

Information:

6	Other Reference-Patent/App/Search documents	POZNP0027US_C35.pdf	4139961 0ded4c9fea021c4515bee8a9be3a3cba1f25ece7	no	10

Warnings:

Information:

7	Fee Worksheet (SB06)	fee-info.pdf	30336 4e464958fae46da9cf5f227118c7aba169176131	no	2

Warnings:

Information:

Total Files Size (in bytes):	9818995

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/822,612	Filing Date 06/24/2010	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT **05/30/2014**

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 16	Minus	** 68	= 0	X $80 =	0
Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $420 =	0
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	0

AMENDMENT

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/Tina J. Barden/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/822,612	06/24/2010	Brian Ault	POZN.P0027US	6136

108197 7590 04/28/2014

Parker Highlander PLLC
1120 South Capital of Texas Highway
Bldg. 1, Suite 200
Austin, TX 78746

EXAMINER	
MILLIGAN, ADAM C	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
04/28/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@phiplaw.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	12/822,612	AULT ET AL.	
	Examiner	Art Unit	
	ADAM C. MILLIGAN	1612	

All participants (applicant, applicant's representative, PTO personnel):

(1) *ADAM C. MILLIGAN*.

(3) *STEVEN L. HIGHLANDER*.

(2) *LAUREN STEVENS*.

(4)_____.

Date of Interview: *4/14/2014*.

Type: ☐ Telephonic ☐ Video Conference
☒ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *All Pending*.

Identification of prior art discussed: *Prior art of record*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicants representitives presented slides detailing unexpected results that were present in the instant specification at tables 3 and 5. Applicants argued that the unexpected results were commensurate in scope with the instantly recited claims. Examiner disagreed that the results were commensurate in scope with the instant claims as outlined in the Office action dated 4/2/2014. Examiner was not persuaded by FDA findings as the FDA evaluates using much different perameters than the USPTO uses during a patentability determination. Applicants will consider filing a formal response to the office action dated 4/2/2014 which reflects the discussion about the claims being commensurate in scope with the demonstrated results.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/ADAM C MILLIGAN/ Primary Examiner, Art Unit 1612	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

PTO/SB/84 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

AUTHORIZATION TO ACT IN A REPRESENTATIVE CAPACITY

In re Application of: Brian AULT et al.	
Application No. 12/822,612	
Filed: June 24, 2010	
Title: Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer	
Attorney Docket No. POZN.P0027US	Art Unit: 1612

The practitioner named below is authorized to conduct interviews and has the authority to bind the principal concerned. (Note: pursuant to 37 CFR 10.57(c), a practitioner cannot authorize other registered practitioners to conduct interviews without consent of the client after full disclosure.) Furthermore, the practitioner is authorized to file correspondence in the above-identified application pursuant to 37 CFR 1.34:

Name	Registration Number
Lauren Stevens	36,691

This is not a Power of Attorney to the above-named practitioner. Accordingly, the practitioner named above does **not** have authority to sign a request to change the correspondence address, a request for an express abandonment, a disclaimer, a power of attorney, or other document requiring the signature of the applicant, assignee of the entire interest or an attorney of record. If appropriate, a separate Power of Attorney to the above-named practitioner should be executed and filed in the United States Patent and Trademark Office.

SIGNATURE of Practitioner of Record

Signature	/Steven L. Highlander/	Date April 13, 2014
Name	Steven L. Highlander	Registration No., if applicable 37,642
Telephone	512-334-2901	

Electronic Acknowledgement Receipt

EFS ID:	18747853
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	108197
Filer:	Steven Lee Highlander/Richard Ortiz
Filer Authorized By:	Steven Lee Highlander
Attorney Docket Number:	POZN.P0027US
Receipt Date:	13-APR-2014
Filing Date:	24-JUN-2010
Time Stamp:	20:31:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	POZNP0027US__Authorization-Rep-Capacity.pdf	74744 47408d97c55705932eb317ea82647f3f830adb82	no	1

Warnings:	
Information:	

Total Files Size (in bytes):	74744

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/822,612	06/24/2010	Brian Ault	POZN.P0027US	6136

108197 7590 04/02/2014

Parker Highlander PLLC
1120 South Capital of Texas Highway
Bldg. 1, Suite 200
Austin, TX 78746

EXAMINER	
MILLIGAN, ADAM C	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
04/02/2014	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@phiplaw.com

Office Action Summary	Application No. 12/822,612	Applicant(s) AULT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/17/2014*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-4,13-15,17-20,22,23,25,26,31,36-38,42-48 and 64-67* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-4,13-15,17-20,22,23,25,26,31,36-38,42-48 and 64-67* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/17/2014 has been entered.

Applicants' arguments, filed 1/17/2014, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections – 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Claims 1-4, 13-15, 17-20, 22, 23, 25, 26, 31, 36-38, 42-45 and 48 and 64-67 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Plachetka (U.S. 6,926,907 – see patent cite #39 on 12 page IDS dated 8/28/2012).

Plachetka teaches non-steroidal anti-inflammatory drugs (NSAIDs) are widely accepted for pain control, but can lead to the development of gastrointestinal (GI) ulcers in susceptible individuals (col.1, lines 21-39 and col.2, lines 64-67). Plachetka teaches a method for reducing the risk of gastrointestinal side effects for people taking NSAIDs during chronic treatment by administration of a single, coordinated, unit-dose product that combines an agent which actively raises gastric pH to levels associated with less risk of NSAID-induced ulcers and an NSAID that is specially formulated to be released in a coordinated way to minimize adverse effects (col.3, lines 1-17). Figure 1 and Example 6 demonstrates a dosage having a naproxen (500mg) core layer, which is

surrounded by a barrier layer, which is then surrounded by an enteric coating, which is then surrounded by acid inhibitor releasing layer (Example 6). The outermost omeprazole layer raises the gastrointestinal pH to above 4 (col.15, lines 1-16). The third layer prevents the release of the naproxen until the pH is above about 4 (col.14, lines 59-67). The second layer protects the naproxen, and the first layer contains the naproxen and suitable excipients (col.14, lines 40-58). Results demonstrate that after a week of twice a day administration, patients taking the tablet of Plachetka had substantially less grade 3-4 gastrointestinal damage than those taking naked or enteric coated NSAIDs without an acid inhibitor (Example 10). Other than naproxen, which is typically administered at amounts of 250mg to 500mg, suitable NSAIDs include aspirin (col.1, lines 39-45), which is typically administered in amounts between about 250mg and 1000mg (col 5, lines 55-59). Suitable acid inhibitors include omeprazole (col. 3, lines 18-38 and Examples 6, 7 and 8), which may be administered between about 5mg and 50mg (col.7, lines 1-18) and esomeprazole, which may be administered at 5mg to 100mg. Omeprazole is administered with an alkalizing agent such as sodium bicarbonate, potassium bicarbonate or sodium hydroxide to help solubilize and protect the omeprazole (col.15, lines 34-45). The tablet dosage discussed above may alternatively be formulated as a capsule formulation wherein the capsule contains pellets and granules (See e.g. Example 7).

Plachetka does not teach the administration specific time periods over a week or administration to specific patient subpopulations.

With regard to claims 2, 4, 5, 26-28, 31 and 61-63, it would have been obvious to use the method of Plachetka on any patient who requires prolonged given that NSAIDs are taught to inducing GI ulcers. Accordingly, it would have been obvious to administer the tablets of Plachetka to subsets of these patients where the subsets are included in the group of patients needing prolonged NSAID treatment.

With regard to claims 10-12, 39-41, 53-55 and 58-60, given that the prior art method is demonstrated to lesson gastric ulcers over the course of a week trial and is taught for use by chronic NSAID users, it would have been obvious to continue the twice per day (BID) regimen for periods of time well beyond a week and up to the lifetime of the patient.

With regard to claim 18, it would have been obvious to one of ordinary skill in the art to substitute sodium bicarbonate for potassium bicarbonate or sodium hydroxide given that each of the above are taught to act as alkalizing agents. MPEP 2144.06(II).

With regard to claims 21, 23, 33 and 34, in the case where the claimed ranges overlap or lie inside ranges disclosed by the prior art, a prima facie case of obviousness exists. *see* MPEP 2144.05. Here, the prior art teaches that naproxen may administered at amounts of 250mg to 500mg and esomeprazole may be administered in amounts of 5mg to 100mg.

With regard to claim 43, the recited “beads or minitablets” recited are interpreted to include the "granules” and “pellets” of Example 7 of the prior art which are placed into the capsule.

Applicants present the following arguments against the rejection.

Applicants agree with the Examiner that the Plachetka (i.e. '907 patent) teaches that the NSAID core may be naproxen and the acid inhibitor coating may be esomeprazole, but nonetheless argue that Plachetka does not teach the species (i.e. naproxen dosage, esomeprazole dosage, duration of treatment and patient subsets) recited by the instant claims and thus a prima facie case of obviousness has not been established.

Examiner disagrees. The recited dosages of 20mg of esomeprazole and 35 or 500mg naproxen are rendered obvious by Plachetka's teaching a dosage of naproxen is 250mg to 500mg and esomeprazole is 5mg to 100mg.

Regarding the duration of treatment, Claim 1 does not require a specific duration of treatment. Dependent claims (e.g. claims 10-12) recite durations of over at least about 1 month or longer. Given that the prior art method is demonstrated to lesson gastric ulcers over the course of a 1-week trial and is taught for use by chronic NSAID users, it would have been obvious to continue the twice per day (BID) regimen for periods of time well beyond a week and up to the lifetime of the patient.

Regarding the patient population, Claim 1 does not require a specific patient population. The specific populations recited in the dependent claims (e.g. claims 3 and 4) would have been obvious given Plachetka teaches the use of the acid inhibitor coated NSAID on any patient who requires prolonged NSAID administration. Accordingly, it would have been obvious to administer the acid inhibitor coated NSAID

to patients regardless of the reasons the patient is taking the NSAID (e.g. pain, inflammation, etc.).

Applicants argue that that a post filing reference by Angiolillo *et al.* discloses data which supports the patentability of the instant claims. There is a general expectation in the art that patients taking low-dose aspirin (LDA) are more prone to developing gastric ulcers. Angiolillo teaches that in contrast to the general expectation that patients taking LDA in combination with NAP/ESO (500mg enteric coated naproxen and 20mg esomeprazole magnesium) showed less incidence of gastric ulcers than patients taking NAP/ESO and no LDA. Applicants argue that the same data can be found in the instant specification at paragraph [0155] and tables 3 and 5. Applicants conclude that they have demonstrated an unexpected result which overcomes the rejection and thus the rejection should be withdrawn.

Examiner disagrees. While the result demonstrated by Angiolillo does appear to be unexpected, the instant specification does not appear to support such a result. Paragraph [0155] teaches PN400 (i.e. NAP/ESO) was associated with a significantly lower incidence of GU versus EC-naproxen regardless of age. Similar to [0155], instant tables 3 and 5 compare PN400 to EC-naproxen, but provide no teaching that PN400 with LDA results in fewer gastric ulcers than PN400 without LDA. Thus, the unexpected result demonstrated by Angiolillo does not appear to be present in the instant application. Moreover, the presently recited claims are not commensurate in scope with the unexpected result demonstrated by Angiolillo.

Objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support. MPEP 716.02(d). Here, the instant claims permit the naproxen dosage to be 375mg or 500mg and a portion of the naproxen to be surrounded by a coating that is substantially insoluble at a pH below 3.5. In contrast, the data of Angiolillo is based on 500mg of naproxen, all of which is enteric coated.

Claims 46 and 47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Plachetka (U.S. 6,926,907 – see patent cite #39 on 12 page IDS dated 8/28/2012) in view of Phillips (U.S. 2004/0048896 – see publication cite #12 on 18 page IDS dated 8/28/2012).

Plachetka is discussed above but does not teach the addition of a pharmacologically inert water-soluble coating over the outermost, esomeprazole containing, layer of the tablet.

Phillips teaches that when administering bitter tasting proton pump inhibitors such as omeprazole or esomeprazole, sweeteners such a sucrose and aspartame may be added to the formulation.

Phillips does not teach the addition of naproxen.

It would have been obvious to one of ordinary skill in the art to add a water-soluble coating comprising sucrose or aspartame to the formulation of Plachetka in order to mask the bitter taste associated with esomeprazole as taught by Phillips.

Applicants present no arguments specific to this rejection.

For the reasons provided in the rejection over Plachetka, the rejection is maintained.

Nonstatutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 13-15, 17-20, 22, 23, 25, 26, 31, 36-38, 42-48 and 64-67 stand provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/823,082 in view of Plachetka (U.S. 6,926,907 – see IDS dated 8/28/2012).

The copending applications teach a method of treating a patient at risk of developing an NSAID-associated ulcer by administering a unit dose comprising omeprazole in an amount sufficient to raise the gastric pH of the patient to at least 3.5 and the NSAID aspirin surrounded by a coating that is substantially insoluble in an aqueous medium below 3.5.

Plachetka is discussed above and additionally teaches that both aspirin and naproxen are suitable NSAIDs (col.3, lines 18-38) and that both omeprazole and esomeprazole are suitable acid inhibitors (col.3, lines 18-38).

It would have been obvious to one of ordinary skill in the art to substitute aspirin for naproxen given that Plachetka teaches both are substitutable equivalent NSAIDs. See MPEP 2144.06(II). Further, one of ordinary skill in the art would understand that esomeprazole is the S-enantiomer of omeprazole, and thus contained in omeprazole.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants argue that for the reasons provided above, this rejection should be withdrawn.

Examiner disagrees. For the reasons provided in the rejection over Plachetka, the rejection is maintained.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ADAM MILLIGAN whose telephone number is (571)270-7674. The examiner can normally be reached on M-F 9:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ADAM C MILLIGAN/
Examiner, Art Unit 1612

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12822612	AULT ET AL.
	Examiner	Art Unit
	ADAM C MILLIGAN	1612

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
PALM Inventor Search	9/9/2012	AM
EAST Search - see attached search history	9/9/2012	AM
STN Search - caplus - esomeprazole, naproxen, NSAID induced GI ulcer, enteric coating	9/9/2012	AM
Updated EAST and STN searches	3/20/2014	AM

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

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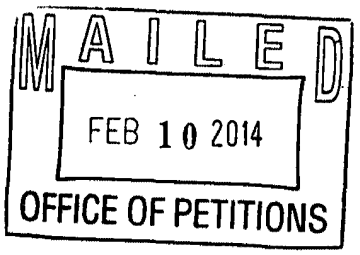
AUSTIN TX 78746



Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 12/822,612

1. THE REQUEST FILED January 17, 2014 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☐ for an original nonprovisional application (Track I).
B. ☒ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to **Michelle R. Eason** at (571) 272-4231. In his/her absence, calls may be directed to Brian W. Brown at (571) 272-5338.

/Michelle R. Eason/
(*Signature*)

Paralegal Specialist, Office of Petitions
(Title)

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	12/822,612	Filing Date	2010-06-24	Docket Number (if applicable)	POZN.P0027US	Art Unit	1612
First Named Inventor	Brian AULT			Examiner Name	Adam C. Milligan		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- ☐ Other _____

☒ Enclosed

- ☒ Amendment/Reply
- ☐ Information Disclosure Statement (IDS)
- ☐ Affidavit(s)/ Declaration(s)
- ☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 505902

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Steven L. Highlander/	Date (YYYY-MM-DD)	2014-01-17
Name	Steven L. Highlander	Registration Number	37642

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/22 (03-13)
Approved for use through 3/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): POZN.P0027US

Application Number: 12/822,612

Filed: June 24, 2010

For: Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer

Art Unit: 1612

Examiner: Adam C. Milligan

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	Micro Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$200	$100	$50	$
☐	Two months (37 CFR 1.17(a)(2))	$600	$300	$150	$
☑	Three months (37 CFR 1.17(a)(3))	$1,400	$700	$350	$ 1,400.00
☐	Four months (37 CFR 1.17(a)(4))	$2,200	$1,100	$550	$
☐	Five months (37 CFR 1.17(a)(5))	$3,000	$1,500	$750	$

☐ Applicant asserts small entity status. See 37 CFR 1.27.

☐ Applicant certifies micro entity status. See 37 CFR 1.29.
Form PTO/SB/15A or B or equivalent must either be enclosed or have been submitted previously.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-5902/POZN.P0027US.

☑ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant.

☑ attorney or agent of record. Registration number 37,642.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

/Steven L. Highlander/ — Signature

January 17, 2014 — Date

Steven L. Highlander — Typed or printed name

512-334-2900 — Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☑ * Total of 1 forms are submitted.

Electronic Patent Application Fee Transmittal

Application Number:	12822612
Filing Date:	24-Jun-2010
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Filer:	Steven Lee Highlander/Richard Ortiz
Attorney Docket Number:	POZN.P0027US

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Request for Prioritized Examination	1817	1	4000	4000
Pages:				
Claims:				
Miscellaneous-Filing:				
Publ. Fee- Early, Voluntary, or Normal	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	1830	1	140	140
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1400	1400
Miscellaneous:				
Request for Continued Examination	1801	1	1200	1200
		Total in USD ($)		**6740**

Electronic Acknowledgement Receipt

EFS ID:	17948022
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	108197
Filer:	Steven Lee Highlander/Richard Ortiz
Filer Authorized By:	Steven Lee Highlander
Attorney Docket Number:	POZN.P0027US
Receipt Date:	17-JAN-2014
Filing Date:	24-JUN-2010
Time Stamp:	15:15:05
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$6740
RAM confirmation Number	1781
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		POZNP0027US_AMNDT-RESPONSE.pdf	110780 ea5268119f2153ccdeecf2b5fe26a21ff6921d9c	yes	16

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment Submitted/Entered with Filing of CPA/RCE	1	2
Claims	3	9
Applicant Arguments/Remarks Made in an Amendment	10	16

Warnings:					
Information:					
2	TrackOne Request	POZNP0027US_TrackOneReq.pdf	103130 5f9d9f23691889d74803daad41f3ea9741fdf003	no	1
Warnings:					
Information:					
3	Request for Continued Examination (RCE)	POZNP0027US_RCE.pdf	73657 1ad4758aba38ab1aea461fa56cb6b493285af864	no	2
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
4	Extension of Time	POZNP0027US_EOT.pdf	106494 b608bd75e3bf0467ab4e6155b138b018bdb788e2	no	1
Warnings:					
Information:					
5	Fee Worksheet (SB06)	fee-info.pdf	39417 9e79218de240dadd402bb09c330299b052e1e72c	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	433478		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brian AULT *et al.*	Group Art Unit: 1612
Serial No. 12/822,612	Examiner: Adam C. Milligan
Filed: June 24, 2010	Atty. Dkt. No.: POZN.P0027US
For: METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER	Confirmation No.: 6136

CERTIFICATE OF ELECTRONIC TRANSMISSION
37 C.F.R. § 1.8

I hereby certify that this response is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:

January 17, 2014 — Date
/Steven L. Highlander/ — Steven L. Highlander

AMENDMENT AND RESPONSE TO ACCOMPANY REQUEST FOR CONTINUED EXAMINATION UNDER 37 C.F.R. §1.114

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Dear Sir:

This is in response to the Office Action ("the Action") mailed on July 18, 2013, and the Examiner is respectfully requested to enter the following amendments. The Commissioner is requested to consider this statement as a Petition for Extension of Time under 37 C.F.R. § 1.136(a)(1) of three months to and including January 18, 2014, which falls on a Saturday and is therefore extended until Tuesday, January 21, 2014, under 37 C.F.R. § 1.7(a), because Monday, January 20, 2014, is a Federal holiday. No other fees are believed to be due in connection with the filing of this response; however, should any fees be missing or deficient, or should any other

fees under 37 C.F.R. §§ 1.16 to 1.21 be deemed necessary for any reason relating to these materials, the Commissioner is authorized to deduct the appropriate fees from Parker Highlander PLLC Deposit Account No.: 50-5902/POZN.P0027US/SLH.

Amendments to the Claim begin on page 3 of this response; **Remarks** begin on page 10.

AMENDMENTS TO THE CLAIMS

Listing of Claims

The following listing of claims replaces all previous listings or versions thereof:

1. (Currently amended) A method of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, wherein the method comprises administering to said patient in need thereof a pharmaceutical composition in unit dose form comprising:

(a) 20 mg of esomeprazole, or pharmaceutically acceptable salt thereof, in a form and route sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and

(b) 375 mg or 500 mg of naproxen, or pharmaceutically acceptable salt thereof; wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen such that:

(i) at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium; and

(ii) at least a portion of said [[the]] naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher; and

wherein said pharmaceutical composition in unit dose form reduces the incidence of NSAID-associated ulcers in said patient.

2. (Currently amended) The method according to claim 1, wherein ~~said patient is in need of~~ the risk is associated with chronic NSAID treatment.

3. (Previously presented) The method according to claim 1, wherein said disease or disorder is selected from pain and inflammation.

4. (Previously presented) The method according to claim 1, wherein said disease or disorder is selected from osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and a combination thereof.

5-12. (Canceled)

13. (Currently amended) The method according to claim 1, wherein said pharmaceutical composition in unit dose form is a multilayer tablet comprising at least one core and at least a first layer and a second layer, wherein:

(a) said core comprises said at least a portion of said [[the]] naproxen, or a pharmaceutically acceptable salt thereof;

(b) said first layer is a coating that at least begins to release said at least a portion of said [[the]] naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is about 3.5 or greater; and

(c) said second layer comprises the esomeprazole, or a pharmaceutically acceptable salt thereof, wherein said esomeprazole, or a pharmaceutically acceptable salt thereof, is released at a pH of from about 0 or greater.

14. (Original) The method according to claim 13, wherein said esomeprazole, or a pharmaceutically acceptable salt thereof, is released at a pH of from about 1 or greater.

15. (Original) The method according to claim 13, wherein said esomeprazole, or a pharmaceutically acceptable salt thereof, is released at a pH of from about 0 to about 2.

16. (Canceled)

17. (Previously presented) The method according to claim 13, wherein said first layer is an enteric coating.

18. (Previously presented) The method according to claim 13, wherein said multi-layer tablet is at least about 95% free of sodium bicarbonate.

19. (Currently amended) The method according to claim 13, wherein said first layer begins to release said at least a portion of said [[the]] naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 4.0 or greater.

20. (Currently amended) The method according to claim 13, wherein said first layer begins to release said at least a portion of said [[the]] naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 4.5 or greater.

21. (Canceled)

22. (Currently amended) The method according to claim 1 ~~or claim 13~~, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is 500 mg.

23. (Currently amended) The method according to claim 1, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is 375 mg.

24. (Canceled)

25. (Currently amended) A method ~~comprising~~ of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, wherein the method comprises administering to the patient a pharmaceutical composition in unit dosage form suitable for oral administration comprising:

(a) 20 mg of esomeprazole or a pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms, and

(b) 375 mg or 500 mg of naproxen or pharmaceutically acceptable salt thereof, wherein at least a portion of said [[the]] naproxen or a pharmaceutically acceptable salt thereof is surrounded by a coating that is substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of about 37° C; and

wherein said pharmaceutical composition in unit dose form reduces the incidence of NSAID-related ulcers in said patient.

26. (Original) The method of claim 25, wherein the risk is associated with chronic NSAID treatment.

27-30. (Canceled)

31. (Previously presented) The method of claim 25, wherein the patient is treated for a disease or disorder selected from pain, inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and combinations thereof.

32-35. (Canceled)

36. (Previously presented) The method of claim 25, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is 375 mg.

37. (Previously presented) The method of claim 25, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is 500 mg.

38. (Previously presented) The method of claim 25, wherein the pharmaceutical composition is formulated to be administered to a patient twice daily.

39-41. (Canceled)

42. (Previously presented) The method according to claim 25, wherein the unit dosage form is a tablet.

43. (Previously presented) The method according to claim 25, wherein the unit dosage form is a capsule containing beads or minitablets.

44. (Currently amended) The method according to claim 25, wherein the unit dosage form is a tablet comprising a core and two or more layers, in which

(a) said at least a portion of said [[the]] naproxen, or a pharmaceutically acceptable salt thereof, is in the core;

(b) a first layer surrounds the core and is a coating substantially insoluble in aqueous medium at a pH below 3.5 and at a temperature of about 37° C.; and

(c) at least one second layer comprising the esomeprazole, or a pharmaceutically acceptable salt thereof, surrounds the coating of the first layer.

45. (Currently amended) The method according to claim 25, wherein the unit dosage form is a multilayer tablet comprising a core and at least a first layer enclosing the core, and a second layer enclosing the first layer, wherein:

(a) the core comprises <u>said at least a portion of said</u> [[the]] naproxen, or a pharmaceutically acceptable salt thereof;

(b) the first layer is a coating that releases less than 10% of the naproxen or a pharmaceutically acceptable salt thereof after 2 hours when tested using the USP Paddle Method in 1000 ml of 0.1N HCl at 75 rpm at 37° C +/-0.5° C; and

(c) the second layer comprises esomeprazole, or a pharmaceutically acceptable salt thereof and at least one excipient, wherein the second layer is at least 95% soluble after 30 minutes when tested using the USP Paddle Method in 1000 ml of 0.1N HCl for two hours at 75 rpm at 37° C+/-0.5° C.

46. (Previously presented) The method according to claim 44, wherein the unit dosage form further comprises a pharmacologically inert, water soluble coating or film surrounding the outermost layer of the unit dosage form.

47. (Previously presented) The method of claim 46, wherein the inert coating or film comprises a water soluble sugar.

48. (Previously presented) The method of claim 25, wherein administration of the unit dosage form is more effective at reducing the risk of ulcer than treatment with enteric coated naproxen or a pharmaceutically acceptable salt thereof.

49-63. (Canceled)

64. (New) A method of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, wherein the method comprises administering to said patient in need thereof twice a day for 1 month a pharmaceutical composition in unit dose form:

(a) 20 mg of esomeprazole, or pharmaceutically acceptable salt thereof, in a form and route sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and

(b) 375 mg or 500 mg of naproxen, or pharmaceutically acceptable salt thereof; wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen such that:

(i) at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium; and

(ii) at least a portion of said naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher; and

wherein said pharmaceutical composition in unit dose form reduces the incidence of NSAID-associated gastric ulcers in said patient as compared to patients taking low dose aspirin who are administered twice a day for 1 month enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

65. (New) A method of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, wherein the method comprises administering to said patient in need thereof twice a day for 3 months a pharmaceutical composition in unit dose form:

(a) 20 mg of esomeprazole, or pharmaceutically acceptable salt thereof, in a form and route sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and

(b) 375 mg or 500 mg of naproxen, or pharmaceutically acceptable salt thereof; wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen such that:

(i) at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium; and

(ii) at least a portion of said naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher; and

wherein said pharmaceutical composition in unit dose form reduces the incidence of NSAID-associated gastric ulcers in said patient as compared to patients taking low dose aspirin who are administered twice a day for 3 months enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

66. (New) The method according to claim 13, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is 500 mg.

67. (New) The method according to claim 13, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is 375 mg.

REMARKS

I. Status of the Claims

Claims 1-20, 22, 23, 25-31, 36-48 and 51-63 are pending in the application and stand rejected, variously, under 35 U.S.C. §103 and for alleged obviousness-type double-patenting. Claims 1, 2, 13, 19-20, 23, 25, 44-45 and 61-62 have been amended and claims 5-12, 16, 27-30, 40, 41 and 51-63 have been canceled herein, respectively, without prejudice and without disclaimer. In addition, new claims 64-67 have been added. Claims 1-4, 13-15, 17-20, 22, 23, 25, 26, 31, 36-38, 42-48 and 64-67 are therefore currently pending in the application.

Applicant reserves the right to pursue the subject matter of the amended and canceled claims in a continuation application of the present application. The specific grounds for rejection, and Applicant's response thereto, are set forth in detail below.

II. Support for Amendments

Support for the amended claims and newly added claims can be found throughout the specification and claims as originally filed. Specific support for the claim amendments and newly added claims can be found at least in part in paragraphs **[0003]**, **[0005]**, **[0006]**, **[0018]**, **[0024]**, **[0031]**, **[0048]**, **[0058]**, **[0087]**, **[0114]**, and **[0155]** of the specification as originally filed. No new matter is included in the amended claims and newly added claims.

III. Rejection Under 35 U.S.C. §103

Claims 1-20, 22, 23, 25-31, 36-45, 48 and 51-63 remain rejected as obvious over the '907 patent. Although Applicant respectfully disagrees with the arguments presented in the Action that the '907 patent renders obvious the claims presented in the Amendment and Request for

Reconsideration filed on March 14, 2013 ("March 2013 Response"), during the prosecution of the present application, Applicant has amended claims 1 and 25 to recite methods of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, solely in order to progress the present case more rapidly to allowance. Attached as Exhibit A is a peer-reviewed publication by Angiolillo *et al.*, *J Thromb Thrombolysis* (published online: December 25, 2013) ("Angiolillo"), which discloses data that supports the patentability of the amended claims over the '907 patent, either alone or in view of Phillips, as set forth in further detail below. Before this discussion, however, Applicant wishes to clarify certain arguments made in the March 2013 Response, in light of positions taken by the Examiner in the Action.

A. Arguments Presented in the March 2013 Response

The Action states that "Applicants argue that [the '907 patent] fails to teach or suggest the combination of naproxen and esomeprazole" in the March 2013 Response. *See* Action, p. 3. This sentence takes arguments presented by Applicant out of context from the March 2013 Response, and suggests that Applicant presented an argument it did not intend to make in the March 2013 Response. Applicant wishes to clarify that the argument related to the combination of naproxen and esomeprazole that Applicant presented in the March 2013 Response is that the '907 patent fails to teach or suggest the combination of the specific dosage of naproxen with the specific dosage of esomeprazole, for the claimed duration of treatment and patient subsets for treatment, as set forth in the then-pending claims. This argument is set forth repeatedly in the March 2013 Response. In other words, the claims presented in the March 2013 Response are a patentable species over the more broadly disclosed genus of the '907 patent. Applicant agrees with the Examiner that the '907 patent teaches, and likewise properly claims, that the NSAID

core may be naproxen, and the acid inhibitor coating may be esomeprazole. But again, the '907 patent does not teach or suggest the species of the pending claims. As such, no *prima facie* case of obviousness has been established by the Action. Nevertheless, as stated above, Applicant has amended the claims to progress the present case more rapidly to allowance, as discussed below.

B. The Amended Claims are Non-Obvious over the '907 Patent

Applicant has amended claims 1 and 25 to recite methods of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, based on surprising clinical data in this subset of patients. As set forth in the present application, while NSAIDs are a key therapy for pain and inflammation, there is a substantial risk of gastric ulcers associated with such treatment, particularly in subsets of patients with certain risk factors. While there are many risk factors associated NSAID patients developing gastric ulcers, one such risk factor is concomitant use of low-dose aspirin ("LDA"). As such, one of skill in the art understood that patients receiving NSAIDs and concomitant LDA are at an increased risk of upper gastrointestinal complications and ulcers. *See* Angiolillo, Discussion ("The evidence has come from populations studies and randomized trials where LDA consumption has been documented but not part of a formal randomization scheme [citations omitted].").

Angiolillo pooled data from 5 Phase III clinical studies of a fixed-dose combination of enteric-coated naproxen (500 mg) and immediate-release esomeprazole magnesium (20 mg) ("NAP/ESO") in patients (as compared to enteric-coated ("EC") naproxen (500 mg) alone), and stratified the data based on LDA use (≤325 mg daily, administered at any time during the study)

and LDA non-use. *Id.*[1] Angiolillo analyzed data from 2317 patients receiving treatment, of which 1157 received NAP/ESO. Of the patients that received NAP/ESO, 298 also received concomitant LDA.

Surprisingly, the studies analyzed in Angiolillo found "that NAP/ESO-treated patients were substantially less likely than those taking EC naproxen to develop [a gastric ulcer], *irrespective* of whether they were taking LDA or not." *See* Angiolillo, Discussion (emphasis in original). In addition, and even more surprising, there was also "a trend in the NAP/ESO group for those ***taking LDA*** to be less likely to have a [gastric ulcer] at each of months 1, 3, and 6 than those ***not taking [LDA]***." *Id.* (emphasis added). This finding is illustrated in Figure 2 of Angiolillo (shown below), which summarizes data of the incidence of gastric ulcers in LDA users versus LDA non-users from the pooled clinical trials.

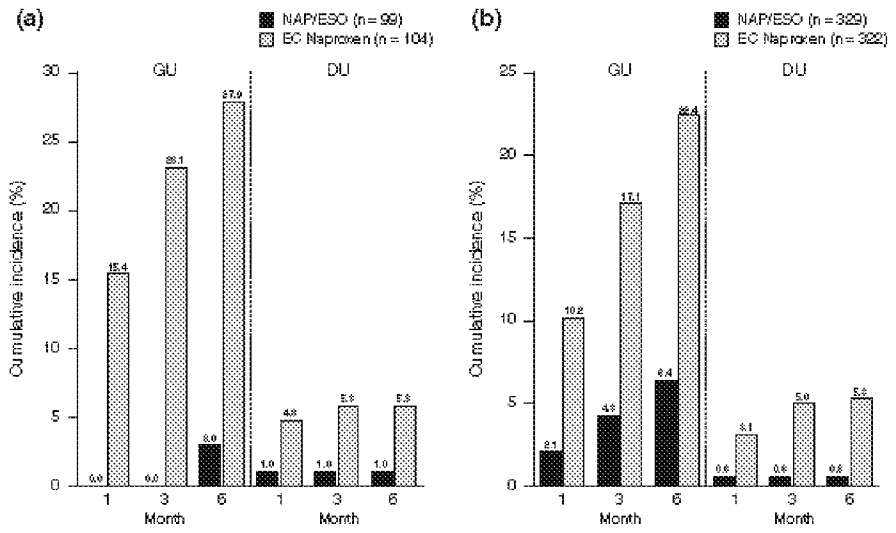


Fig. 2 Pooled cumulative observed incidence of gastric ulcers and duodenal ulcers at Month 0, 3, and 6 in **a** LDA users and **b** LDA non users (intent to treat population, pooled data from studies 301 and 302). *EC* enteric coated, *LDA* low dose aspirin, *NAP/ESO* naproxen/esomeprazole magnesium

These data are particularly surprising given that the incidence of gastric ulcers in LDA users taking NAP/ESO is ***lower*** than in LDA non-users taking NAP/ESO (0% versus 2.1% at 1 month, 0% versus 4.3% at 3 months, and 3.0% versus 6.4% at 6 months, respectively), while the

[1] For clarity, some of this data is also disclosed in the specification of the present application, but Angiolillo provides helpful analysis of the pooled data with respect to LDA use versus LDA non-use.

incidence of gastric ulcers in LDA users taking EC naproxen is higher than in LDA non-users taking EC naproxen (15.4% versus 10.2% at 1 month, 23.1% versus 17.1% at 3 months, and 27.9% versus 22.4% at 6 months, respectively).

Thus, in patients taking both LDA and EC naproxen, higher incidences of gastric ulcers occurred as expected (based on the observation that users of NSAIDs and concomitant LDA are at an increased risk of upper gastrointestinal complications and ulcers), as compared to patients taking EC naproxen but not LDA (at 6 months, 27.9% versus 22.4%, respectively). In contrast, in patients taking both LDA and NAP/ESO, a lower incidence of gastric ulcers occurred (despite the expectation that these patients would be at an increased risk for developing such ulcers based on the concomitant use of LDA) as compared to patients taking NAP/ESO but not LDA (at 6 months, 3% versus 6%, respectively). As noted in Angiolillo (*see* Discussion), statistical tests for the direct comparisons set forth in this paragraph were not performed because the patients in the pooled clinical studies were not randomized to take or not take LDA (statistical testing was confined to comparisons where patients were randomly allocated to treatments). Nevertheless, the data shows an unexpected and surprising trend in the subset of patients taking LDA and NAP/ESO.

Data showing an unexpected and surprising trend in the subset of patients taking LDA and NAP/ESO is also found in the specification of the pending application. For example, in patients taking both LDA and EC naproxen, higher incidences of gastric ulcers occurred as compared to patients taking EC naproxen but not LDA (at 6 months, 28.4% versus 22.2%, respectively). *See* paragraph **[0155]** and **Tables 3** and **5**. In contrast, in patients taking both LDA and NAP/ESO, a lower incidence of gastric ulcers occurred (again, despite the expectation that these patients would be at an increased risk for developing such ulcers based on the

concomitant use of LDA) as compared to patients taking NAP/ESO but not LDA (at 6 months, 3% versus 6.4%, respectively). *Id.* Thus, the data in the specification again shows this unexpected and surprising trend in the subset of patients taking LDA and NAP/ESO.

Based on this unexpected and surprising data, Applicant has amended claims 1 and 25 to recite methods of reducing the incidence of NSAID-associated gastric ulcers in patients taking LDA who are at risk of developing such ulcers. Nothing in the '907 patent, either alone or in view of Phillips, would suggest this unexpected and surprising result.

IV. Rejection for Obviousness-Type Double-Patenting

Claims 1-20, 22, 23, 25-31, 36-48 and 51-63 are provisionally rejected over claims 1-20 of copending application U.S. Serial No. 12/823,082 in view of the '907 patent. Although the rejection is provisional nature, Applicants traverse the rejection as follows.

As noted above, the claims as presented here now all recite methods of reducing the incidence of NSAID-associated gastric ulcers in patients taking low dose aspirin who are at risk of developing such ulcers, based on surprising clinical data in this subset of patients. The detailed discussion will not be repeated here, but is merely incorporated by reference. Thus, in light of similar considerations, it is believed that this rejection also is overcome. Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

V. Conclusion

In light of the foregoing, Applicant respectfully submits that all claims are in condition for allowance, and an early notification to the effect is earnestly solicited. The Examiner is invited to contact the undersigned representative with any questions or concerns regarding this submission or the application.

Respectfully submitted,

/Steven L. Highlander/

Steven L. Highlander
Reg. No. 37,642

Date: January 17, 2014

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Fax: 512-334-2999

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/SB/424 (12-11)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Brian AULT	Nonprovisional Application Number (if known):	12/822,612
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. ☐ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed oath or declaration under 37 CFR 1.63 is filed with the application.

II. ☑ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Steven L. Highlander/	Date January 17, 2014
Name (Print/Typed) Steven L. Highlander	Practitioner Registration Number 37,642

Note: *Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below*.*

☐ *Total of _____ forms are submitted.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/822,612	Filing Date 06/24/2010	☐ To be Mailed

ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	01/17/2014	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 31	Minus	** 68	= 0	X $80 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $420 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/LINDA HUMES/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/822,612	06/24/2010	Brian Ault	PZAZ.P0002US	6136

108197 7590 07/18/2013

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1120 South Capital of Texas Highway
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Austin, TX 78746

EXAMINER	
MILLIGAN, ADAM C	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
07/18/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@phiplaw.com

Office Action Summary	Application No. 12/822,612	Applicant(s) AULT ET AL.	
	Examiner ADAM C. MILLIGAN	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2013*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-20,22,23,25-31,36-48 and 51-63* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-20,22,23,25-31,36-48 and 51-63* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

Continuation of Attachment(s) 2). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :4pgs(3/14/2013),2pgs(3/21/2013),1pg(5/16/2013) .

DETAILED ACTION

Applicants' arguments, filed 3/14/2013, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-20, 22, 23, 25-31, 36-45, 48 and 51-63 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Plachetka (U.S. 6,926,907 – see patent cite #39 on 12 page IDS dated 8/28/2012).

Applicants argue that the specific duration of treatment and the particular patient subsets are missing from the '907 patent, so it would not have been obvious to choose the recited duration and patient populations

Examiner disagrees. Claim 1 does not require a specific patient population. The specific populations recited in the dependent claims (e.g. claims 3 and 4) would have been obvious given Plachetka teaches the use of the acid inhibitor coated NSAID on any patient who requires prolonged NSAID administration. Accordingly, it would have also been obvious to choose to administer the coated given that NSAIDs are taught to induce GI ulcers. Accordingly, it would have been obvious to administer the acid inhibitor coated

NSAID to patients regardless of the reasons the patient is taking the NSAID e.g. pain, inflammation, etc. Claim 1 also does not require a specific duration of treatment. Dependent claims (e.g. claims 10-12) recite durations of over at least about 1 month or longer. Given that the prior art method is demonstrated to lesson gastric ulcers over the course of a 1-week trial and is taught for use by chronic NSAID users, it would have been obvious to continue the twice per day (BID) regimen for periods of time well beyond a week and up to the lifetime of the patient.

Applicants argue that the specific dosages of naproxen (375-500mg) and esomeprazole (20mg) are not taught by Plachetka.

In the case where the claimed ranges overlap or lie inside ranges disclosed by the prior art, a prima facie case of obviousness exists. *see* MPEP 2144.05. Here, the prior art teaches that naproxen (NSAID) may administered at amounts of 250mg to 500mg and esomeprazole may be administered in amounts of 5mg to 100mg. Applicants present no evidence of unexpectedness regarding the narrower ranges recited. Thus, the rejection is maintained.

Applicants argue that Plachetka fails to teach or suggest the combination of naproxen with esomeprazole.

Examiner disagrees. Plachetka teaches the NSAID core is naproxen (Fig. 1) and the acid inhibitor coating may be esomeprazole (col.7, lines 1-18). Also,

the specific combination of naproxen and omeprazole is taught at Example 6 (cols 14-17). Note that omeprazole includes the S-enantiomer esomeprazole.

Applicants argue that to arrive at the present claims, one would be required to select on of 24 NSAIDs, one of 12 gastric acid inhibitors, select one dosage for the gastric acid inhibitor and two for the NSAID, select a duration of treatment, and a patient population from the teachings of Plachetka which would constitute excessive picking and choosing.

Examiner disagrees. Plachetka teaches naproxen as the desired NSAID in a dosage form containing a gastric acid inhibitor (Fig.1). The duration and patient population are discussed above. Thus, the only selection from a group required is that of a gastric acid inhibitor. In formulating the tablet of Plachetka's Figure 1, it would have been obvious to choose a gastric acid inhibitor from those taught in the reference, which include esomeprazole.

Claims 46 and 47 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Plachetka (U.S. 6,926,907 – see patent cite #39 on 12 page IDS dated 8/28/2012) in view of Phillips (U.S. 2004/0048896 – see publication cite #12 on 18 page IDS dated 8/28/2012).

Applicants argue that for the reasons provided above, the rejection should be withdrawn.

Examiner disagrees. For the reasons provided above with regard to Plachetka, the rejection is maintained.

Obvious-Type Nonstatutory Double Patenting

The text regarding the basis for nonstatutory double patenting not included in this action can be found in a prior Office Action.

Claims 1-20, 22, 23, 25-31, 36-48 and 51-63 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/823082 in view of Plachetka (U.S. 6,926,907 – see IDS dated 8/28/2012).

Applicants request that the rejection be held in abeyance until such time that allowable subject matter is indicated.

Accordingly, the rejection is maintained.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory

action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ADAM MILLIGAN whose telephone number is (571)270-7674. The examiner can normally be reached on M-F 9:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ADAM C MILLIGAN/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12822612	AULT ET AL.
	Examiner	Art Unit
	ADAM C MILLIGAN	1612

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
PALM Inventor Search	9/9/2012	AM
EAST Search - see attached search history	9/9/2012	AM
STN Search - caplus - esomeprazole, naproxen, NSAID induced GI ulcer, enteric coating	9/9/2012	AM
Updated EAST and STN searches		

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

Form PTO-1449 (modified)	Atty. Docket No.: PZAZ.P0002US	Serial No.: 12/822,612
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	Applicant: Brian AULT *et al.*	
	Filing Date: June 24, 2010	Group: 1612

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1*	*See Page 1-2*

Exam. Init.	Ref. Des.	Document Number	Date	Name
	A22	2009-0075950	03/19/2009	Taneja

Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Country	Language
	B13	AU 2006235929	11/30/06	Australia	English
	B14	JP 2005-145894	06/09/05	Japan	Japanese (English abstract)

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C33	Office Communication issued in Egyptian Patent Application No. 2121/2011, dated April 13, 2013. (English summary of Arabic text) (Attorney Docket No. PZAZ.P0002EG)

{00054587}

EXAMINER:	/Adam Milligan/	DATE CONSIDERED:	07/10/2013

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

Form PTO-1449 (modified)	Atty. Docket No.: PZAZ.P0002US	Serial No.: 12/822,612
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	Applicant: Brian AULT *et al.*	
	Filing Date: June 24, 2010	Group: 1612

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page2*	*See Pages 2-4*

U.S. Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name	Class	Sub Class	Filing Date of App.
	A1	2001-0036473	11/01/01	Scott *et al.*	424	463	04/17/01
	A2	2001-0044410	11/22/01	Gelber *et al.*	514	27	01/05/01
	A3	2002-0111370	08/15/02	Bergman *et al.*	514	338	12/20/01
	A4	2002-0155153	12/24/02	Depui *et al.*	424	452	03/04/02
	A5	2002-0160046	10/31/02	Robinson *et al.*	424	469	11/21/01
	A6	2003-0040537	02/27/03	Plachetka *et al.*	514	406	09/26/02
	A7	2003-0129235	07/10/03	Chen *et al.*	424	470	10/28/02
	A8	2003-0232876	12/18/03	Plachetka	514	419	04/16/03
	A9	2004-0022846	02/05/04	Depui *et al.*	424	452	07/17/03
	A10	2004-0180089	09/16/04	Plachetka *et al.*	424	4	12/22/03
	A11	2005-0249811	11/10/05	Plachetka	424	472	05/16/05
	A12	2006-0177504	08/10/06	Sudharadas	424	488	02/08/06
	A13	2007-0207200	09/06/07	Plachetka *et al.*	424	451	03/02/07
	A14	2009-0297594	12/03/09	Depui *et al.*	424	451	02/09/09
	A15	5,690,960	11/25/97	Bengtsson *et al.*	424	480	09/27/94
	A16	5,872,145	02/16/99	Plachetka	514	415	08/14/97
	A17	6,060,499	05/09/00	Plachetka	514	415	09/11/98
	A18	6,126,816	10/03/00	Ruiz Jr.	210	95	07/14/99
	A19	7,030,162	04/18/06	Plachetka *et al.*	514	619	09/26/02
	A20	7,060,694	06/13/06	Plachetka *et al.*	514	177	10/29/02
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	Filing Date: June 24, 2010	Group: 1612

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page2*	*See Pages 2-4*

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	B1	EP 0 005 129 A1	10/31/79	Europe	English
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	B12	WO 2002/98352	12/12/02	WIPO	English

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Exam. Init.	Ref. Des.	Citation
	C1	"Astrazeneca AB, Astrazeneca LP, KBI-E Inc., and Pozen, Inc. v Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd.: Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd's. Invalidity contentions pursuant to L. Pat. R. 3.6(c)," dated November 23, 2011.
	C2	"Astrazeneca AB, Astrazeneca LP, KBI-E Inc., and Pozen, Inc. V Lupin Ltd. And Lupin Pharmaceuticals, Inc.: Defendants Lupin Ltd. And Lupin Pharmaceuticals, Inc's Amended Invalidity Contentions Pursuant to L. PAT. R. 3.3 and 3.6(c)," dated April 20, 2012.
	C3	"Astrazeneca AB, Astrazeneca LP, KBI-E Inc., and Pozen, Inc. v Lupin Ltd. And Lupin Pharmaceuticals Inc.: Defendants Lupin Ltd. And Lupin Pharmaceuticals, Inc.'s Invalidity Contentions Pursuant to L. Pat. R. 3.3 and 3.6(c)," dated November 23, 2011.
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Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C5	"Astrazeneca AB, Astrazeneca LP, KBI-E Inc., and Pozen, Inc. v. Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratoriese Ltd.: Plaintiffs' Response to DRL's First Set of Interrogatories to Plaintiffs (Nos. 1-5)," dated March 5, 2012.
	C6	"Notice of Paragraph IV Certification Re: Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Naproxen and Esomeprazole Magnesium Delayed Release Tablets; U.S. Patent No. 6,926,907, from Dr. Reddy's Laboratories, Ltd./Dr. Reddy's Laboratories, Inc., dated March 11, 2011.
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	C8	Jacques *et al.*, "Final purification, enrichment, of partially resolved enantiomer mixtures," In: *Enantiomers, Racemates, and Resolutions*, 423-434, 1981.
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	C15	Office Communication issued in European Patent Application No. 0273602.2, dated June 21, 2010.
	C16	PCT International Preliminary Report on Patentability issued in International Application No. PCT/US2009/003281 dated December 9, 2010.
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	C19	Ramage *et al.*, "Inhibition of food stimulated acid secretion by misoprostol, an orally active synthetic E1 analogue prostaglandin," *Br. J. Clin Pharmac.*, 19:9-12, 1985.
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	C23	Wilson *et al.*, "Effects of misoprostol on gastric acid and mucus secretion in man," *Digestive Diseases and Sciences*, 31(2): 126S-129S, 1986.

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Foreign Patent Documents

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	C26	Fass, "Erosive Esophagitis and Nonerosive Reflux Disease (NERD): Comparison of Epidemiologic, Physiologic, and Therapeutic Characteristics," *J. Clin. Gastroenterol.*, 41(2):131-137, 2007.
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	C32	Yeomans *et al.*, "Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin," *American Journal of Gastroenterology*, 103:1-9, 2008.

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Exam. Init.	Ref. Des.	Document Number	Date	Name
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Exam. Init.	Ref. Des.	Document Number	Date	Country	Language
	B13	AU 2006235929	11/30/06	Australia	English
	B14	JP 2005-145894	06/09/05	Japan	Japanese (English abstract)

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C33	Office Communication issued in Egyptian Patent Application No. 2121/2011, dated April 13, 2013. (English summary of Arabic text) (Attorney Docket No. PZAZ.P0002EG)

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(12) STANDARD PATENT APPLICATION (11) Application No. **AU 2006235929 A1**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Pharmaceutical compositions for the coordinated delivery of NSAIDs

(51) International Patent Classification(s)
A61K 9/22 (2006.01)

(21) Application No: **2006235929** (22) Date of Filing: **2006.11.09**

(43) Publication Date: **2006.11.30**
(43) Publication Journal Date: **2006.11.30**

(62) Divisional of:
2002305758

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(74) Agent / Attorney
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Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs

Abstract

The present invention is directed to drug dosage forms that release an agent that raises the pH of a patient's gastrointestinal tract, followed by a non-steroidal anti-inflammatory drug. The dosage form is designed so that the NSAID is not released until the intragastric pH has been raised to a safe level. The invention also encompasses methods of trating patients by administering this coordinated release, gastroprotective, antiarthitic/analgesic combination unit dosage form to achieve pain and symptom relief with a reduced risk of developing gastrointestinal damage such as ulcers, erosions and hemorrhages.

S&F Ref: 658414D1

AUSTRALIA

PATENTS ACT 1990

COMPLETE SPECIFICATION

FOR A STANDARD PATENT

Name and Address of Applicant :	Pozen Inc., of Suite 400, 1414 Raleigh Road, Chapel Hill, North Carolina, 27517, United States of America
Actual Inventor(s):	John R. Plachetka
Address for Service:	Spruson & Ferguson St Martins Tower Level 35 31 Market Street Sydney NSW 2000 (CCN 3710000177)
Invention Title:	Pharmaceutical compositions for the coordinated delivery of NSAIDs

The following statement is a full description of this invention, including the best method of performing it known to me/us:-

Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs

Field of the Invention

The present invention is directed to pharmaceutical compositions that provide for the coordinated release of an acid inhibitor and a non-steroidal anti-inflammatory drug (NSAID). These compositions have a reduced likelihood of causing unwanted side effects, especially gastrointestinal side effects, when administered as a treatment for pain, arthritis and other conditions amenable to treatment with NSAIDs.

Background of the Invention

Although non-steroidal anti-inflammatory drugs are widely accepted as effective agents for controlling pain, their administration can lead to the development of gastroduodenal lesions, *e.g.*, ulcers and erosions, in susceptible individuals. It appears that a major factor contributing to the development of these lesions is the presence of acid in the stomach and upper small intestine of patients. This view is supported by clinical studies demonstrating an improvement in NSAID tolerability when patients are also taking independent doses of acid inhibitors (*Dig. Dis. 12*:210-222 (1994); *Drug Safety 21*:503-512 (1999); *Aliment. Pharmacol. Ther. 12*:135-140 (1998); *Am. J. Med. 104(3A)*:67S-74S (1998); *Clin. Ther. 17*:1159-1173 (1995)). Other major factors contributing to NSAID-associated gastropathy include a local toxic effect of NSAIDs and inhibition of protective prostaglandins (*Can. J. Gastroenterol. 13*: 135-142 (1999) and *Pract. Drug Safety 21*:503-512, (1999)), which may also make some patients more susceptible to the ulcerogenic effects of other noxious stimuli.

In general, more potent and longer lasting acid inhibitors, such as proton pump inhibitors, are thought to be more protective during chronic administration of NSAIDs than shorter acting agents, *e.g.*, histamine H_2 receptor antagonists (H-2 blockers) (*N. Eng. J. Med. 338*:719-726 (1998); *Am. J. Med. 104(3A)*:56S-61S (1998)). The most likely explanation for this is that gastric pH fluctuates widely throughout the dosing interval with short acting acid inhibitors leaving the mucosa vulnerable for significant periods of time. In particular, the pH is at its lowest point, and hence the mucosa is most vulnerable, at the end of the dosing interval (least amount of acid inhibition) and for some time after the subsequent dose of acid

inhibitor. In general, it appears that when a short acting acid inhibitor and an NSAID are administered simultaneously, NSAID-related mucosal damage occurs before the pH of the gastrointestinal tract can be raised and after the acid inhibiting effect of the short acting acid inhibitor dissipates.

Although longer lasting agents, such as proton pump inhibitors (PPIs), usually maintain a consistently higher gastroduodenal pH throughout the day, after several days dosing, their antisecretory effect may be delayed for several hours and may not take full effect for several days (*Clin. Pharmacokinet. 20*:38-49 (1991)). Their effect may be diminished toward the end of the usual dosing interval. Intragastric pH rises particularly slowly with the first dose in a course of treatment since this class of drugs is enteric coated to avoid destruction by stomach acid. As a result, absorption is delayed for several hours. Even then, some patients fail to respond consistently to drugs of this type and suffer from "acid breakthrough" which again leaves them vulnerable to NSAID-associated gastroduodenaldamage (*Aliment. Pharmacol. Ther. 14*:709-714 (2000)). Despite a significant reduction in gastroduodenal lesions with the concomitant administration of a proton pump inhibitor during six months of NSAID therapy, up to 16% of patients still develop ulcers, indicating that there remains substantial room for improvement (*N. Eng. J. Med. 338*:727-734 (1998)). Thus, the addition of a pH sensitive enteric coating to an NSAID could provide additional protection against gastroduodenal damage not provided by the H2 blocker or PPI alone. In addition, although long acting acid inhibitors may reduce the risk of GI lesions in chronic NSAID users, there are questions about the safety of maintaining an abnormally elevated pH in a patient's GI tract for a prolonged period of time (*Scand. J. Gastroenterol. Suppl. 178*:85-92 (1990)).

Recognizing the potential benefits of PPIs for the prevention of NSAID-induced gastroduodenal damage, others have disclosed strategies for combining the two active agents for therapeutic purposes. However, these suggestions do not provide for coordinated drug release or for reducing intragastric acid levels to a non-toxic level prior to the release of NSAID (U.S. 5,204,118; U.S. 5,417,980; U.S. 5,466,436; and U.S. 5,037,815). In certain cases, suggested means of delivery would expose the gastrointestinal tract to NSAIDs prior to onset of PPI activity (U.S. 6,365,184).

Attempts to develop NSAIDs that are inherently less toxic to the gastrointestinal tract have met with only limited success. For example, the recently developed cyclooxygenase-2 (COX-2) inhibitors show a reduced tendency to produce gastrointestinal ulcers and erosions, but a significant risk is still present, especially if the patient is exposed to other ulcerogens (*JAMA 284*:1247-1255 (2000); *N. Eng. J. Med. 343*:1520-1528 (2000)). In this regard, it appears that even low doses of aspirin will negate most of the benefit relating to lower gastrointestinal lesions. In addition, the COX-2 inhibitors may not be as effective as other NSAIDs at relieving some types of pain and have been associated with significant cardiovascular problems (*JADA 131*:1729-1737 (2000); *SCRIP 2617*, pg. 19, Feb. 14, 2001); NY Times, May 22, 2001, pg. C1)).

Other attempts to produce an NSAID therapy with less gastrointestinal toxicity have involved the concomitant administration of a cytoprotective agent. In 1998, Searle began marketing Arthrotec™ for the treatment of arthritis in patients at risk for developing GI ulcers. This product contains misopristol (a cytoprotective prostaglandin) and the NSAID diclofenac. Although patients administered Arthrotec™ do have a lower risk of developing ulcers, they may experience a number of other serious side effects such as diarrhea, severe cramping and, in the case of pregnant women, potential damage to the fetus.

Another approach has been to produce enteric coated NSAID products. However, even though these have shown modest reductions in gastroduodenal damage in short term studies (*Scand. J. Gastroenterol. 20*: 239–242 (1985) and *Scand. J. Gastroenterol. 25*:231–234 (1990)), there is no consistent evidence of a long term benefit during chronic treatment.

Overall, it may be concluded that the risk of inducing GI ulcers is a recognized problem associated with the administration of NSAIDs and that, despite considerable effort, an ideal solution has not yet been found.

Summary of the Invention

The present invention is based upon the discovery of a new method for reducing the risk of gastrointestinal side effects in people taking NSAIDs for pain relief and for other conditions, particularly during chronic treatment. The method involves the administration of a single, coordinated, unit-dose product that combines: a) an agent that actively raises

intragastric pH to levels associated with less risk of NSAID-induced ulcers; and b) an NSAID that is specially formulated to be released in a coordinated way that minimizes the adverse effects of the NSAID on the gastroduodenal mucosa. Either short or long acting acid inhibitors can be effectively used in the dosage forms. This method has the added benefit of being able to protect patients from other gastrointestinal ulcerogens whose effect may otherwise be enhanced by the disruption of gastroprotective prostaglandins due to NSAID therapy.

In its first aspect, the invention is directed to a pharmaceutical composition in unit dosage form suitable for oral administration to a patient. The composition contains an acid inhibitor present in an amount effective to raise the gastric pH of a patient to at least 3.5, preferably to at least 4, and more preferably to at least 5, when one or more unit dosage forms are administered. The gastric pH should not exceed 7.5 and preferably should not exceed 7.0. The term "acid inhibitor" refers to agents that inhibit gastric acid secretion and increase gastric pH. In contrast to art teaching against the use of H2 blockers for the prevention of NSAID-associated ulcers (*N. Eng. J. Med. 340*: 1888–1899 (1999)), these agents are preferred compounds in the current invention. Specific, H2 blockers that may be used include cimetidine, ranitidine, ebrotidine, pabutidine, lafutidine, loxtidine or famotidine. The most preferred acid inhibitor is famotidine present in dosage forms in an amount of between 5 mg and 100 mg. Other agents that may be effectively used include proton pump inhibitors such as omeprazole, esomeprazole, pantoprazole, lansoprazole or rabeprazole.

The pharmaceutical composition also contains a non-steroidal anti-inflammatory drug in an amount effective to reduce or eliminate pain or inflammation. The NSAID may be a COX-2 inhibitor such as celecoxib, rofecoxib, meloxicam, piroxicam, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337 or NS398. Alternatively, the NSAID may be aspirin, acetaminophen, ibuprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin, etodolac, indomethacin, ketorolac, lornoxicam, nabumetone, or diclofenac. The most preferred NSAID is naproxen in an amount of between 50 mg and 1500 mg, and more preferably, in an amount of between 200 mg and 600 mg. It will be understood that, for the purposes of the present invention, reference to an acid inhibitor, NSAID, or analgesic agent will include all of the common forms of these compounds and, in particular, their pharmaceutically acceptable salts. The amounts of NSAIDs which are therapeutically effective may be lower in the current

invention than otherwise found in practice due to potential positive kinetic interaction and NSAID absorption in the presence of an acid inhibitor.

The term "unit dosage form" as used herein refers to a single entity for drug administration. For example, a single tablet or capsule combining both an acid inhibitor and an NSAID would be a unit dosage form. A unit dosage form of the present invention preferably provides for coordinated drug release, in a way that elevates gastric pH and reduces the deleterious effects of the NSAID on the gastroduodenal mucosa, *i.e.*, the acid inhibitor is released first and the release of NSAID is delayed until after the pH in the GI tract has risen. In a preferred embodiment, the unit dosage form is a multilayer tablet, having an outer layer comprising the acid inhibitor and an inner core which comprises the NSAID. In the most preferred form, coordinated delivery is accomplished by having the inner core surrounded by a polymeric barrier coating that does not dissolve unless the surrounding medium is at a pH of at least 3.5, preferably at least 4 and more preferably, at least 5. Alternatively, a barrier coating may be employed which controls the release of NSAID by time, as opposed to pH, with the rate adjusted so that NSAID is not released until after the pH of the gastrointestinal tract has risen to at least 3.5, preferably at least 4, and more preferably at least 5. Thus, a time-release formulation may be used to prevent the gastric presence of NSAID until mucosal tissue is no longer exposed to the damage enhancing effect of very low pH.

The invention includes methods of treating a patient for pain, inflammation and/or other conditions by administering the pharmaceutical compositions described above. Although the method may be used for any condition in which an NSAID is effective, it is expected that it will be particularly useful in patients with osteoarthritis or rheumatoid arthritis. Other conditions that may be treated include, but are not limited to: all form of headache, including migraine headache; acute musculoskeletal pain; ankylosing spondylitis; dysmenorrhoea; myalgias; and neuralgias.

In a more general sense, the invention includes methods of treating pain, inflammation and/or other conditions by orally administering an acid inhibitor at a dose effective to raise a patient's gastric pH to at least 3.5, preferably to at least 4 or and more preferably to at least 5. The patient is also administered an NSAID, for example in a

coordinated dosage form, that has been coated in a polymer that only dissolves at a pH of least 3.5, preferably at least 4 and, more preferably, 5 or greater or which dissolves at a rate that is slow enough to prevent NSAID release until after the pH has been raised. When acid inhibitor and NSAID are administered in separate doses, *e.g.*, in two separate tablets, they should be given concomitantly (*i.e.*, so that their biological effects overlap) and may be given concurrently, *i.e.*, NSAID is given within one hour after the acid inhibitor. Preferably, the acid inhibitor is an H2 blocker and, in the most preferred embodiment, it is famotidine at a dosage of between 5 mg and 100 mg. Any of the NSAIDs described above may be used in the method but naproxen at a dosage of between 200 and 600 mg is most preferred. It is expected that the inhibitor and analgesic will be typically delivered as part of a single unit dosage form which provides for the coordinated release of therapeutic agents. The most preferred dosage form is a multilayer tablet having an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

The invention also provides a method for increasing compliance in a patient requiring frequent daily dosing of NSAIDs by providing both an acid inhibitor and NSAID in a single convenient, preferably coordinated, unit dosage form, thereby reducing the number of individual doses to be administered during any given period.

Brief Description of the Drawings

Figure 1 is a schematic diagram of a four layer tablet dosage form. There is a naproxen core layer surrounded by a barrier layer. A third, enteric coating, layer delays the release of naproxen sodium until the pH is at a specific level, *e.g.*, above 4. Finally, there is an outer layer that releases an acid inhibitor such as famotidine.

Figure 2 illustrates a three layer dosage form. An acid inhibitor, *e.g.*, famotidine, is released immediately after ingestion by a patient in order to raise the pH of the gastrointestinal tract to above a specific pH, *e.g.*, above 4. The innermost layer contains naproxen. Thus, the dosage form has a naproxen core, an enteric film coat and an acid inhibitor film coat.

Figure 3 illustrates a naproxen sodium pellet which contains a subcoat or barrier coat prior to the enteric film coat.

Detailed Description of the Invention

The present invention is based upon the discovery of improved pharmaceutical compositions for administering NSAIDs to patients. In addition to containing one or more NSAIDs, the compositions include acid inhibitors that are capable of raising the pH of the GI tract of patients. All of the dosage forms are designed for oral delivery and provide for the coordinated release of therapeutic agents, *i.e.*, for the sequential release of acid inhibitor followed by analgesic.

The NSAIDs used in preparations may be either short or long acting. As used herein, the term "long acting" refers to an NSAID having a pharmacokinetic half-life of at least 2 hours, preferably at least 4 hours and more preferably, at least 8-14 hours. In general, its duration of action will equal or exceed about 6-8 hours. Examples of long-acting NSAIDs are: flurbiprofen with a half-life of about 6 hours; ketoprofen with a half-life of about 2 to 4 hours; naproxen or naproxen sodium with half-lives of about 12 to 15 hours and about 12 to 13 hours respectively; oxaprozin with a half life of about 42 to 50 hours; etodolac with a half-life of about 7 hours; indomethacin with a half life of about 4 to 6 hours; ketorolac with a half-life of up to about 8-9 hours, nabumetone with a half-life of about 22 to 30 hours; mefenamic acid with a half-life of up to about 4 hours; and piroxicam with a half-life of about 4 to 6 hours. If an NSAID does not naturally have a half-life sufficient to be long acting, it can, if desired, be made long acting by the way in which it is formulated. For example, NSAIDs such as acetaminophen and aspirin may be formulated in a manner to increase their half-life or duration of action. Methods for making appropriate formulations are well known in the art (see *e.g.* Remington's Pharmaceutical Sciences, 16th ed., A. Oslo editor, Easton, PA (1980)).

It is expected that a skilled pharmacologist may adjust the amount of drug in a pharmaceutical composition or administered to a patient based upon standard techniques well known in the art. Nevertheless, the following general guidelines are provided:

Indomethacin is particularly useful when contained in tablets or capsules in an amount from about 25 to 75 mg. A typical daily oral dosage of indomethacin is three 25 mg doses taken at intervals during the day. However, daily dosages of up to about 150 mg are useful in some patients.

Aspirin will typically be present in tablets or capsules in an amount of between about 250 mg and 1000 mg. Typical daily dosages will be in an amount ranging from 500 mg to about 10 g.

Ibuprofen may be provided in tablets or capsules of 50, 100, 200, 300, 400, 600, or 800 mg. Daily doses should not exceed 3200 mg. 200 mg - 800 mg may be particularly useful when given 3 or 4 times daily.

Flurbiprofen is useful when in tablets at about from 50 to 100 mg. Daily doses of about 100 to 500 mg, and particularly from about 200 to 300 mg, are usually effective.

Ketoprofen is useful when contained in tablets or capsules in an amount of about 25 to 75 mg. Daily doses of from 100 to 500 mg and particularly of about 100 to 300 mg are typical as is about 25 to 50 mg every six to eight hours.

Naproxen is particularly useful when contained in tablets or capsules in an amount of from 250 to 500 mg. For naproxen sodium, tablets of about 275 or about 550 mg are typically used. Initial doses of from 100 to 1250 mg, and particularly 350 to 800 mg are also used, with doses of about 550 mg being generally preferred.

Oxaprozin may be used in tablets or capsules in the range of roughly 200 mg to 1200 mg, with about 600 mg being preferred. Daily doses of 1200 mg have been found to be particularly useful and daily doses should not exceed 1800 mg or 26 mg/kg.

Etodolac is useful when provided in capsules of 200 mg to 300 mg or in tablets of about 400 mg. Useful doses for acute pain are 200-400 mg every six-eight hours, not to exceed 1200 mg/day. Patients weighing less than 60 kg are advised not to exceed doses of 20 mg/kg. Doses for other uses are also limited to 1200 mg/day in divided doses, particularly 2, 3 or 4 times daily.

Ketorolac is usefully provided in tablets of 1-50 mg, with about 10 mg being typical. Oral doses of up to 40 mg, and particularly 10-30 mg/day have been useful in the alleviation of pain.

Nabumetone may be provided in tablets or capsules of between 500 mg and 750 mg. Daily doses of 1500-2000 mg, after an initial dose of 100 mg, are of particular use.

Mefenamic acid is particularly useful when contained in tablets or capsules of 50 mg to 500 mg, with 250 mg being typical. For acute pain, an initial dosage of 1-1000 mg, and particularly about 500 mg, is useful, although other doses may be required for certain patients.

Lornoxicam is provided in tablets of 4 mg or 8 mg. Useful doses for acute pain are 8 mg or 16 mg daily, and for arthritis are 12 mg daily.

One particular group of long acting NSAIDs that may be used are the cyclooxygenase-2 inhibitors. These include: celecoxib, rofecoxib, meloxicam, piroxicam, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337, or NS398. JTE-522, L-745,337 and NS398 as described, *inter alia*, in Wakatani, *et al.* (*Jpn. J. Pharmacol. 78*:365-371 (1998)) and Panara, *et al.* (*Br. J. Pharmacol. 116*:2429-2434 (1995)). The amount present in a tablet or administered to a patient will depend upon the particular COX-2 inhibitor being used. For example:

Celecoxib may be administered in a tablet or capsule containing from about 100 mg to about 500 mg or, preferably, from about 100 mg to about 200 mg.

Piroxicam may be used in tablets or capsules containing from about 10 to 20 mg.

Rofecoxib will typically be provided in tablets or capsules in an amount of 12.5, 25 or 50 mg. The recommended initial daily dosage for the management of acute pain is 50 mg.

Meloxicam is provided in tablets of 7.5 mg, with a recommended daily dose of 7.5 or 15 mg for the management of osteoarthritis.

Valdecoxib is provided in tablets of 10 or 20 mg, with a recommended daily dose of 10 mg for arthritis or 40 mg for dysmenorrhea.

With respect to acid inhibitors, tablets or capsules may contain anywhere from 1 mg to as much as 1g. Typical amounts for H2 blockers are: cimetidine, 100 to 800 mg/unit dose; ranitidine, 50-300 mg/unit dose; famotidine, 5-100 mg/unit dose; ebrotidine 400 – 800 mg/unit dose; pabutidine 40 mg/unit dose; lafutidine 5–20 mg/unit dose; and nizatidine, 50-600 mg/unit dose. Proton pump inhibitors will typically be present at about 5 mg to 600 mg per unit dose. For example, the proton pump inhibitor omeprazole should be present in tablets or capsules in an amount from 5 to 50 mg, with about 20 mg per unit dosage form being preferred. Other typical amounts are: esomeprazole, 5–100 mg, with about 40 mg per unit dosage form being preferred; lansoprazole, 15-150 mg, with about 30 mg per unit dosage form being preferred; pantoprazole, 10-200 mg, with about 40 mg per unit dosage form being preferred; and rabeprazole, 5-100 mg, with about 20 mg per unit dosage form being preferred.

Making of Pharmaceutical Preparations

The pharmaceutical compositions of the invention include tablets, dragees, liquids and capsules and can be made in accordance with methods that are standard in the art (see, *e.g.*, Remington's Pharmaceutical Sciences, 16th ed., A Oslo editor, Easton, Pa. (1980)). Drugs and drug combinations will typically be prepared in admixture with conventional excipients. Suitable carriers include, but are not limited to: water; salt solutions; alcohols; gum arabic; vegetable oils; benzyl alcohols; polyethylene glycols; gelatin; carbohydrates such as lactose, amylose or starch; magnesium stearate; talc; silicic acid; paraffin; perfume oil; fatty acid esters; hydroxymethylcellulose; polyvinyl pyrrolidone; etc. The pharmaceutical preparations can be sterilized and, if desired, mixed with auxiliary agents such as: lubricants, preservatives, disintegrants; stabilizers; wetting agents; emulsifiers; salts; buffers; coloring agents; flavoring agents; or aromatic substances.

Enteric coating layer(s) may be applied onto the core or onto the barrier layer of the core using standard coating techniques. The enteric coating materials may be dissolved or dispersed in organic or aqueous solvents and may include one or more of the following materials: methacrylic acid copolymers, shellac, hydroxypropylmethcellulose phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose trimellitate, carboxymethylethyl-cellulose, cellulose acetate phthalate or other suitable enteric coating polymer(s). The pH at which the enteric coat will dissolve can be controlled by the polymer or combination of polymers selected and/or ratio of pendant groups. For example, dissolution characteristics of the polymer film can be altered by the ratio of free carboxyl groups to ester groups. Enteric coating layers also contain pharmaceutically acceptable plasticizers such as triethyl citrate, dibutyl phthalate, triacetin, polyethylene glycols, polysorbates or other plasticizers. Additives such as dispersants, colorants, anti-adhering and anti-foaming agents may also be included.

The Making of Tablet Dosage Forms

Preferably, the combination of an acid inhibitor and an NSAID will be in the form of a bi- or multi-layer tablet. In a bilayer configuration, one portion of the tablet contains the acid inhibitor in the required dose along with appropriate excipients, agents to aid dissolution, lubricants, fillers, etc. The second portion of the tablet will contain the NSAID, preferably naproxen, in the required dose along with other excipients, dissolution agents, lubricants, fillers, etc. In the most preferred embodiment, the NSAID layer is surrounded by a polymeric coating which does not dissolve at a pH of less than 4. The naproxen may be granulated by methods such as slugging, low- or high- shear granulation, wet granulation, or fluidized-bed granulation. Of these processes, slugging generally produces tablets of less hardness and greater friability. Low-shear granulation, high-shear granulation, wet granulation and fluidized-bed granulation generally produce harder, less friable tablets.

Examples

Example 1: Enteric Coated Naproxen Sodium Core and Famotidine Immediate Release

A schematic diagram of a four layer tablet dosage form is shown in Figure 1. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, PA). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above about 4 or 5. The enteric coating does not dissolve in areas of the GI tract where the pH may be below about 4 or 5 such as in an unprotected stomach. Methacrylic acid copolymers are used as the enteric coating ingredient, triethyl citrate and dibutyl phthalate are plasticisers, and ammonium hydroxide is used to adjust the pH of the dispersion. The coating dissolves only when the local pH is above, for example, 5.5 and, as a result, naproxen sodium is released.

The outermost layer contains an "acid inhibitor" in an effective amount which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably the H2 blocker famotidine, which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of famotidine in the dosage form will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Clear® YS-1-7006 which helps in the formation of the film and in uniformly distributing famotidine within the fourth layer without tablets sticking to the coating pan or to each other during application of the film coat. Other ingredients may include: plasticisers such as triethyl citrate, dibutyl phthalate, and polyethylene glycol; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	% W/W	mg/Tablet
Naproxen sodium, USP	74.074	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.166	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Barrier Film Coating Ingredients	% W/W
Opadry Clear® YS-1-7006	5.00
Purified water USP	95.00
Total	100.00

Enteric Coating Dispersion Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L-100-55)	7.30
Methacrylic Acid Copolymer, NF (Eudragit L-100)	7.30
Triethyl Citrate, NF	2.95
Dibutyl Phthalate, NF	1.17
Ammonium Hydroxide (30%), NF	0.87
Purified water, USP	80.41
Total	100.00

Famotidine Coating Dispersion Ingredients	% W/W
Famotidine, USP	3.0
Opadry Clear® (YS-1-7006)	5.0
Talc, USP	3.0

Purified Water, USP	89.0
Total	100.0

Example 2: Enteric Coated Naproxen Core and Famotidine Immediate Release

Figure 2 illustrates a three layered dosage form which releases famotidine immediately after ingestion by the patient in order to raise the pH of the gastrointestinal tract to above about 4. The innermost layer contains naproxen uniformly distributed throughout a matrix of pharmaceutically acceptable excipients. These excipients perform specific functions and may serve as binders, disintegrants, or lubricants. A pharmaceutically acceptable enteric coating surrounds the naproxen core. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the harshly acidic pH of the unprotected stomach. It contains methacrylic acid copolymers which prevent the release of naproxen in the unprotected stomach. Also included are: triethyl citrate, a plasticiser; simethicone emulsion, an anti-foaming agent; and sodium hydroxide which is used to adjust the pH of the dispersion.

The outermost layer contains an "acid inhibitor" in an effective amount which is released from the dosage form immediately after administration to the patient. The acid inhibitor in this example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which raises the pH of the stomach to above 4. A typical film coating formulation contains Opadry Clear® YS-1-7006 which helps in the formation of the film and in uniformly distributing famotidine in the fourth layer without tablets sticking to the coating pan or sticking to each other during application of the film coat. Other ingredients are: plasticisers such as polyethylene glycol 8000; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate;, and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	**% W/W**	**mg /Tablet**
Naproxen, USP	90.91	500.00
Povidone K-90, USP	2.00	11.00
Starch, USP	2.59	14.25

Croscarmellose Sodium, USP	4.00	22.00
Magnesium Stearate, NF	0.50	2.75
Total	100.00	550.00
Purified Water, USP qs		

Enteric Coating Dispersion Ingredients	**% W/W**
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5
Talc, USP	3.8
Sodium Hydroxide, NF	0.2
Triethyl Citrate, NF	1.7
Simethicone Emulsion, USP	0.02
Purified Water, USP	79.78
Total	100.00

Famotidine Coating Dispersion Ingredients	**% W/W**
Famotidine, USP	3.0
Opadry Clear® (YS-1-7006)	5.0
Talc, USP	3.0
Purified Water, USP	89.0
Total	100.0

Example 3: Naproxen Controlled Release Core and Famotidine Immediate Release

A trilayer tablet which separates famotidine contained in the film coat from controlled-release naproxen may be used in the present invention. The core tablet of naproxen is formulated using excipients which control the drug release for therapeutic relief from pain and inflammation for 24 hours. Figure 2 shows an example of an appropriate trilayer tablet. In this particular example, naproxen is mixed with a polymeric material, hydroxypropyl-methylcellulose and granulated with water. The granules are dried, milled, and blended with a lubricant, such as magnesium stearate. They are then compacted into tablets.

The controlled-release core tablet of naproxen is film coated with a pharmaceutically acceptable enteric coating. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the extremely acidic pH of the unprotected stomach. The function of methacrylic acid copolymers is to prevent the release of naproxen until the pH of the stomach rises. Triethyl citrate is a plasticiser, simethicone emulsion is a anti-foaming agent, and sodium hydroxide is used to adjust the pH of the dispersion.

The outermost layer contains an "acid inhibitor" which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which consistently raises the pH of the stomach to above 4. The typical effective amount of famotidine in the dosage will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Blue® YS-1-4215 which is essential for film formation and for the uniform application of famotidine to the core tablet. Polymer film coating ingredients, hydroxypropylmethylcellulose or Opaspray® K-1-4210A (Colorcon, West Point, PA) may also be used. Other ingredients which help in the formation of the film and in the uniform application of famotidine to the core tablet are: plasticisers such as triethyl citrate and dibutyl phthalate; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	**% W/W**	**mg/Tablet**
Naproxen, USP	94.00	750
Hydroxypropyl methylcellulose 2208, USP (viscosity 15000 cps)	5.00	39.9
Magnesium Stearate, NF	1.00	7.95
Total	100.00	797.85

Enteric Coating Dispersion Ingredients	% W/W
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5
Talc, USP	3.8
Sodium Hydroxide, NF	0.2
Triethyl Citrate, NF	1.7
Simethicone Emulsion, USP	0.02
Purified Water, USP	79.78
Total	100.00

Famotidine Coating Dispersion Ingredients	% W/W
Famotidine, USP	2.0
Opadry Blue® (YS-1-4215)	10.0
Talc, USP	9.0
Purified Water, USP	79.0
Total	100.0

Example 4: Naproxen and Famotidine Controlled Release Core and Famotidine Immediate Release

A trilayer tablet which separates famotidine contained in the film coat from controlled-release naproxen and famotidine may be used in the present invention. The core tablet of naproxen and famotidine is formulated using excipients which control the drug release for therapeutic relief from pain and inflammation for 24 hours. Figure 2 is an example of an appropriate trilayer tablet. In this particular example, naproxen and famotidine are mixed with a polymeric material, hydroxypropylmethylcellulose and granulated with water. The granules are dried, milled, and blended with a lubricant, such as magnesium stearate. They are then compacted into tablets.

The controlled-release core tablet of naproxen and famotidine is film coated with a pharmaceutically acceptable enteric coating. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the extrememly acidic pH of the unprotected stomach. The function of methacrylic acid copolymers is to prevent the release of naproxen

in the pH of the stomach rises. Triethyl citrate is a plasticiser, simethicone emulsion is a anti-foaming agent, and sodium hydroxide is used to adjust the pH of the dispersion.

The outermost later contains an "acid inhibitor" which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which consistently raises the pH of the stomach to above 4. The typical effective amount of famotidine in the dosage will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Blue® YS-1-4215 which is essential for film formation and for the uniform application of famotidine to the core tablet. Polymer film coating ingredients, hydroxypropylmethylcellulose or Opaspray® K-1-4210A (Colorcon, West Point, PA) may also be used. Other ingredients which help in the formation of the film and in the uniform application of famotidine to the core tablet are: plasticisers such as triethyl citrate and dibutyl phthalate; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	**% W/W**	**mg/Tablet**
Naproxen, USP	88.05	500
Famotidine, USP	3.52	20.0
Hydroxypropyl methylcellulose 2208, USP (viscosity 15000 cps)	7.03	39.9
Magnesium Stearate, NF	1.40	7.95
Total	100.00	567.85

Enteric Coating Dispersion Ingredients	**% W/W**
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5
Talc, USP	3.8
Sodium Hydroxide, NF	0.2
Triethyl Citrate, NF	1.7
Simethicone Emulsion, USP	0.02

Purified Water, USP	79.78
Total	100.00

Famotidine Coating Dispersion Ingredients	**% W/W**
Famotidine, USP	2.0
Opadry Blue® (YS-1-4215)	10.0
Talc, USP	9.0
Purified Water, USP	79.0
Total	100.0

Example 5: Enteric Coated Naproxen Sodium Core and Pantoprazole Immediate Release in Film Coat

A schematic diagram of a four layer tablet dosage form is shown in Figure 1. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, PA). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The third layer is an enteric film coat. It does not dissolve in areas of the GI tract where the pH may be below 4 such as in an unprotected stomach but it dissolves only when the local pH is above about 4. Therefore, the function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above 4. In this example, hydroxypropylmethylcellulose phthalate is the enteric coating ingredient, cetyl alcohol is a plasticiser and acetone and alcohol are solvents.

The fourth layer contains an "acid inhibitor" in an effective amount which is released from the dosage form as soon as the film coat dissolves. The acid inhibitor in this example is

a proton pump inhibitor, pantoprazole which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of pantoprazole in the dosage form may vary from 10 mg to 200 mg. The film coat is applied by conventional pan coating technology and the weight of film coat may vary from 4% to 8% of the core tablet weight. Other ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide, and ammonium hydroxide to adjust the pH of the dispersion. The film coating is thin and rapidly releases pantoprazole for absorption. Therefore, pantoprazole releases first and then the core erodes and releases naproxen sodium.

Core Tablet Ingredients	**% W/W**	**mg/tablet**
Naproxen sodium, USP	74.075	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.165	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Naproxen sodium, 50% microcrystalline cellulose and povidone are dry mixed and wet granulated in an appropriate granulator with sufficient purified water. The wet granules are dried, milled, and blended with the remaining 50% microcrystalline cellulose, talc and magnesium stearate. The final granule blend is compressed into tablets.

Barrier Film Coating Ingredients	**%W/W**
Opadry® Clear YS-1-7006	5.00
Purified Water, USP	95.00
Total	100.00

Opadry clear is added slowly to purified water and mixing is continued until Opadry is fully dispersed. The solution is sprayed on to the tablet cores in a conventional coating pan until proper amount of Opadry clear is deposited on the tablets.

Enteric Coating Ingredients	**%W/W**
Hydroxypropyl methylcellulose phthalate, NF	5.5
Cetyl alcohol, NF	0.3
Acetone, NF	66.3
Alcohol, USP	27.9
Total	100.00

Hydroxypropylmethylcellulose phthalate and cetyl alcohol are dissolved in a mixture of alcohol and acetone. The solution is then sprayed on to the tablet bed in proper coating equipment. A sample of the tablets is tested for gastric resistance and the coating stopped if the tablets pass the test.

Pantoprazole Film Coating Ingredients	**%W/W**
Pantoprazole sodium, USP	5.00
Opadry® Clear YS-1-7006	5.00
Sodium carbonate, NF	1.20
Purified Water, USP	88.80
Total	100.00

Pantoprazole sodium is dissolved in purified water containing sodium carbonate in solution. After thorough mixing, Opadry clear is added slowly and mixing is continued until Opadry is fully dispersed. The suspension is sprayed on to the tablet cores in a conventional coating pan until the proper amount of pantoprazole sodium is deposited.

Example 6: Enteric Coated Naproxen Sodium Core and Omeprazole Immediate Release in Film Coat

A schematic diagram of a four layer tablet dosage form is shown in Figure 1. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, PA). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The third layer is an enteric film coat. It does not dissolve in areas of the GI tract where the pH is below 4 such as in an unprotected stomach but it dissolves only when the local pH is above 4. Therefore, the function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above about 4. In this example, hydroxypropylmethylcellulose phthalate is the enteric coating ingredient, cetyl alcohol is a plasticiser and acetone and alcohol are solvents.

The fourth layer contains an "acid inhibitor" in an effective amount which is released from the dosage form as soon as the film coat dissolves. The acid inhibitor in this example is a proton pump inhibitor, omeprazole, which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of omeprazole in the dosage form may vary from 5 mg to 50 mg. The film coat is applied by conventional pan coating technology and the weight of film coat may vary from 4% to 8% of the core tablet weight. Other ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide, and ammonium hydroxide to adjust the pH of the dispersion. The film coating is thin and rapidly releases omeprazole for absorption. Therefore, omeprazole is released first and then the core erodes and releases naproxen sodium.

Core Tablet Ingredients	**% W/W**	**mg/tablet**
Naproxen sodium, USP	74.075	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.165	115.87

Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Naproxen sodium, 50% microcrystalline cellulose and povidone are dry mixed and wet granulated in an appropriate granulator with sufficient purified water. The wet granules are dried, milled, and blended with the remaining 50% microcrystalline cellulose, talc and magnesium stearate. The final granule blend is compressed into tablets.

Barrier Film Coating Ingredients	**%W/W**
Opadry® Clear YS-1-7006	5.00
Purified Water, USP	95.00
Total	100.00

Opadry clear is added slowly to purified water and mixing is continued until Opadry is fully dispersed. The solution is sprayed on to the tablet cores in a conventional coating pan until the proper amount of Opadry clear is deposited on the tablets.

Enteric Coating Ingredients	**%W/W**
Methacrylic Acid Copolymer, NF (Eudragit L-100-55)	6.0
Triethyl Citrate, NF	0.6
Talc, USP	3.0
Purified Water, USP	5.0
Isopropyl Alcohol, USP	85.40
Total	100.00

Methacrylic acid copolymer, triethyl citrate, and talc are dissolved in a mixture of isopropyl alcohol and water. The solution is then sprayed on to the tablet bed in a proper coating equipment. A sample of the tablets is tested for gastric resistance and the coating is stopped if the tablets pass the test.

Omeprazole Film Coating Ingredients	%W/W
Omeprazole, USP	5.00
Opadry® Clear YS-1-7006	5.00
Purified Water, USP	10.00
Isopropyl Alcohol, USP	80.00
Total	100.00

Omeprazole is dissolved in a purified water and isopropyl alcohol mixture. After thorough mixing, Opadry clear is added slowly and mixing is continued until Opadry is fully dispersed. The suspension is sprayed on to the tablet cores in a conventional coating pan until proper amount of omeprazole is deposited on the tablets.

Example 7: Naproxen Sodium Delayed Release and Omeprazole Immediate Release Capsule

A coordinated delivery dosage may be used to provide fast release of an acid inhibitor, a proton pump inhibitor, omeprazole which raises the pH of the gastrointestinal tract to above 4, and the delayed release of a non-steroidal anti-inflammatory drug, naproxen sodium. Omeprazole granules modify the pH of the stomach such that the drug readily dissolves and is absorbed in the stomach without significant degradation. The typical effective amount of omeprazole in the dosage form may vary from 5 mg to 50 mg. The release of naproxen sodium is delayed by enteric coating.

Omeprazole granules contain an alkalizing excipient such as sodium bicarbonate. Other soluble alkalizing agents such as potassium bicarbonate, sodium carbonate, sodium hydroxide, or their combinations may also be used. The alkalizing agent helps solubilize and protect omeprazole from degradation before its absorption. Sodium lauryl sulfate helps in the wetting of omeprazole. Other surfactants may be used to perform the same function. In the present example, hydroxypropyl methylcellulose helps in granule formation, sodium starch glycolate is a disintegrant, and magnesium stearate is a lubricant. Other excipients may also be used to perform these functions.

Naproxen sodium pellets as shown in Figure 3 are prepared by the wet massing technique and the conventional extrusion and spheronization process. The excipients used in the formulation are microcrystalline cellulose, and povidone. The pellets after drying and

classification are coated with a protective subcoating containing povidone. Other coating ingredients may also be used such as Opaspray K-1-4210A or Opadry YS-1-7006 (trademarks of Colorcon, West Point, PA). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a subcoating suspension are also alternatives. Other ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide.

The subcoated pellets are enteric coated using enteric coating polymers. In this example, the enteric coating polymer is methacrylic acid copolymer and the plasticizer is dibutyl phthalate which are dissolved in a mixture of acetone and alcohol. The enteric film does not dissolve in the acidic pH but dissolves when the pH in the gut is above about pH 6 and releases naproxen sodium.

Omeprazole Granules	**% W/W**	**mg/capsule**
Omeprazole, USP	12.9	20.00
Sodium Bicarbonate, USP	82.40	127.72
Hydroxypropyl methylcellulose, USP	2.00	3.10
Sodium lauryl sulfate, NF	0.20	0.31
Sodium starch glycolate, NF	2.00	3.10
Magnesium stearate, NF	0.50	0.77
Total	100	100

Hydroxypropylmethylcellulose is dissolved in water, then sodium lauryl sulfate is added and the solution is mixed. Omeprazole, microcrystalline cellulose, and sodium bicarbonate are dry mixed together and granulated with the granulating solution. The granulation is mixed until proper granule formation is reached. The granulation is then dried, milled, and blended with magnesium stearate.

Pellet Ingredients	% W/W	mg/tablet
Naproxen sodium, USP	86.80	250.00
Microcrystalline cellulose, NF (Avicel PH 200)	11.10	32.00
Povidone (K90), USP	2.10	6.00
Total	100.00	288.00

Povidone is dissolved in water. Naproxen sodium and microcrystalline cellulose are dry mixed and granulated with povidone solution. The wet mass is mixed until proper consistency is reached. The wet mass is then pressed through an extruder and spheronized to form pellets. The pellets are then dried and classified into suitable particle size range.

Subcoat Ingredients	% W/W
Povidone (K29-32), USP	10.00
Alcohol, USP	90.00
Total	100.00

The pellet cores are coated using povidone solution by a conventional coating pan method to a weight gain of 1-2%.

Enteric Coating Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L-100)	8.20
Diethyl Phthalate, NF	1.70
Acetone, NF	33.30
Isopropyl Alcohol, USP	56.80
Total	100.0

Eudragit L-100 is dissolved in isopropanol and acetone and diethyl phthalate is dissolved. The solution is sprayed on the pellet cores using proper film coating equipment. A sample of the pellets is tested for gastric resistance before stopping the coating process.

Omeprazole fast release granules and naproxen sodium delayed release pellets are blended together and filled into appropriate size capsules to contain 250 mg naproxen sodium and 20 mg omeprazole per capsule.

Example 8: Naproxen Delayed Release and Omeprazole Immediate Release Capsule

The present Example is directed to a coordinated delivery dosage form containing omeprazole and naproxen. The formulation contains 10 mg omeprazole and uses methylcellulose as a binder and croscarmellose sodium as a disintegrant. Naproxen pellets as shown in Figure 3 do not need a subcoating layer and are enteric coated with an aqueous dispersion of methacrylic acid copolymer. Optionally, these pellets could be compressed into a core and film coated with an acid inhibitor and thereby form a bilayer tablet.

Omeprazole Granules	**% W/W**	**mg/capsule**
Omeprazole, USP	6.45	10.00
Sodium Bicarbonate, USP	88.85	137.71
Methylcellulose, USP	2.00	3.10
Sodium lauryl sulfate, NF	0.20	0.31
Croscarmellose sodium, NF	2.00	3.10
Magnesium stearate, NF	0.50	0.78
Total	100	100

Methylcellulose is dissolved in water, then sodium lauryl sulfate is added to the solution and mixed. Omeprazole, microcrystalline cellulose, and sodium bicarbonate are dry mixed together and granulated with the granulating solution. The granulation is mixed until proper granule formation is reached. The granulation is then dried, milled, and blended with magnesium stearate.

Pellet Ingredients	% W/W	mg/tablet
Naproxen, USP	76.22	250.00
Microcrystalline cellulose, NF (Avicel PH 200)	21.78	71.44
Povidone (K90), USP	2.00	6.56
Total	100.00	328.00

Povidone is dissolved in water. Naproxen and microcrystalline cellulose are dry mixed and granulated with povidone solution. The wet mass is mixed until proper consistency is reached. The wet mass is then pressed through an extruder and spheronized to form pellets. The pellets are then dried and classified into a suitable particle size range.

Enteric Coating Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L30D 30% dispersion)	15.60
Talc, USP	7.60
Triethyl citrate, NF	1.60
Simethicone Emulsion, USP (Silicone antifoam emulsion SE 2)	0.20
Purified Water, USP	74.80

Eudragit 30D is dispersed in purified water and simethicone emulsion. Talc and triethyl citrate are then dispersed. The suspension is sprayed on the pellet cores using proper film coating equipment. A sample of the pellets is tested for gastric resistance before stopping the coating process. Omeprazole fast release granules and naproxen sodium delayed release pellets are blended together and filled into appropriate size capsules to contain 250 mg naproxen and 10 mg omeprazole per capsule.

Example 9: Clinical Study of the Relationship of Gastric pH to NSAID-induced Gastric Ulcers

Sixty-two subjects were enrolled in a clinical study and randomly assigned to three groups. The following three groups were administered study medication twice daily for five

days: (a) 550 mg naproxen sodium (n=10), (b) 40 mg famotidine given with 550 mg of naproxen or famotidine followed 90 minutes later by 550 mg naproxen, (n=39) or (c) 20 mg omeprazole followed by 550 mg naproxen sodium (n=13). Gastric pH was measured hourly beginning at the time of dosing of the final daily dose of study medication and for 8 – 10 hours thereafter. Subjects had a gastric endoscopy performed at the beginning and on Day 5 prior to the morning dose of study medication to identify gastric and duodenal irritation; no subjects were admitted to the study if gastric irritation was present at the time of initial endoscopy.

Five patients, three (33%) in the naproxen alone group and two (5%) in the famotidine/naproxen group, presented with gastroduodenal ulcers at the end of the study. In the naproxen alone group, the pH was greater than 4 only 4% of the time, and in the famotidine/naproxen group the pH was greater than 4 forty-nine percent of the time during the 8 – 10 hours following naproxen sodium dosing. Additionally, Lanza grade 3 or 4 damage was present in 28% (n=11) of the subjects receiving famotidine/naproxen sodium, and present 100% (n=10) in the naproxen sodium treatment group. Monitoring of gastric acidity on day 5 indicated that patients with Lanza scores of greater than 2 had integrated gastric acidity of greater than 100 mmol-hr./L. Only 20 – 40% of patients with integrated gastric acidity of less than 100 mmol-hr/L had gastric pathology, whereas all patients with integrated gastric acidity greater than 100 mmol-hr/L had pathology.

Example 10. Famotidine and Enteric Coated Naproxen Reduce Gastroduodenal Damage Due to NSAID Therapy

Forty patients are randomized to two groups for a one week study of twice-daily dosing of: 500mg enteric coated naproxen, and 500mg enteric coated naproxen preceded by 40mg famotidine. Endoscopies are conducted on all patients prior to first dosing and on the final day of the study. No subjects have any evidence of gastroduodenal damage at the beginning of the study (at first endoscopy).

At the second endoscopy, Lanza scores for gastroduodenal damage are assessed for all subjects. Subjects in the enteric coated naproxen 500mg group have a lower incidence of grade 3-4 gastroduodenal damage than subjects previously treated with non-enteric coated naproxen 500mg. Importantly, subjects administered 500mg enteric coated naproxen and

40mg famotidine have substantially lower incidence of grade 3 – 4 gastroduodenal damage than subjects who had previously taken naproxen alone (either naked or enteric coated) which demonstrates the need for and the value of combining acid inhibition with enteric coating to minimize the gastrointestinal damage of NSAID.

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The claims defining the invention are as follows:

1. A pharmaceutical composition in unit dose form suitable for oral administration to a patient, comprising:

(a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms;

(b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms;

and wherein said unit dosage form provides for the coordinated release of said acid inhibitor followed by said NSAID.

2. The pharmaceutical composition of claim 1, wherein said acid inhibitor is selected from: a proton pump inhibitor and an H2 blocker.

3. The pharmaceutical composition of claim 2, wherein said acid inhibitor is an H2 blocker selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

4. The pharmaceutical composition of claim 3, wherein said H2 blocker is famotidine, present in said unit dosage form in an amount of between 5 mg and 100 mg.

5. The pharmaceutical composition of claim 1, wherein said acid inhibitor is a proton pump inhibitor selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole.

6. The pharmaceutical composition of claim 5, wherein said proton pump inhibitor is pantoprazole, present in said unit dosage form in an amount of between 10 mg and 200 mg.

7. The pharmaceutical composition of claim 1, wherein said NSAID is a cyclooxygenese-2 (COX-2) inhibitor.

8. The pharmaceutical composition of claim 7, wherein said COX-2 inhibitor is selected from the group consisting of celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

9. The pharmaceutical composition of claim 1, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

10. The pharmaceutical composition of claim 9, wherein said NSAID is naproxen present in an amount of between 50 mg and 1500 mg.

11. The pharmaceutical composition of claim 10, wherein said naproxen is present in an amount of between 200 mg and 600 mg.

12. The pharmaceutical composition of claim 1, wherein said unit dosage form is a multilayer tablet.

13. The pharmaceutical composition of claim 12, wherein said unit dosage form is a trilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID.

14. The pharmaceutical composition of claim 12, wherein said unit dosage form is a bilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID.

15. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of the surrounding medium is 3.5 or greater.

16. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of the surrounding medium is 4 or greater.

17. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of the surrounding medium is 5 or greater.

18. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 3.5 or greater.

19. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 4 or greater.

20. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not not released until the pH of the surrounding medium is 5 or greater.

21. The phamaceutical composition of claim 1, wherein said unit dosage form is a capsule.

22. A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of any one of claims 1-14.

23. The method of claim 22, wherein said patient is treated for either osteoarthritis or rheumatoid arthritis.

24. A method of treating a patient for pain or inflammation, comprising:

(a) orally administering to said patient an acid inhibitor at a dose effective to raise the gastric pH of said patient to at least 3.5; and

(b) orally administering to said patient an NSAID that is coated in a polymer that only dissolves at a pH of 3.5 or greater.

25. The method of claim 24, wherein said acid inhibitor is an H2 blocker.

26. The method of claim 25, wherein said H-2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

27. The method of claim 26, wherein said H2 blocker is famotidine administered at a dose of between 5 mg and 100 mg.

28. The method of claim 24, wherein said acid inhibitor is a proton pump inhibitor.

29. The method of claim 28, wherein said proton pump inhibitor is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole.

30. The method of claim 29, wherein said proton pump inhibitor is pantoprazole administered at a dose of between10 mg and 200 mg.

31. The method of any one of claims 24 - 30, wherein said NSAID is a COX-2 inhibitor selected from the group consisting of: celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

32. The method of any one of claims 24 – 30, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

33. The method of claim 32, wherein said NSAID is naproxen administered at a dose of between 50 mg and 1500 mg.

34. The method of claim 33, wherein said naproxen is administered at a dose of between 200 mg and 600 mg.

35. The method of claim 24, wherein said acid inhibitor and said NSAID are delivered as part of a single dosage form providing for the coordinated release of therapeutic agents.

36. The method of claim 35, wherein said single dosage form is a bilayer tablet with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

37. A method of treating a patient for pain or inflammation, comprising:
(a) orally administering to said patient an acid inhibitor at a dose effective to raise the gastric pH of said patient to at least 3.5; and
(b) concurrently administering to said patient an NSAID that is coated in a polymer that dissolves at a rate such that said NSAID is not released until said gastric pH is at 3.5 or higher.

38. The method of claim 37, wherein said acid inhibitor is an H2 blocker.

39. The method of claim 38, wherein said H-2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

40. The method of claim 39, wherein said H2 blocker is famotidine administered at a dose of between 5 mg and 100 mg.

41. The method of claim 37, wherein said acid inhibitor is a proton pump inhibitor.

42. The method of claim 41, wherein said proton pump inhibitor is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole.

43. The method of claim 42, wherein said proton pump inhibitor is pantoprazole administered at a dose of between 10 mg and 200 mg.

44. The method of any one of claims 37 - 43, wherein said NSAID is a COX-2 inhibitor selected from the group consisting of: celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

45. The method of any one of claims 37 – 43, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

46. The method of claim 45, wherein said NSAID is naproxen administered at a dose of between 50 mg and 1500 mg.

47. The method of claim 46, wherein said naproxen is administered at a dose of between 200 mg and 600 mg.

48. The method of claim 47, wherein said acid inhibitor and said NSAID are delivered as part of a single dosage form providing for the coordinated release of therapeutic agents.

49. The method of claim 48, wherein said single dosage form is a bilayer tablet with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

50. A method of improving compliance in patients requiring frequent daily dosages of an acid inhibitor and an NSAID comprising administering said dosages in a coordinated unit dosage form in accordance with claim 1.

Dated 20 October, 2006
Pozen Inc.

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

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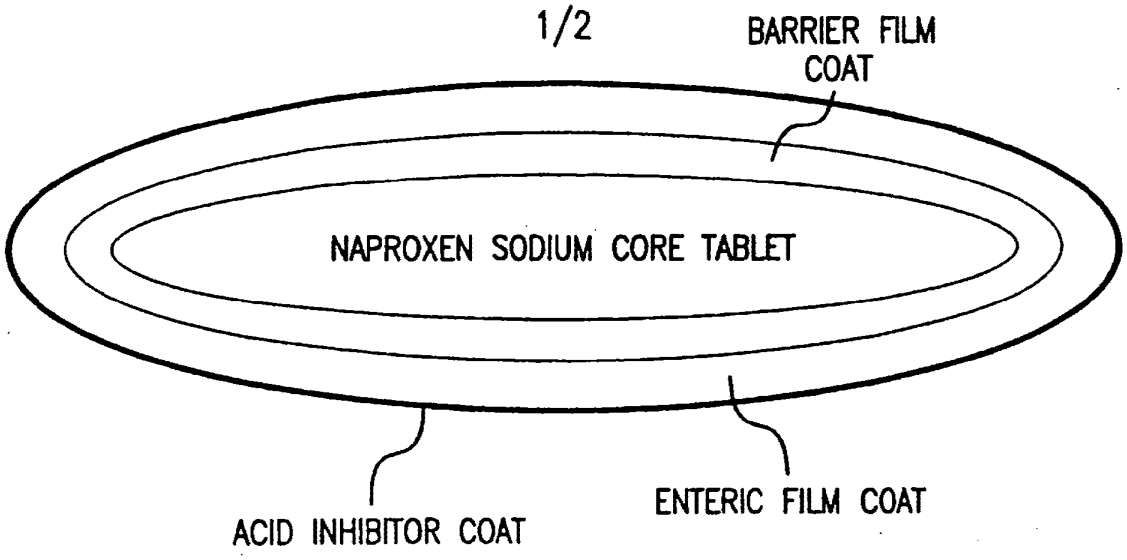

FIG.1

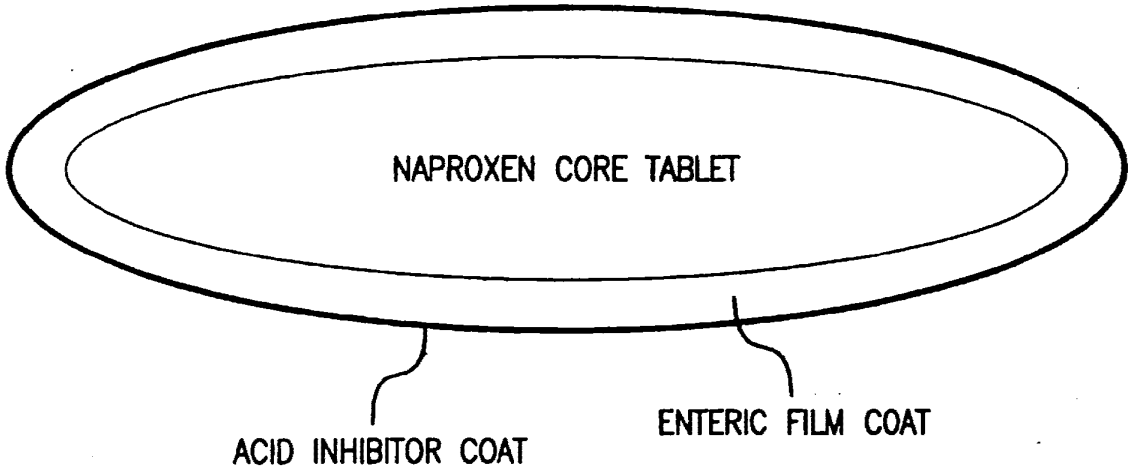

FIG.2

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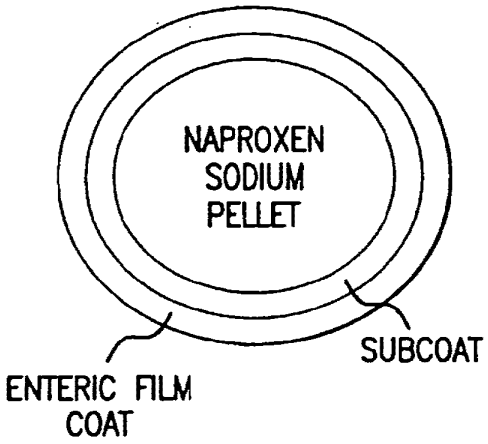

FIG.3

B14

PATENT ABSTRACTS OF JAPAN

(11)Publication number : 2005-145894
(43)Date of publication of application : 09.06.2005

(51)Int.Cl. A61K 45/06
A61K 9/14
A61K 9/16
A61K 9/20
A61K 9/28
A61K 9/48
A61K 31/196
A61K 31/4439
A61P 29/00

(21)Application number : 2003-386548
(22)Date of filing : 17.11.2003

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(54) SOLID PREPARATION

(57)Abstract:
PROBLEM TO BE SOLVED: To provide a solid preparation containing one or more kinds of nonsteroidal antiinflammatory drugs (NSAID), and useful as an antipyretic, antalgic and antiinflammatory agent having a suppressing or reducing effect on the manifestation of gastrointestinal injury by the NSAID.
SOLUTION: This solid preparation comprises a combination of a granules, grain or a tablet containing a proton pump inhibitor (PPI), with granules or grains containing one or more kinds of the nonsteroid antiinflammatory drugs (NSAID). Preferably, the solid preparation is a capsule filled with both thereof.

(19)日本国特許庁(JP)　(12)公開特許公報(A)　(11)特許出願公開番号
特開2005-145894
(P2005-145894A)
(43)公開日　平成17年6月9日(2005.6.9)

(51)Int.Cl.[7]	F I		テーマコード（参考）
A61K 45/06	A61K	45/06	4C076
A61K 9/14	A61K	9/14	4C084
A61K 9/16	A61K	9/16	4C086
A61K 9/20	A61K	9/20	4C206
A61K 9/28	A61K	9/28	

審査請求 未請求　請求項の数 17　ＯＬ　（全 15 頁）　最終頁に続く

(21)出願番号　特願2003-386548 (P2003-386548)
(22)出願日　平成15年11月17日 (2003.11.17)

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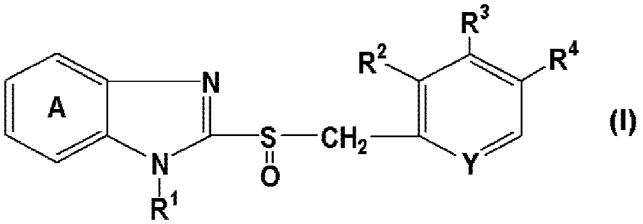
(54)【発明の名称】固形製剤

(57)【要約】
【課題】　１種またはそれ以上の非ステロイド性抗炎症剤（ＮＳＡＩＤ）を含有する製剤であって、ＮＳＡＩＤによる胃腸障害の発現抑制乃至は軽減効果を有する解熱・鎮痛・抗炎症剤として有用な固形製剤を提供すること。
【解決手段】プロトンポンプ阻害剤（ＰＰＩ）を含有する顆粒、細粒または錠剤と１種またはそれ以上の非ステロイド性抗炎症剤（ＮＳＡＩＤ）を含有する顆粒または細粒の組合せから成る固形製剤、好ましくは両者が充填されたカプセル剤。
【選択図】なし

【特許請求の範囲】
【請求項1】
プロトンポンプ阻害剤（ＰＰＩ）を含有する顆粒、細粒または錠剤と１種またはそれ以上の非ステロイド性抗炎症剤（ＮＳＡＩＤ）を含有する顆粒または細粒の組合せから成る固形製剤。
【請求項2】
ＰＰＩがベンツイミダゾール系化合物である請求項１記載の固形製剤。
【請求項3】
ベンツイミダゾール系化合物が式（Ｉ）：
【化1】



〔式中、環Aは置換基を有していてもよいベンゼン環、Ｒ^{1}は水素原子、置換基を有していてもよいアラルキル基、アシル基またはアシルオキシ基、Ｒ^{2}、Ｒ^{3}およびＲ^{4}は、それぞれ同一または異なって、水素原子、置換基を有していてもよいアルキル基、置換基を有していてもよいアルコキシ基または置換基を有していてもよいアミノ基、およびYは窒素原子またはＣＨを示す〕で表される化合物もしくはその光学活性体またはその塩である請求項２記載の固形製剤。
【請求項4】
ベンツイミダゾール系化合物が、ランソプラゾール、オメプラゾール、ラベプラゾール、パントプラゾールもしくはその光学活性体またはその塩である請求項２記載の固形製剤。
【請求項5】
ＰＰＩがイミダゾピリジン系化合物である請求項１記載の固形製剤。
【請求項6】
イミダゾピリジン系化合物がテナトプラゾールもしくはその光学活性体またはその塩である請求項５記載の固形製剤。
【請求項7】
ＰＰＩを含有する顆粒、細粒または錠剤が腸溶性被覆を施されている請求項１記載の固形製剤。
【請求項8】
ＮＳＡＩＤを含有する顆粒または細粒が持続性顆粒または細粒である請求項１記載の固形製剤。
【請求項9】
ＰＰＩを含有する顆粒、細粒または錠剤と１種またはそれ以上のＮＳＡＩＤを含有する顆粒または細粒の組合せが１つのユニットに充填された請求項１記載の固形製剤。
【請求項10】
１つのユニットがカプセルである請求項９記載の固形製剤。
【請求項11】
ＮＳＡＩＤがフェニル酢酸系化合物、プロピオン酸系化合物、サリチル酸系化合物、インドール酢酸系化合物、アントラニル酸系化合物、オキシカム系化合物またはそれらの塩である請求項１記載の固形製剤。
【請求項12】
ＮＳＡＩＤがＣＯＸ－２阻害剤である請求項１記載の固形製剤。
【請求項13】
ランソプラゾール、オメプラゾール、ラベプラゾール、パントプラゾールおよびテナトプラゾール、それらの光学活性体並びにそれらの塩から選ばれるＰＰＩを含有する腸溶性被

覆顆粒とジクロフェナックナトリウム、イブプロフェン、ケトプロフェン、ナプロキセン、ロキソプロフェンナトリウム、アスピリン、インドメタシン、メフェナム酸、ピロキシカム、ロフェコキシブ、セレコキシブおよびバルデコキシブから選ばれる１種またはそれ以上のＮＳＡＩＤを含有する顆粒がカプセルに充填された請求項９記載の固形製剤。
【請求項14】
ＰＰＩと１種またはそれ以上のＮＳＡＩＤを３対１ないし１対３００の重量比で含有する請求項１記載の固形製剤。
【請求項15】
ランソプラゾールとジクロフェナックナトリウムを１対１ないし１対２０の重量比で含有する請求項１４記載の固形製剤。
【請求項16】
ランソプラゾールとピロキシカムを２対１ないし１対２の重量比で含有する請求項１４記載の固形製剤。
【請求項17】
ＮＳＡＩＤによる胃腸障害の予防、治療、軽減効果を有する解熱・鎮痛・抗炎症剤である請求項１記載の固形製剤。

【発明の詳細な説明】
【技術分野】
【0001】
本発明は、慢性関節リウマチ治療薬、変形性関節症治療薬、抗炎症薬、解熱鎮痛薬などとして有用な、非ステロイド性抗炎症剤（ＮＳＡＩＤ）とプロトンポンプ阻害剤（ＰＰＩ）とを含有する固形製剤に関する。
【背景技術】
【0002】
酸に不安定なプロトンポンプ阻害剤（ＰＰＩ）と非ステロイド性抗炎症剤（ＮＳＡＩＤ）とを含有する製剤としては、下記の製剤が報告されている。
１）ＰＰＩが腸溶性皮膜でコーティングされたペレットとしてＮＳＡＩＤの少なくとも１種を含有する錠剤中に分散しているマルチプルユニット錠剤（特許文献１参照）。
２）ＮＳＡＩＤを含有する錠剤表面にＰＰＩをコーティングし、さらに腸溶性皮膜でコーティングした錠剤、あるいはＮＳＡＩＤを含有する錠剤と腸溶性皮膜でコーティングしたＰＰＩ粒子をカプセルに充填した固形製剤（特許文献２参照）。
【0003】
【特許文献1】米国特許第６３６５１８４号明細書
【特許文献2】国際公開第ＷＯ０２／２２１０８号
【発明の開示】
【発明が解決しようとする課題】
【0004】
本発明は、慢性関節リウマチ治療薬、変形性関節症治療薬、抗炎症薬、解熱鎮痛薬などとして有用であり、ＮＳＡＩＤによる胃腸障害の治療と予防などにおいて優れる、酸に不安定なＰＰＩと１種またはそれ以上のＮＳＡＩＤとを含有する固形製剤を提供することを目的とする。食事の有無によって各薬物の吸収性などの体内動態が影響されにくい剤形であり、かつ安定性、配合性に優れ、それぞれ薬物の体内動態が併用投与時と変わらない固形製剤の開発が望まれている。
【課題を解決するための手段】
【0005】
本発明者らは、ＮＳＡＩＤと酸に不安定なＰＰＩとを含有する配合固形製剤を製造するに際し、各成分を含有する顆粒等の２種類以上の固形製剤の適量を１つのユニットに充填することによって、ＮＳＡＩＤによる胃腸障害の治療と予防などにおいて優れ、食事の影響を受け難くかつ安定性、配合性に優れ、各薬物の体内動態が併用投与時と変わらない慢

性関節リウマチ治療薬、変形性関節症治療薬、抗炎症薬、解熱鎮痛薬などとして有用な固形製剤が得られることを見出した。本発明者らは、この知見に基づいて、さらに研究を進めた結果、本発明を完成した。

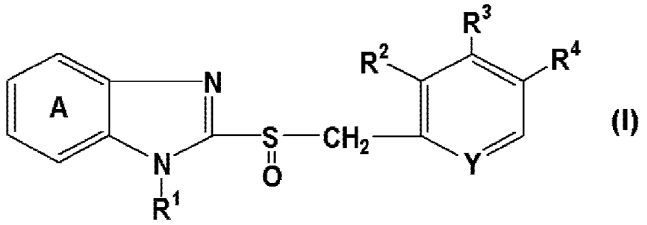
すなわち、本発明は、

（１）プロトンポンプ阻害剤（ＰＰＩ）を含有する顆粒、細粒または錠剤と１種またはそれ以上の非ステロイド性抗炎症剤（ＮＳＡＩＤ）を含有する顆粒または細粒の組合せから成る固形製剤、

（２）ＰＰＩがベンツイミダゾール系化合物である前記（１）記載の固形製剤、

（３）ベンツイミダゾール系化合物が式（Ｉ）：

【化1】



(I)

〔式中、環Aは置換基を有していてもよいベンゼン環、R^1は水素原子、置換基を有していてもよいアラルキル基、アシル基またはアシルオキシ基、R^2、R^3およびR^4は、それぞれ同一または異なって、水素原子、置換基を有していてもよいアルキル基、置換基を有していてもよいアルコキシ基または置換基を有していてもよいアミノ基、およびYは窒素原子またはＣＨを示す〕で表される化合物もしくはその光学活性体またはその塩である前記（２）記載の固形製剤、

（４）ベンツイミダゾール系化合物が、ランソプラゾール、オメプラゾール、ラベプラゾール、パントプラゾールもしくはその光学活性体またはその塩である前記（２）記載の固形製剤、

（５）ＰＰＩがイミダゾピリジン系化合物である前記（１）記載の固形製剤、

（６）イミダゾピリジン系化合物がテナトプラゾールもしくはその光学活性体またはその塩である前記（５）記載の固形製剤、

（７）ＰＰＩを含有する顆粒、細粒または錠剤が腸溶性被覆を施されている前記（１）記載の固形製剤、

（８）ＮＳＡＩＤを含有する顆粒または細粒が持続性顆粒または細粒である前記（１）記載の固形製剤、

（９）ＰＰＩを含有する顆粒、細粒または錠剤と１種またはそれ以上のＮＳＡＩＤを含有する顆粒または細粒の組合せが１つのユニットに充填された前記（１）記載の固形製剤、

（１０）１つのユニットがカプセルである前記（９）記載の固形製剤、

（１１）ＮＳＡＩＤがフェニル酢酸系化合物、プロピオン酸系化合物、サリチル酸系化合物、インドール酢酸系化合物、アントラニル酸系化合物、オキシカム系化合物またはそれらの塩である前記（１）記載の固形製剤、

（１２）ＮＳＡＩＤがＣＯＸ－２阻害剤である前記（１）記載の固形製剤、

（１３）ランソプラゾール、オメプラゾール、ラベプラゾール、パントプラゾールおよびテナトプラゾール、それらの光学活性体並びにそれらの塩から選ばれるＰＰＩを含有する腸溶性被覆顆粒とジクロフェナックナトリウム、イブプロフェン、ケトプロフェン、ナプロキセン、ロキソプロフェンナトリウム、アスピリン、インドメタシン、メフェナム酸、ピロキシカム、ロフェコキシブ、セレコキシブおよびバルデコキシブから選ばれる１種またはそれ以上のＮＳＡＩＤを含有する顆粒がカプセルに充填された前記（９）記載の固形製剤、

（１４）ＰＰＩと１種またはそれ以上のＮＳＡＩＤを３対１ないし１対３００の重量比で含有する前記（１）記載の固形製剤、

（１５）ランソプラゾールとジクロフェナックナトリウムを１対１ないし１対２０の重量比で含有する前記（１４）記載の固形製剤、

（１６）ランソプラゾールとピロキシカムを２対１ないし１対２の重量比で含有する前記（１４）記載の固形製剤、
（１７）ＮＳＡＩＤによる胃腸障害の予防、治療、軽減効果を有する解熱・鎮痛・抗炎症剤である前記（１）記載の固形製剤等に関する。

【発明の効果】

【0006】

本発明の固形製剤は、慢性関節リウマチ治療薬、変形性関節症治療薬、抗炎症薬、解熱・鎮痛薬などとして有用でありかつＮＳＡＩＤによる潰瘍や出血などの胃腸障害の治療と予防などにおいて優れる。加えて食事の有無によって、ＰＰＩあるいはＮＳＡＩＤの吸収性などの体内動態が影響されにくい剤形であり、また安定性、配合性に優れ、各薬物の体内動態が併用投与時と変わらない固形製剤である。

さらに、本発明の固形製剤は、簡便な方法によって容易に製造することができる。

【発明を実施するための最良の形態】

【0007】

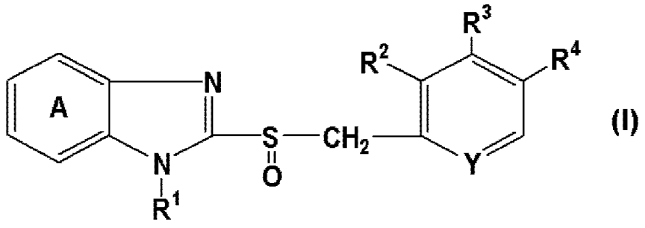
本発明において用いられるＮＳＡＩＤは、慢性関節リウマチ治療薬、変形性関節症治療薬、抗炎症薬、解熱鎮痛薬などとして有用な薬剤であればよい。ＮＳＡＩＤの具体例としては、例えば、フェニル酢酸系化合物（例、ジクロフェナック、フェンブフェン）、プロピオン酸系化合物（例、イブプロフェン、ケトプロフェン、ナプロキセン、ロキソプロフェン、プラノプロフェン）、サリチル酸系化合物（例、アスピリン）、インドール酢酸系化合物（例、インドメタシン、スリンダク）、アントラニル酸系化合物（例、メフェナム酸）、オキシカム系化合物（例、ピロキシカム、メロキシカム）またはその塩が挙げられる。ＣＯＸ－２阻害剤のようなＮＳＡＩＤ（例、ロフェコキシブ、セレコキシブ、バルデコキシブ）も本願発明に適用される。

本発明において、ＮＳＡＩＤは、１種を単独で用いてもよく、または２種以上を適宜の割合で組み合わせて用いてもよい。本発明において用いられるＰＰＩは、ＮＳＡＩＤによる胃腸障害の治療と予防効果を有し、このような障害を軽減できる薬剤であればよい。

ＰＰＩの具体例としては、例えば、ベンツイミダゾール系化合物（例、ランソプラゾール、オメプラゾール、ラベプラゾール、パントプラゾールまたはそれらの光学活性体）、イミダゾピリジン系化合物（例、テナトプラゾールまたはその光学活性体）またはその塩が挙げられる。

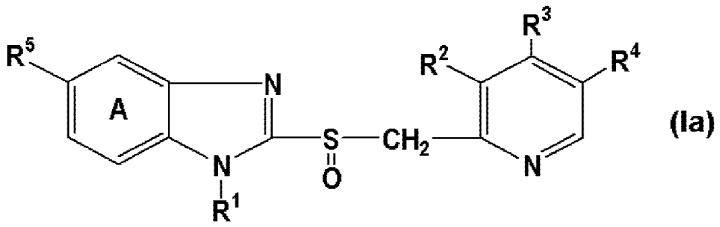
本発明で用いられるＰＰＩであるベンツイミダゾール系化合物としては、式（Ｉ）：r/>

【化2】



(I)

【化3】



〔式中、R^1は水素原子、R^2はC_{1-3}アルキル基またはC_{1-3}アルコキシ基、R^3はハロゲン化されているかまたはC_{1-3}アルコキシ基で置換されていてもよいC_{1-3}アルコキシ基、R^4は水素原子またはC_{1-3}アルキル基、R^5は、水素原子、ハロゲン化されていてもよいC_{1-3}アルコキシ基またはピロリル基（例えば、１－，２－または３－ピロリル基）を示す〕で表される化合物である。

式（Ｉａ）において、R^1が水素原子、R^2がC_{1-3}アルキル基、R^3がハロゲン化されていてもよいC_{1-3}アルコキシ基、R^4が水素原子、R^5が水素原子またはハロゲン化されていてもよいC_{1-3}アルコキシ基である化合物が特に好ましい。

【0008】

上記式（Ｉ）で表される化合物〔以下、化合物（Ｉ）と称する〕中、環Ａで示される「置換基を有していてもよいベンゼン環」の「置換基」としては、例えば、ハロゲン原子、シアノ基、ニトロ基、置換基を有していてもよいアルキル基、ヒドロキシ基、置換基を有していてもよいアルコキシ基、アリール基、アリールオキシ基、カルボキシ基、アシル基、アシルオキシ基、５ないし１０員複素環基などが挙げられ、これらの置換基はベンゼン環に１ないし３個程度置換していてもよい。置換基の数が２個以上の場合、各置換基は同一または異なっていてもよい。これらの置換基のうち、ハロゲン原子、置換基を有していてもよいアルキル基、置換基を有していてもよいアルコキシ基などが好ましい。

ハロゲン原子としては、フッ素、塩素、臭素原子などが挙げられる。なかでもフッ素が好ましい。

「置換基を有していてもよいアルキル基」の「アルキル基」としては、例えば、C_{1-7}アルキル基（例えば、メチル、エチル、プロピル、イソプロピル、ブチル、イソブチル、sec－ブチル、tert－ブチル、ペンチル、ヘキシル、ヘプチル基など）が挙げられる。

「置換基を有していてもよいアルキル基」の「置換基」としては、例えば、ハロゲン原子、ヒドロキシ基、C_{1-6}アルコキシ基（例えば、メトキシ、エトキシ、プロポキシ、ブトキシ等）、C_{1-6}アルコキシ－カルボニル基（例えば、メトキシカルボニル、エトキシカルボニル、プロポキシカルボニル基等）、カルバモイル基などで例示でき、これらの置換基の数は１ないし３個程度であってもよい。置換基の数が２個以上の場合、各置換基は同一または異なっていてもよい。

「置換基を有していてもよいアルコキシ基」の「アルコキシ基」としては、例えば、C_{1-6}アルコキシ基（例えば、メトキシ、エトキシ、プロポキシ、イソプロポキシ、ブトキシ、イソブトキシ、ペントキシ等）などが挙げられる。「置換基を有していてもよいアルコキシ基」の「置換基」としては、上記「置換基を有していてもよいアルキル基」の「置換基」と同様のものが例示でき、置換基の置換数も同様である。

「アリール基」としては、例えば、C_{6-14}アリール基（例えば、フェニル、１－ナフチル、２－ナフチル、ビフェニル、２－アンスリル基等）などが挙げられる。

「アリールオキシ基」としては、例えば、C_{6-14}アリールオキシ基（例えば、フェニルオキシ、１－ナフチルオキシ、２－ナフチルオキシ基等）などが挙げられる。

「アシル基」としては、例えば、ホルミル、アルキルカルボニル、アルコキシカルボニル、カルバモイル、アルキルカルバモイル、アルキルスルフィニル、アルキルスルホニル

基などが挙げられる。

「アルキルカルボニル基」としては、C_{1-6}アルキル－カルボニル基（例えば、アセチル、プロピオニル基等）などが挙げられる。

「アルコキシカルボニル基」としては、例えば、C_{1-6}アルコキシ－カルボニル基（例えば、メトキシカルボニル、エトキシカルボニル、プロポキシカルボニル、ブトキシカルボニル基等）などが挙げられる。

「アルキルカルバモイル基」としては、Ｎ－C_{1-6}アルキル－カルバモイル基（例えば、メチルカルバモイル、エチルカルバモイル基等）、Ｎ，Ｎ－ジC_{1-6}アルキル－カルバモイル基（例えば、Ｎ，Ｎ－ジメチルカルバモイル、Ｎ，Ｎ－ジエチルカルバモイル基等）などが挙げられる。

「アルキルスルフィニル基」としては、例えば、C_{1-7}アルキルスルフィニル基（例えば、メチルスルフィニル、エチルスルフィニル、プロピルスルフィニル、イソプロピルスルフィニル基等）などが挙げられる。

「アルキルスルホニル基」としては、例えば、C_{1-7}アルキルスルホニル基（例えば、メチルスルホニル、エチルスルホニル、プロピルスルホニル、イソプロピルスルホニル基等）などが挙げられる。

「アシルオキシ基」としては、例えば、アルキルカルボニルオキシ基、アルコキシカルボニルオキシ基、カルバモイルオキシ基、アルキルカルバモイルオキシ基、アルキルスルフィニルオキシ基、アルキルスルホニルオキシ基などが挙げられる。

「アルキルカルボニルオキシ基」としては、C_{1-6}アルキル－カルボニルオキシ基（例えば、アセチルオキシ、プロピオニルオキシ基等）などが挙げられる。

「アルコキシカルボニルオキシ基」としては、例えばC_{1-6}アルコキシ－カルボニルオキシ基（例えば、メトキシカルボニルオキシ、エトキシカルボニルオキシ、プロポキシカルボニルオキシ、ブトキシカルボニルオキシ基等）などが挙げられる。

「アルキルカルバモイルオキシ基」としては、C_{1-6}アルキル－カルバモイルオキシ基（例えば、メチルカルバモイルオキシ、エチルカルバモイルオキシ基等）などが挙げられる。

「アルキルスルフィニルオキシ基」としては、例えばC_{1-7}アルキルスルフィニルオキシ基（例えば、メチルスルフィニルオキシ、エチルスルフィニルオキシ、プロピルスルフィニルオキシ、イソプロピルスルフィニルオキシ基等）などが挙げられる。

「アルキルスルホニルオキシ基」としては、例えばC_{1-7}アルキルスルホニルオキシ基（例えば、メチルスルホニルオキシ、エチルスルホニルオキシ、プロピルスルホニルオキシ、イソプロピルスルホニルオキシ基等）などが挙げられる。

「５ないし１０員複素環基」としては、例えば、炭素原子以外に窒素原子、硫黄原子および酸素原子から選ばれるヘテロ原子を１個以上（例えば、１～３個）を含む５ないし１０員（好ましくは５または６員）複素環基が挙げられ、具体例としては、２－または３－チエニル基、２－、３－または４－ピリジル基、２－または３－フリル基、１－、２－または３－ピロリル基、２－、３－、４－、５－または８－キノリル基、１－、３－、４－または５－イソキノリル基、１－、２－または３－インドリル基などが挙げられる。このうち好ましくは１－、２－または３－ピロリル基などの５または６員複素環基である。

好ましくは環Ａは、ハロゲン原子、ハロゲン化されていてもよいC_{1-4}アルキル基、ハロゲン化されていてもよいC_{1-4}アルコキシ基および５または６員複素環基から選ばれる置換基を１または２個有していてもよいベンゼン環である。

【0009】

R^1で示される「置換基を有していてもよいアラルキル基」の「アラルキル基」としては、例えば、C_{7-16}アラルキル基（例えば、ベンジル、フェネチルなどのC_{6-10}アリールC_{1-6}アルキル基等）などが挙げられる。「置換基を有していてもよいアラルキル基」の「置換基」としては、上記「置換基を有していてもよいアルキル基」の「置換基」と同様の置換基が例示でき、置換基の数は１ないし４個程度である。置換基の数が２個以上の場合、各置換基は同一または異なっていてもよい。

R^1で示される「アシル基」としては、例えば、上記環Aの置換基として記載した「アシル基」が挙げられる。

R^1で示される「アシルオキシ基」としては、例えば、上記環Aの置換基として記載した「アシルオキシ基」が挙げられる。

好ましいR^1は水素原子である。

R^2、R^3またはR^4で示される「置換基を有していてもよいアルキル基」としては、上記環Aの置換基として記載した「置換基を有していてもよいアルキル基」が挙げられる。

R^2、R^3またはR^4で示される「置換基を有していてもよいアルコキシ基」としては、上記環Aの置換基として記載した「置換基を有していてもよいアルコキシ基」が挙げられる。

R^2、R^3またはR^4で示される「置換基を有してもよいアミノ基」としては、例えば、アミノ基、モノ－C_{1-6}アルキルアミノ基（例えば、メチルアミノ、エチルアミノ等）、モノ－C_{6-14}アリールアミノ基（例えば、フェニルアミノ、１－ナフチルアミノ、２－ナフチルアミノ等）、ジ－C_{1-6}アルキルアミノ基（例えば、ジメチルアミノ、ジエチルアミノ等）、ジ－C_{6-14}アリールアミノ基（例えば、ジフェニルアミノ等）などが挙げられる。

好ましいR^2は、C_{1-6}アルキル基、C_{1-6}アルコキシ基、C_{1-6}アルコキシ－C_{1-6}アルコキシ基、ジ－C_{1-6}アルキルアミノ基である。さらに好ましいR^2はC_{1-3}アルキル基またはC_{1-3}アルコキシ基である。

好ましいR^3は、水素原子、C_{1-6}アルコキシ－C_{1-6}アルコキシ基またはハロゲン化されていてもよいC_{1-6}アルコキシ基である。さらに好ましいR^3はハロゲン化されているかまたはC_{1-3}アルコキシ基で置換されていてもよいC_{1-3}アルコキシ基である。

好ましいR^4は、水素原子またはC_{1-6}アルキル基である。さらに好ましいR^4は水素原子またはC_{1-3}アルキル基（特に水素原子）である。

好ましいYは窒素原子である。

【0010】

化合物（Ｉ）の具体例としては、下記の化合物が挙げられる。

２－［［［３－メチル－４－（２，２，２－トリフルオロエトキシ）－２－ピリジニル］メチル］スルフィニル］－１Ｈ－ベンズイミダゾール、２－［［（３，５－ジメチル－４－メトキシ－２－ピリジニル）メチル］スルフィニル］－５－メトキシ－１Ｈ－ベンズイミダゾール、２－［［［４－（３－メトキシプロポキシ）－３－メチル－２－ピリジニル]メチル]スルフィニル］－１Ｈ－ベンズイミダゾール・ナトリウム塩、５－ジフルオロメトキシ－２－［［（３，４－ジメトキシ－２－ピリジニル）メチル］スルフィニル］－１Ｈ－ベンズイミダゾールなど。

これらの化合物のうち、２－［［［３－メチル－４－（２，２，２－トリフルオロエトキシ）－２－ピリジニル］メチル］スルフィニル］－１Ｈ－ベンズイミダゾール（ランソプラゾール）が好ましい

なお、上記化合物（Ｉ）は、ラセミ体であってもよく、Ｒ－体、Ｓ－体などの光学活性体であってもよい。例えば、（Ｒ）－２－［［［３－メチル－４－（２，２，２－トリフルオロエトキシ）－２－ピリジニル］メチル］スルフィニル］－１Ｈ－ベンズイミダゾール（ランソプラゾール　Ｒ体と呼ぶことがある）などの光学活性体であってもよく、また好ましい。

【0011】

化合物（Ｉ）の塩としては、薬学的に許容される塩が好ましく、例えば、無機塩基との塩、有機塩基との塩、塩基性アミノ酸との塩などが挙げられる。

無機塩基との塩の好適な例としては、例えば、ナトリウム塩、カリウム塩などのアルカリ金属塩；カルシウム塩、マグネシウム塩などのアルカリ土類金属塩；アンモニウム塩などが挙げられる。

有機塩基との塩の好適な例としては、例えば、アルキルアミン（トリメチルアミン、トリエチルアミンなど）、複素環式アミン（ピリジン、ピコリンなど）、アルカノールアミン（エタノールアミン、ジエタノールアミン、トリエタノールアミンなど）、ジシクロヘキシルアミン、Ｎ,Ｎ’－ジベンジルエチレンジアミンなどとの塩が挙げられる。

塩基性アミノ酸との塩の好適な例としては、例えば、アルギニン、リジン、オルニチンなどとの塩が挙げられる。

これらの塩のうち好ましくは、アルカリ金属塩またはアルカリ土類金属塩である。とりわけナトリウム塩が好ましい。

本願製剤に用いることのできるＰＰＩとしては、化合物（Ｉ）あるいはその他のベンツイミダゾール系化合物のＰＰＩやイミダゾピリジン系化合物のＰＰＩのプロドラッグ化合物も用いることができる。このようなプロドラッグとしては、例えば、ＷＯ２００３－２７０９８、米国特許４０４５５６３、米国特許６０９３７３４、米国特許５０３９８０６、ＷＯ２００２／３０９２０等に記載のプロドラッグが挙げられる。

化合物（Ｉ）は、自体公知の方法により製造でき、例えば、特開昭６１－５０９７８号、米国特許４，６２８，０９８、特開平１０－１９５０６８号、ＷＯ　９８／２１２０１等に記載の方法またはこれらに準じた方法により製造される。なお、光学活性な化合物（Ｉ）は、光学分割法（分別再結晶法、キラルカラム法、ジアステレオマー法、微生物または酵素を用いる方法など）不斉酸化などの方法で得ることができる。例えばランソプラゾール　Ｒ体の場合は、ＷＯ　００／７８７４５、ＷＯ　０１／８３４７３、ＷＯ　０１／８７８７４およびＷＯ　０２／４４１６７記載の方法に従って製造することもできる。

本発明で用いるＰＰＩとしては、ランソプラゾール、オメプラゾール、ラベプラゾール、パントプラゾールのような抗潰瘍作用を有するベンツイミダゾール系化合物およびテナトプラゾールのようなイミダゾピリジン化合物、またはそれらの光学活性体ならびにそれらの薬学的に許容される塩が好ましい。ＰＰＩとしては、より好ましくはランソプラゾール、オメプラゾール、テナトプラゾールなどであり、特に好ましくはランソプラゾールである。

【0012】

ＰＰＩ化合物の塩としては、化合物（Ｉ）の塩として上記したような薬理学的に許容し得る塩、例えば無機塩基との塩、有機塩基との塩、無機酸との塩、有機酸との塩、塩基性または酸性アミノ酸との塩などが挙げられる。

具体的には、無機塩基との塩の好適な例としては、例えばナトリウム，カリウムなどのアルカリ金属、カルシウム，マグネシウムなどのアルカリ土類金属、ならびにアルミニウム、アンモニウムなどとの塩が挙げられる。

有機塩基との塩の好適な例としては、例えばトリメチルアミン、トリエチルアミン、ピリジン、ピコリン、エタノールアミン、ジエタノールアミン、トリエタノールアミン、ジシクロヘキシルアミン、Ｎ，Ｎ－ジベンジルエチレンジアミンなどとの塩が挙げられる。

無機酸との塩の好適な例としては、例えば塩酸、臭化水素酸、硝酸、硫酸、リン酸などとの塩が挙げられる。

有機酸との塩の好適な例としては、例えばギ酸、酢酸、トリフルオロ酢酸、フマール酸、シュウ酸、酒石酸、マレイン酸、クエン酸、コハク酸、リンゴ酸、メタンスルホン酸、ベンゼンスルホン酸、ｐ－トルエンスルホン酸などとの塩が挙げられる。

塩基性アミノ酸との塩の好適な例としては、例えばアルギニン、リジン、オルニチンなどとの塩が挙げられ、酸性アミノ酸との塩の好適な例としては、例えばアスパラギン酸、グルタミン酸などとの塩が挙げられる。

【0013】

本発明におけるＰＰＩを含有する顆粒、細粒、錠剤としては、通常の経口固形製剤に用いられる顆粒、細粒、錠剤、ペレットなどのマルチプルユニット製剤と称せられる比較的粒度の小さい粒子状固形製剤であればよく、錠剤の場合、ミニタブレットが好ましい。ＰＰＩ含有製剤としては顆粒が通常好ましい。ＮＳＡＩＤ含有顆粒または細粒も同様なマルチプルユニット製剤と称せられる固形製剤であればよいが、顆粒、細粒が好ましく特に顆

粒が好ましい。本発明においては、ＰＰＩ含有顆粒等とＮＳＡＩＤ含有顆粒等を基本的に複数個をカプセルあるいは分包剤に充填した形態で患者に経口投与されるのが好ましい。本発明における顆粒、細粒、錠剤（好ましくはミニタブレット）等のマルチプルユニット製剤（以下総称してマルチプルユニット製剤と称することがある）としては、好ましくは平均粒子径が３ｍｍ以下の粒子状の製剤あるいは直径７ｍｍ以下のミニタブレットが好適である。さらに好ましくは、平均粒子径が２ｍｍ以下の顆粒あるいは細粒である。錠剤の場合には食事の有無によって製剤の胃排出速度が大きく影響され、薬物の体内動態にバラツキが現れやすいが、本発明の製剤はマルチプルユニットであるため、ＰＰＩ及びＮＳＡＩＤの吸収性などの体内動態が食事の有無によって影響されにくいことを特徴とする。

【0014】

本発明において用いられるＰＰＩを含有するマルチプルユニット製剤は酸に不安定であるので、腸溶性基剤で被覆された形態が好ましく、具体的には腸溶性被覆顆粒、腸溶性被覆細粒などの剤形が挙げられる。これらの２種以上を適宜の割合で組み合わせて用いてもよい。これらのうち、特に好ましい剤形は腸溶性被覆顆粒である。

本発明において用いられるＮＳＡＩＤを含有するマルチプルユニット製剤としては、顆粒、細粒、ペレットなどについて、それぞれ速放性、腸溶性、徐放性等の持続性製剤が挙げられるが、これらの２種以上を適宜の割合で組み合わせて用いてもよい。これらのうち、特に好ましい剤形は一日一回投与の持続性顆粒である。このような一日一回投与顆粒等にすることによりＰＰＩと組合わせた製剤は一日一回投与製剤として服薬のコンプライアンスが改善される効果を有する。

【0015】

本発明において用いられるＰＰＩを含有するマルチプルユニット製剤と１種またはそれ以上のＮＳＡＩＤを含有するマルチプルユニット製剤の組合せはユニットに充填された製剤の形態であることが好ましい。ＰＰＩを含有するマルチプルユニット製剤と１種またはそれ以上のＮＳＡＩＤを含有するマルチプルユニット製剤は同一の１つのユニット内に充填されて、混合されていてもよく、また同一ユニット内で混合されることなく別群に分かれて充填されていてもよい。組合せるユニットとしては、カプセル、分包剤などの形態が挙げられるが、カプセルがより好ましい。カプセルとしては、ゼラチン硬カプセル、ヒドロキシプロピルメチルセルロース硬カプセルなどが挙げられる。

【0016】

本発明の固形製剤におけるＰＰＩとＮＳＡＩＤとのとりわけ好ましい組合せは、ランソプラゾールとジクロフェナックナトリウムとの組合せあるいはランソプラゾールとピロキシカムとの組合せである。ＰＰＩと１種またはそれ以上のＮＳＡＩＤは用いる薬剤にもよるが、３対１ないし１対３００の重量比程度で組合わせてユニットに充填するのが好ましい。

例えば、ランソプラゾールとジクロフェナックナトリウムとの組合せの固形製剤の場合、約１対１ないし１対２０の重量比で含有する固形製剤が好ましい。

また、ランソプラゾールとピロキシカムの組合せの固形製剤の場合、約２対１ないし１対２の重量比で含有する固形製剤にするのが通常好適である。

【0017】

本発明におけるＰＰＩあるいはＮＳＡＩＤを含有するマルチプルユニット製剤の密度は約０．５～約２．０であるが、好ましくは約０．７～約１．７である。

本発明の各マルチプルユニット製剤は物理的に十分な硬さを有し、硬カプセルに充填する際にも破損することなく、その特性を維持する。また、輸送時にも硬カプセル内で各マルチプルユニット製剤が破損することなく、その特性を維持する。

本発明におけるＰＰＩを含有する腸溶性マルチプルユニット製剤とＮＳＡＩＤを含有するマルチプルユニット製剤をカプセルに充填して得た製剤は、安定性、配合性に優れ、長期保存後においても製剤が着色することもなく、また各薬物の含量が低下することなく、さらに各薬物の製剤からの溶出性も変化することがないなど優れた特性を有する。

本発明は、このように、プロトンポンプ阻害剤（ＰＰＩ）を含有するマルチプルユニッ

ト製剤と１種またはそれ以上の非ステロイド性抗炎症剤（ＮＳＡＩＤ）を含有するマルチプルユニット製剤とを１つのユニットに充填することを特徴とする固形製剤の新規製造法も提供する。

本発明におけるＰＰＩを含有する腸溶性顆粒とＮＳＡＩＤを含有する顆粒を同一のカプセルに充填して得た製剤を経口投与後の各薬物の体内動態は、ＰＰＩ腸溶性顆粒を含有するカプセルとＮＳＡＩＤ顆粒を含有するカプセルを併用投与時と変わらない。

【0018】

本発明の固形製剤は、製剤技術分野において慣用の添加剤を含有していてもよい。該添加剤としては、例えば賦形剤、崩壊剤、結合剤、滑沢剤、着色剤、ｐＨ調整剤、界面活性剤、安定化剤、酸味料、香料、流動化剤などが挙げられる。これら添加剤は、製剤技術分野において慣用の量が用いられる。

賦形剤としては、例えばトウモロコシデンプン、馬鈴薯デンプン、コムギコデンプン、コメデンプン、部分アルファー化デンプン、アルファー化デンプン、有孔デンプン等のデンプン類；乳糖、果糖、ブドウ糖、マンニトール、ソルビトール等の糖または糖アルコール類：無水リン酸カルシウム、結晶セルロース、沈降炭酸カルシウム、ケイ酸カルシウムなどが挙げられる。

崩壊剤としては、例えばカルボキシメチルセルロース、カルボキシメチルセルロースカルシウム、カルボキシメチルスターチナトリウム、クロスカルメロースナトリウム、クロスポビドン、低置換度ヒドロキシプロピルセルロース、ヒドロキシプロピルスターチ等が用いられる。該崩壊剤の使用量は、固形製剤１００重量部に対して、好ましくは０．５～２５重量部、さらに好ましくは１～１５重量部である。

結合剤としては、例えばヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、ポリビニルピロリドン、アラビアゴム末などが挙げられる。該結合剤の使用量は、固形製剤１００重量部に対して、好ましくは０．１～５０重量部、さらに好ましくは０．５～４０重量部である。結合剤は、好ましくは、ヒドロキシプロピルセルロースあるいはポリビニルピロリドンである。

滑沢剤の好適な例としては、例えばステアリン酸マグネシウム、ステアリン酸カルシウム、タルク、蔗糖脂肪酸エステル、フマル酸ステアリルナトリウムなどが挙げられる。

着色剤としては、例えば食用黄色５号、食用赤色２号、食用青色２号などの食用色素、食用レーキ色素、三二酸化鉄などが挙げられる。

ｐＨ調整剤としては、クエン酸塩、リン酸塩、炭酸塩、酒石酸塩、フマル酸塩、酢酸塩、アミノ酸塩などが挙げられる。

界面活性剤として、ラウリル硫酸ナトリウム、ポリソルベート８０、ポリオキシエチレン（１６０）ポリオキシプロピレン（３０）グリコールなどが挙げられる。

【0019】

安定化剤としては、例えばトコフェロール、エデト酸四ナトリウム、ニコチン酸アミド、シクロデキストリン類などが挙げられる。

酸味料としては、例えばアスコルビン酸、クエン酸、酒石酸、リンゴ酸などが挙げられる。

香料としては、例えばメントール、ハッカ油、レモン油、バニリンなどが挙げられる。

流動化剤としては、例えば軽質無水ケイ酸、含水二酸化ケイ素などが挙げられる。ここで、軽質無水ケイ酸は、含水二酸化ケイ素（$SiO_2 \cdot nH_2O$）　（ｎは整数を示す）を主成分とするものであればよく、その具体例として、例えばサイリシア３２０（商品名、富士シリシア化学（株））、アエロジル２００（商品名、日本アエロジル（株））等が挙げられる。

上記した添加剤は、２種以上を適宜の割合で混合して用いてもよい。

【0020】

本発明で用いられるＰＰＩの含量は、活性成分の種類、投与量によっても異なるが、例えば本発明の固形製剤１００重量部に対して、例えば１～４０重量部、好ましくは３～３０重量部である。

とりわけ、ＰＰＩがランソプラゾールである場合、本発明の固形製剤におけるランソプラゾールの含量は、例えば本発明の固形製剤１００重量部に対して、好ましくは１～４０重量部、さらに好ましくは５～３０重量部である。

本発明の固形製剤中におけるＮＳＡＩＤの含量は、例えば本発明の固形製剤１００重量部に対して、例えば１～６０重量部、好ましくは５～５０重量部である。

とりわけ、ＮＳＡＩＤがジクロフェナックナトリウムである場合、本発明の固形製剤におけるジクロフェナックナトリウムの含量は、例えば本発明の固形製剤１００重量部に対して、好ましくは５～６０重量部、さらに好ましくは１５～５０重量部である。

また、ＮＳＡＩＤがピロキシカムである場合、本発明の固形製剤におけるピロキシカムの含量は、例えば本発明の固形製剤１００重量部に対して、好ましくは５～３０重量部、さらに好ましくは１０～２０重量部である。

【0021】

本発明の固形製剤は、常法に従って、製造することができる。代表的な製法としては、ＰＰＩを含有する製剤、好ましくは腸溶性被覆などコーティングを必要により施したマルチプルユニット製剤およびＮＳＡＩＤを含有するマルチプルユニット製剤を別途製造した後、１つのユニット（好ましくはカプセル）に適量づつを充填することによって製造される。具体的には、例えば、ランソプラゾールとジクロフェナックナトリウム含有製剤の場合、ランソプラゾールの腸溶性顆粒ならびにジクロフェナックナトリウムの徐放性顆粒を別途製造した後、ゼラチン硬カプセルに適量づつを充填することによって製造される。該腸溶性顆粒の製造法は例えば、米国特許第６３６５１８４号明細書に記載される製造法で製造できる。また、該徐放性顆粒の製造法としては、既知の種々の製造法が採用され得るが、例えば、国際公開第ＷＯ０２／２２１０８号に記載される製造法で製造することもできる。

【0022】

上記マルチプルユニット製剤を製造する際のコーティング基剤としては、例えば腸溶性フィルムコーティング基剤、徐放性フィルムコーティング基剤などが挙げられる。

腸溶性フィルムコーティング基剤としては、例えばヒドロキシプロピルメチルセルロース　フタレート、ヒドロキシプロピルメチルセルロース　アセテートサクシネート、カルボキシメチルエチルセルロース、酢酸フタル酸セルロースなどのセルロース系高分子；メタアクリル酸コポリマーＬ〔オイドラギットＬ（商品名）、ロームファルマ社〕、メタアクリル酸コポリマーＬＤ〔オイドラギットＬ－３０Ｄ５５（商品名）、ロームファルマ社〕、メタアクリル酸コポリマーＳ〔オイドラギットＳ（商品名）、ロームファルマ社〕などのアクリル酸系高分子；セラックなどの天然物などが挙げられる。

徐放性フィルムコーティング基剤としては、例えばエチルセルロースなどのセルロース系高分子；アミノアルキルメタアクリレートコポリマーＲＳ〔オイドラギットＲＳ（商品名）、ロームファルマ社〕、アクリル酸エチル・メタアクリル酸メチル共重合体懸濁液〔オイドラギットＮＥ（商品名）、ロームファルマ社〕などのアクリル酸系高分子などが挙げられる。

【0023】

上記したコーティング基剤は、その２種以上を適宜の割合で混合して用いてもよい。また、コーティングの際に、コーティング添加剤を用いてもよい。

該コーティング添加剤としては、例えば酸化チタン、タルク、三二酸化鉄などの遮光剤および／または着色剤；ポリエチレングリコール、クエン酸トリエチル、ヒマシ油、ポリソルベート類などの可塑剤；クエン酸、酒石酸、リンゴ酸、アスコルビン酸などの有機酸などが挙げられる。

【0024】

本発明におけるＰＰＩを含有する腸溶性被覆マルチプルユニット製剤は、マルチプルユニット製剤全量に対して約６重量％～約４０重量％のＰＰＩを含有し、ＰＰＩの１重量部に対し約０．２重量部～約１．０重量部のナトリウム塩、カリウム塩、アルミニウム塩、マグネシウム塩およびカルシウム塩の塩基性塩からなる群から選ばれる１種以上の塩基性

無機塩とを含有するのが好ましい。このような主薬層上に、腸溶性被膜層を設けるのが好適である。必要に応じて、該主薬層上に形成された中間被覆層を有しても良い。

本発明におけるＮＳＡＩＤを含有する徐放性マルチプルユニット製剤は、全量に対して約１５重量％～約６０重量％のＮＳＡＩＤと適当な賦形剤とを含有する主薬層と、アクリル酸系高分子などから成る徐放性被膜層とを有する。

【0025】

本発明で用いる活性成分ＰＰＩおよびＮＳＡＩＤはともに低毒性の医薬であるので、本発明の固形製剤は、哺乳動物（例、マウス、ラット、ウサギ、ネコ、イヌ、ウシ、ウマ、サル、ヒトなど）に対して、経口的に安全に投与することができる。

本発明の固形製剤は、ＮＳＡＩＤによる胃腸障害の予防、治療、軽減効果を有する解熱・鎮痛・抗炎症剤等として有用である。ＮＳＡＩＤとしてアスピリン等を用いた場合、血小板凝集欲製薬、狭心症、心筋梗塞等の予防、治療薬等として有用である。

本願発明の固形製剤は、所望により、その他の薬剤をさらに配合した合剤にしてもよく、また他の薬剤を含む医薬製剤と併用してもよい。このような配合乃至併用薬として、例えば、その他の抗炎症剤、抗生物質（例、ペニシリン系抗生物質（例えば、アモキシシリン等）およびエリスロマイシン系抗生物質（例えば、クラリスロマイシン等））、抗菌剤、制酸剤、選択的ムスカリン受容体拮抗薬、抗ガストリン薬、胃腸運動調節薬（消化管運動促進剤）（モサプリド、シサプリド等の５-HT_4受容体アゴニストなど）等が挙げられる。

【0026】

本発明の固形製剤の投与量は、該固形製剤に含まれるＰＰＩおよびＮＳＡＩＤとしての有効量であればよい。

ここで、ＰＰＩの有効量は、例えば成人（体重６０ｋｇ）１人あたり、通常０．０１～５００ｍｇ／日、好ましくは０．１～１００ｍｇ／日である。

とりわけ、ＰＰＩがランソプラゾールである場合、ランソプラゾールの有効量は、成人（体重６０ｋｇ）１人あたり、通常７．５～６０ｍｇ／日、好ましくは１５～３０ｍｇ／日である。

ＮＳＡＩＤの有効量は、例えば成人（体重６０ｋｇ）１人あたり、通常０．０１～１０００ｍｇ／日、好ましくは０．１～５０００ｍｇ／日である。

とりわけ、ＮＳＡＩＤがフェニル酢酸系化合物（好ましくはジクロフェナックナトリウム、フェンブフェン）である場合、ジクロフェナックナトリウムの有効量は、成人（体重６０ｋｇ）１人あたり、通常１０～５００ｍｇ／日、好ましくは２５～２００ｍｇ／日である。フェンブフェンの有効量は、成人（体重６０ｋｇ）１人あたり、通常６００～１０００ｍｇ／日である。また、ＮＳＡＩＤがプロピオン酸系化合物（好ましくはイブプロフェン、ケトプロフェン、ナプロキセン、ロキソプロフェンナトリウム、プラノプロフェン）である場合、プロピオン酸系化合物（好ましくはイブプロフェン、ケトプロフェン、ナプロキセン、ロキソプロフェンナトリウム）の有効量は、成人（体重６０ｋｇ）１人あたり、通常５０～１０００ｍｇ／日、好ましくは１５０～６００ｍｇ／日である。

また、ＮＳＡＩＤがサリチル酸系化合物（好ましくはアスピリン）である場合、サリチル酸系化合物（好ましくはアスピリン）の有効量は、成人（体重６０ｋｇ）１人あたり、通常１００～５０００ｍｇ／日、好ましくは１０００～４５００ｍｇ／日である。

また、ＮＳＡＩＤがインドール酢酸系化合物（好ましくはインドメタシン、スリンダク）である場合、インドメタシンの有効量は、成人（体重６０ｋｇ）１人あたり、通常１０～１００ｍｇ／日、好ましくは２５～７５ｍｇ／日である。スリンダクの有効量は、成人（体重６０ｋｇ）１人あたり、通常１００～６００ｍｇ／日、好ましくは２５０～３５０ｍｇ／日である。

また、ＮＳＡＩＤがアントラニル酸系化合物（例、メフェナム酸）である場合、アントラニル酸系化合物（例、メフェナム酸）の有効量は、成人（体重６０ｋｇ）１人あたり、通常２００～１０００ｍｇ／日、好ましくは４００～６００ｍｇ／日である。

また、ＮＳＡＩＤがオキシカム系化合物（好ましくはピロキシカム、メロキシカム）で

ある場合、ピロキシカムの有効量は、成人（体重６０ｋｇ）１人あたり、通常１０～５０ｍｇ／日、好ましくは２０～３０ｍｇ／日である。メロキシカムの有効量は、成人（体重６０ｋｇ）１人あたり、通常５～２０ｍｇ／日、好ましくは１０～２０ｍｇ／日である。

また、ＮＳＡＩＤがＣＯＸ－２阻害剤（好ましくはロフェコキシブ、セレコキシブ、バルデコキシブ）である場合、ロフェコキシブの有効量は、成人（体重６０ｋｇ）１人あたり、通常１０～５０ｍｇ／日である。セレコキシブの有効量は、成人（体重６０ｋｇ）１人あたり、通常１００～４００ｍｇ／日、好ましくは２００～４００ｍｇ／日である。バルデコキシブの有効量は、成人（体重６０ｋｇ）１人あたり、通常１０～４０ｍｇ／日である。

本発明の固形製剤の前記哺乳動物への１日あたりの投与回数は、好ましくは１日１ないし２回、さらに好ましくは１日１回である。

【0027】

本発明のＰＰＩおよび１種またはそれ以上のＮＳＡＩＤの投与量の代表例は上記したが、これらは臨床上用いられている用量を基準として適宜選択することができる。また、本発明の固形製剤の配合比は、投与対象、対象疾患、症状、組合わせなどにより適宜選択することができる。例えば投与対象がヒトである場合、ＰＰＩの１重量部に対し、ＮＳＡＩＤを０．５ないし３００重量部用いればよい。より好ましくは、例えば、ランソプラゾールの１重量部に対し、ＮＳＡＩＤを１ないし２０重量部用いればよい。

このように、ＰＰＩのマルチプルユニット製剤とＮＳＡＩＤのマルチプルユニット製剤を組み合わせて用いることにより、ＮＳＡＩＤによる胃腸障害の治療と予防などの優れた効果を有する解熱・鎮痛・抗炎症剤が得られる。

【0028】

以下に実施例を挙げて本発明をさらに詳しく説明するが、本発明はこれらにより限定されるものではない。

なお、以下の実施例において、ステアリン酸マグネシウムなどの各種添加剤としては、日本薬局方第１４改正適合品を用いた。

【0029】

実施例１

ランソプラゾールの腸溶性顆粒は、米国特許第６３６５１８４号明細書に記載される製造法で製造した。また、ジクロフェナックナトリウムの徐放性顆粒は、国際公開第ＷＯ０２／２２１０８号に記載される製造法で製造した。ゼラチン硬カプセル（０号サイズ）にランソプラゾールとして３０ｍｇ相当量含有腸溶性顆粒ならびにジクロフェナックナトリウムとして１００ｍｇ相当量含有徐放性顆粒を充填することによって、目的とする製剤を得た。

【産業上の利用可能性】

【0030】

本発明の固形製剤は、活性成分ＮＳＡＩＤを含有し、慢性関節リウマチ治療薬、変形性関節症治療薬、抗炎症薬、解熱鎮痛薬などとして有用であり、かつ活性成分ＰＰＩの働きにより、ＮＳＡＩＤによる胃腸障害の治療・予防効果を有し、潰瘍等の胃腸障害が軽減できる効果を有する。さらに本発明の製剤は、安定性、配合性に優れ、各薬物の体内動態が併用投与時と変わらず、また食事の影響を受けにくい。

さらに、本発明の固形製剤は、簡便な方法によって容易に製造することができるという工業的実施に有利な特長を有する。

(51)Int.Cl.[7]	F I	テーマコード（参考）
Ａ６１Ｋ　9/48	Ａ６１Ｋ　9/48	
Ａ６１Ｋ　31/196	Ａ６１Ｋ　31/196	
Ａ６１Ｋ　31/4439	Ａ６１Ｋ　31/4439	
Ａ６１Ｐ　29/00	Ａ６１Ｐ　29/00	

Ｆターム(参考) 4C076 AA31 AA36 AA45 AA53 BB01 CC04 CC16 DD41 FF25 FF31
FF67
4C084 AA20 MA02 MA34 MA35 MA37 MA41 MA52 NA06 NA12 NA13
ZA661 ZA662 ZB111 ZB112
4C086 AA02 BC17 GA07 GA08 MA02 MA04 MA34 MA35 MA37 MA41
NA06 NA12 NA13 ZA66 ZB11
4C206 FA31 KA01 MA02 MA04 MA14 MA54 MA55 MA57 MA61 NA06
NA12 NA13 ZA66 ZB11

Electronic Acknowledgement Receipt

EFS ID:	15793636
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	108197
Filer:	Steven Lee Highlander/Richard Ortiz
Filer Authorized By:	Steven Lee Highlander
Attorney Docket Number:	PZAZ.P0002US
Receipt Date:	16-MAY-2013
Filing Date:	24-JUN-2010
Time Stamp:	12:55:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	PZAZP0002US_SIDS.pdf	34972 df22f1b9e92e275c621252f16c5f77265b736229	no	2

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	PZAZP0002US_1449.pdf	31768 e8a4214388540ea5390fffc45b43cd191cb87eb1	no	1
Warnings:					
Information:					
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3	Foreign Reference	PZAZP0002US_REFB13.pdf	1593824 4c590290233975 73d70e20715cef75d6b2454264	no	41
Warnings:					
Information:					
4	Foreign Reference	PZAZP0002US_REFB14.pdf	695422 4ffcdf7c25c89cd0c4b6b1dccaf7cd1517e59c64	no	16
Warnings:					
Information:					
5	Other Reference-Patent/App/Search documents	PZAZP0002US_REFC33.pdf	1132467 8565641c6928f4387ccf6f124d4e1cdc978e55ea	no	7
Warnings:					
Information:					
		Total Files Size (in bytes):	3488453		

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<u>National Stage of an International Application under 35 U.S.C. 371</u>
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<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brian AULT *et al.*	Group Art Unit: 1612
Serial No.: 12/822,612	Examiner: Adam C. Milligan
Filing Date: June 24, 2010	Attorney Docket No.: PZAZ.P0002US
Title: METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER	Confirmation No.: 6136

CERTIFICATE OF ELECTRONIC TRANSMISSION

I hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:

May 16, 2013 /Steven L. Highlander/
Date Steven L. Highlander

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Commissioner:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56, it is respectfully requested that this Supplemental Information Disclosure Statement be entered and the documents listed on attached Form PTO-1449 be considered by the Examiner and made of record. Copies of the listed documents required by 37 C.F.R. § 1.98(a)(2) are attached for the convenience of the Examiner.

In accordance with 37 C.F.R. §§ 1.97(g) and (h), this Supplemental Information Disclosure Statement is not to be construed as a representation that a search has been made, and is not to be construed to be an admission that the information cited is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

In accordance with 37 C.F.R. § 1.97(e)(1), Applicants hereby certify that each item of information contained in this Supplemental Information Disclosure Statement was first cited in any communication from a foreign patent office in a foreign application not more than three months prior to the filing of the present statement, as evidenced by the date of the attached Egyptian office action.

In accordance with 37 C.F.R. § 1.704(d), Applicants hereby certify that each item of information contained in this Information Disclosure Statement was first cited in any communication from a foreign patent office in a counterpart foreign application and that this communication was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty days prior to the filing of this Supplemental Information Disclosure Statement.

It is believed that no fee is due with this communication. However, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to the enclosed document, the Commissioner is authorized to deduct or credit said fees from or to Parker Highlander PLLC Deposit Account No. 50-5902/PZAZ.P0002US.

Applicants respectfully request that the listed documents be made of record in the present application. The examiner is invited to contact the undersigned attorney with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

/Steven L. Highlander/

Steven L. Highlander
Reg. No. 37,642
Attorney for Applicants

Parker Highlander PLLC
1120 S. Capital of Texas Highway
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Austin, Texas 78746
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Date: May 16, 2013

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/822,612	06/24/2010	Brian Ault	PZAZ.P0002US

CONFIRMATION NO. 6136

108197
Parker Highlander PLLC
1120 South Capital of Texas Highway
Bldg. 1, Suite 200
Austin, TX 78746

POA ACCEPTANCE LETTER

OC000000059973390

Date Mailed: 03/28/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/14/2013.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/gbien-aime/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/822,612	06/24/2010	Brian Ault	103786-1 US/NS

CONFIRMATION NO. 6136

POWER OF ATTORNEY NOTICE

22466
ASTRA ZENECA PHARMACEUTICALS LP
GLOBAL INTELLECTUAL PROPERTY
1800 CONCORD PIKE
WILMINGTON, DE 19850-5437

OC000000059973369

Date Mailed: 03/28/2013

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/14/2013.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

/gbien-aime/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Form PTO-1449 (modified)	Atty. Docket No.: PZAZ.P0002US	Serial No.: 12/822,612
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	Applicant: Brian AULT *et al.*	
	Filing Date: June 24, 2010	Group: 1612

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1*	*See Page 1-2*

Exam. Init.	Ref. Des.	Document Number	Date	Name

Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Country	Language

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C24	Bajbouj *et al.*, "A prospective multicenter clinical and endoscopic follow-up study of patients with gastroesophageal reflux disease," *Z. Gastroenterol.*, 43:1303-1307, 2005.
	C25	Chen *et al.*, "Esomeprazole tablet vs. omeprazole capsule in treating erosive esophagitis," *World Journal of Gastroenterology*, 11(20):3112-3117, 2005.
	C26	Fass, "Erosive Esophagitis and Nonerosive Reflux Disease (NERD): Comparison of Epidemiologic, Physiologic, and Therapeutic Characteristics," *J. Clin. Gastroenterol.*, 41(2):131-137, 2007.
	C27	Goldstein *et al.*, "PA32540 (Enteric-coated aspirin 325 mg + immediate-release omeprazole 40mg) is associated with significantly fewer gastric ulcers and significantly less endoscopic erosive esophagitis than enteric-coated aspirin (EC-ASA) alone: Results of two phase 3 studies," *The American Journal of Gastroenterology*, Vol. 107, Suppl. 1, pages S53-S54, 2012.
	C28	Johnson *et al.*, "Esomeprazole once daily for 6 months is effective therapy for maintaining healed erosive esophagitis and for controlling gastroesophageal reflux disease symptoms: A randomized, double-blind, placebo-controlled study of efficacy and safety," *The American Journal of Gastroenterology*, 96(1):27-34, 2001.
	C29	Labenz *et al.*, "Risk factors for erosive esophagitis: A multivariate analysis based on the proGERD study initiative," *American Journal of Gastroenterology*, 99:1652-1656, 2004.
	C30	Miner *et al.*, "PA32540, a tablet containing enteric-coated (EC) aspirin 325 mg and unbuffered immediate-release omeprazole 40 mg, provides percent time gastric pH >4 significantly less than EC omeprazole 40 mg, but with faster onset and less exposure to omeprazole," *Gastroenterology*, Vol. 142, Issue 5, Supplement 1, page S-3, 2012.

{00047759}

EXAMINER:	DATE CONSIDERED:

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

Form PTO-1449 (modified)	Atty. Docket No.: PZAZ.P0002US	Serial No.: 12/822,612
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	Applicant: Brian AULT *et al.*	
	Filing Date: June 24, 2010	Group: 1612

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page 1*	*See Page 1-2*

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C31	Taha *et al.*, "Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase III, randomized, double-blind, placebo-controlled trial," *Lancet*, 374:119-25, 2009.
	C32	Yeomans *et al.*, "Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin," *American Journal of Gastroenterology*, 103:1-9, 2008.

{00047759}

EXAMINER:	DATE CONSIDERED:

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

Electronic Patent Application Fee Transmittal

Application Number:	12822612
Filing Date:	24-Jun-2010
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Filer:	Steven Lee Highlander/Richard Ortiz
Attorney Docket Number:	PZAZ.P0002US

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	15319769
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	108197
Filer:	Steven Lee Highlander/Richard Ortiz
Filer Authorized By:	Steven Lee Highlander
Attorney Docket Number:	PZAZ.P0002US
Receipt Date:	21-MAR-2013
Filing Date:	24-JUN-2010
Time Stamp:	13:38:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$180
RAM confirmation Number	11877
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		PZAZP0002US_SIDS_1449.pdf	1073022 3785b691de24eacff71f840579c16833004463d8	yes	4
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Transmittal Letter		1	2	
	Information Disclosure Statement (IDS) Form (SB08)		3	4	
Warnings:					
Information:					
2	Non Patent Literature	Bajbouj_2005.pdf	3085507 f1338d84d0860a748f2a0d2cd1259c72f5d63630	no	5
Warnings:					
Information:					
3	Non Patent Literature	Chen_2005.pdf	3557181 a6f679fe494452bc48424b6b22687a031ed77112	no	6
Warnings:					
Information:					
4	Non Patent Literature	Fass_2007.pdf	4374715 ccb5a9fcef2c5242486c6a6c2f33a98ed65ff4dd	no	7
Warnings:					
Information:					
5	Non Patent Literature	Goldstein_2012.pdf	1330471 5ded259121f776694298617b63ac90e2422e7bd3	no	2
Warnings:					
Information:					
6	Non Patent Literature	Johnson_2001.pdf	4569082 4b529a0b6372b9616b68af0257e3c083f705da57	no	8
Warnings:					
Information:					
7	Non Patent Literature	Labenz_2004.pdf	2808694 657dfb8ee7f3b6d24da2b95b53c6e2683eabe9f4	no	5
Warnings:					
Information:					
8	Non Patent Literature	Miner_2012.pdf	715519 015707c81304fd80654458d34cf05a2981e13dbd	no	1

Warnings:					
Information:					
9	Non Patent Literature	Taha_2009.pdf	3826547 339bcc271c706bce157eae860b08154a72e5213a	no	7
Warnings:					
Information:					
10	Non Patent Literature	Yeomans_2008.pdf	4564457 90b72589fc802057ac59dae0e652b778fd6a844c	no	9
Warnings:					
Information:					
11	Fee Worksheet (SB06)	fee-info.pdf	30279 36b8ea87407ddc818ff388c690395b1cd27ed01b	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	29935474	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Brian AULT *et al.*

Serial No.: 12/822,612

Filed: June 24, 2010

For: METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER

Group Art Unit: 1612

Examiner: Adam C. Milligan

Atty. Dkt. No.: PZAZ.P0002US

Confirmation No.: 6136

CERTIFICATE OF ELECTRONIC TRANSMISSION

I hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:

March 21, 2013
Date

Steven L. Highlander

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56, it is respectfully requested that this Supplemental Information Disclosure Statement be entered and the documents listed on attached Form PTO-1449 be considered by the Examiner and made of record. Copies of the listed documents required by 37 C.F.R. § 1.98(a)(2) are enclosed for the convenience of the Examiner.

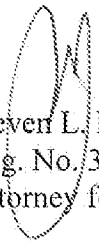
In accordance with 37 C.F.R §§ 1.97(g), (h), this Supplemental Information Disclosure Statement is not to be construed as a representation that a search has been made, and is not to be

construed to be an admission that the information cited is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

A fee as set forth in 37 C.F.R. § 1.17(p) in the amount of $180.00 is enclosed. If an appropriate payment has not been enclosed, or if it is insufficient, the Commissioner is authorized to deduct the appropriate fee from Parker Highlander PLLC Deposit Account No. 50-5902/PZAZ.P0002US.

Applicants respectfully request that the listed documents be made of record in the present case.

Respectfully submitted,



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512-334-2900 (Telephone)
512-334-2999 (Fax)

Date: March 21, 2013

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brian AULT *et al.*	Group Art Unit: 1612
Serial No. 12/822,612	Examiner: Adam C. Milligan
Filed: June 24, 2010	Atty. Dkt. No.: PZAZ.P0002US
For: METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER	Confirmation No.: 6136

CERTIFICATE OF ELECTRONIC TRANSMISSION
37 C.F.R. § 1.8

I hereby certify that this response is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below.

Mar. 14, 2013
Date

/Steven L. Highlander/
Steven L. Highlander

AMENDMENT AND REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.111

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Dear Sir:

This is in response to the Office Action ("the Action") mailed on September 14, 2012, to which a response is now due on March 14, 2013, by virtue of the accompanying Petition for Extension of Time (three months) and payment of fees. No other fees are believed to be due in connection with the filing of this response; however, should any fees be missing or deficient, or should any other fees under 37 C.F.R. §§ 1.16 to 1.21 be deemed necessary for any reason relating to these materials, the Commissioner is authorized to deduct the appropriate fees from Parker Highlander PLLC Deposit Account No.: 50-5902/PZAZ.P0002US/SLH.

Amendments to the Claim begin on page 3 of this response; **Remarks** begin on page 12.

AMENDMENTS TO THE CLAIMS

Listing of Claims

The following listing of claims replaces all previous listings or versions thereof:

1. (Currently amended) A method ~~comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by~~of reducing the incidence of NSAID-associated ulcers in patients at risk of developing such ulcers, wherein the method comprises administering to said patient in need thereof a pharmaceutical composition in unit dose form comprising:

(a) 20 mg of esomeprazole, or pharmaceutically acceptable salt thereof, in ~~an amount~~a form and route sufficient to raise the gastric pH of said patient to at least 3.5 upon administration of one or more of said unit dose forms, and

(b) ~~a therapeutically effective amount of~~375 mg or 500 mg of naproxen, or pharmaceutically acceptable salt thereof; wherein said unit dose form provides for coordinated release of the esomeprazole and the naproxen such that:

(i) at least a portion of said esomeprazole, or pharmaceutically acceptable salt thereof, is released independent of the pH of the surrounding medium; and

(ii) the naproxen, or pharmaceutically acceptable salt thereof, is not released from said unit dose form until the pH of the surrounding medium is 3.5 or higher; and

wherein said pharmaceutical composition in unit dose form ~~decreases the risk of~~reduces the incidence of NSAID-associated ulcers in said patient ~~developing an ulcer~~.

2. (Original) The method according to claim 1, wherein said patient is in need of chronic NSAID treatment.

3. (Previously presented) The method according to claim 1, wherein said disease or disorder is selected from pain and inflammation.

4. (Previously presented) The method according to claim 1, wherein said disease or disorder is selected from osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and a combination thereof.

5. (Previously presented) The method according to claim 1, wherein said patient is taking low dose aspirin.

6. (Previously presented) The method according to claim 1, wherein said pharmaceutical composition decreases the risk of said patient developing a gastroduodenal ulcer.

7. (Previously presented) The method according to claim 1, wherein said pharmaceutical composition decreases the risk of said patient developing a duodenal ulcer.

8. (Previously presented) The method according to claim 1, wherein said pharmaceutical composition decreases the risk of said patient developing a gastric ulcer.

9. (Previously presented) The method according to claim 1, wherein said patient is treated longer with said pharmaceutical composition in unit dose form than with EC-naproxen, or pharmaceutically acceptable salt thereof.

10. (Previously presented) The method according to claim 1, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 1 month.

11. (Previously presented) The method according to claim 1, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 3 months.

12. (Previously presented) The method according to claim 1, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 6 months.

13. (Currently amended) The method according to claim 1, wherein said pharmaceutical composition in unit dose form is a multilayer tablet comprising at least one core and at least a first layer and a second layer, wherein:

(a) said core comprises the naproxen, or a pharmaceutically acceptable salt thereof;

(b) said first layer is a coating that at least begins to release the naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is about 3.5 or greater; and

(c) said second layer [[is]]comprises the esomeprazole, or a pharmaceutically acceptable salt thereof, wherein said esomeprazole, or a pharmaceutically acceptable salt thereof, is released at a pH of from about 0 or greater.

14. (Original) The method according to claim 13, wherein said esomeprazole, or a pharmaceutically acceptable salt thereof, is released at a pH of from about 1 or greater.

15. (Original) The method according to claim 13, wherein said esomeprazole, or a pharmaceutically acceptable salt thereof, is released at a pH of from about 0 to about 2.

16. (Original) The method according to any one of claims 13-15, wherein at least a portion of said esomeprazole, or a pharmaceutically acceptable salt thereof, is not coated with an enteric coating.

17. (Previously presented) The method according to claim 13, wherein said first layer is an enteric coating.

18. (Previously presented) The method according to claim 13, wherein said multi-layer tablet is ~~substantially~~at least about 95% free of sodium bicarbonate.

19. (Previously presented) The method according to claim 13, wherein said first layer begins to release the naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 4.0 or greater.

20. (Previously presented) The method according to claim 13, wherein said first layer begins to release the naproxen, or a pharmaceutically acceptable salt thereof, when the pH of the surrounding medium is at about 4.5 or greater.

21. (Canceled)

22. (Currently amended) The method according to claim 1 or claim 13, wherein the ~~therapeutically effective~~ amount of naproxen, or a pharmaceutically acceptable salt thereof, is ~~selected from 375 mg and~~ 500 mg.

23. (Currently amended) The method according to claim [[22]], wherein the ~~therapeutically effective~~ amount of naproxen, or a pharmaceutically acceptable salt thereof, is 375 mg.

24. (Canceled)

25. (Currently amended) A method comprising~~: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by~~ of reducing the incidence of NSAID-associated ulcers in patients at risk of developing such ulcers, wherein the method comprises administering to the patient a pharmaceutical composition in unit dosage form suitable for oral administration comprising:

(a) 20 mg of esomeprazole or a pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms, and

(b) 375 mg or 500 mg of naproxen or pharmaceutically acceptable salt thereof, wherein the naproxen or a pharmaceutically acceptable salt thereof is surrounded by a coating that is substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of about 37° C; and

wherein said pharmaceutical composition in unit dose form ~~decreases the risk of~~reduces the incidence of NSAID-related ulcers in said patient~~ developing an ulcer~~.

26. (Original) The method of claim 25, wherein the risk is associated with chronic NSAID treatment.

27. (Original) The method of claim 25, wherein the risk is associated with age of the patient.

28. (Original) The method of claim 25, wherein the risk is associated with chronic NSAID treatment and administration of low dose aspirin prior to or during NSAID treatment.

29. (Previously presented) The method of claim 25, wherein the method decreases the risk of the occurrence of a gastroduodenal ulcer.

30. (Previously presented) The method of claim 25, wherein the method decreases the risk of the occurrence of a duodenal ulcer.

31. (Previously presented) The method of claim 25, wherein the patient is treated for a disease or disorder selected from pain, inflammation, osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and combinations thereof.

32-35. (Canceled)

36. (Previously presented) The method of claim 25, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is 375 mg.

37. (Previously presented) The method of claim 25, wherein the amount of naproxen, or a pharmaceutically acceptable salt thereof, is 500 mg.

38. (Previously presented) The method of claim 25, wherein the pharmaceutical composition is formulated to be administered to a patient twice daily.

39. (Previously presented) The method according to claim 25, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 1 month.

40. (Previously presented) The method according to claim 25, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 3 months.

41. (Previously presented) The method according to claim 25, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 6 months.

42. (Previously presented) The method according to claim 25, wherein the unit dosage form is a tablet.

43. (Previously presented) The method according to claim 25, wherein the unit dosage form is a capsule containing beads or minitablets.

44. (Previously presented) The method according to claim 25, wherein the unit dosage form is a tablet comprising a core and two or more layers, in which

(a) the naproxen, or a pharmaceutically acceptable salt thereof, is in the core;

(b) a first layer surrounds the core and is a coating substantially insoluble in aqueous medium at a pH below 3.5 and at a temperature of about 37° C.; and

(c) at least one second layer comprising the esomeprazole, or a pharmaceutically acceptable salt thereof, surrounds the coating of the first layer.

45. (Currently amended) The method according to claim 25, wherein the unit dosage form is a multilayer tablet comprising a core and at least a first layer enclosing the core, and a second layer enclosing the first layer, wherein:

(a) the core comprises the naproxen, or a pharmaceutically acceptable salt thereof;

(b) the first layer is a coating that releases less than 10% of the naproxen or a pharmaceutically acceptable salt thereof after 2 hours when tested using the USP Paddle Method in 1000 ml of 0.1N HCl at 75 rpm at 37° C +/-0.5° C; and

(c) the second layer comprises esomeprazole, or a pharmaceutically acceptable salt thereof and at least one excipient, wherein the second layer is at least 95% soluble after 30 minutes when tested using the USP Paddle Method in 1000 ml of 0.1N HCl for two hours at 75 rpm at 37° C+/-0.5° C.

46. (Previously presented) The method according to claim 44, wherein the unit dosage form further comprises a pharmacologically inert, water soluble coating or film surrounding the outermost layer of the unit dosage form.

47. (Previously presented) The method of claim 46, wherein the inert coating or film comprises a water soluble sugar.

48. (Previously presented) The method of claim 25, wherein administration of the unit dosage form is more effective at reducing the risk of ulcer than treatment with enteric coated naproxen or a pharmaceutically acceptable salt thereof.

49-50. (Canceled)

51. (Currently amended) A method ~~comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by~~of reducing the incidence of NSAID-associated heartburn in patients at risk of developing such heartburns, wherein the method comprises administering to the patient a pharmaceutical composition in unit dosage form suitable for oral administration comprising:

(a) 20 mg of esomeprazole, or a pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms, and

(b) 375 mg or 500 mg of naproxen, or a pharmaceutically acceptable salt thereof, wherein the naproxen, or a pharmaceutically acceptable salt thereof, is surrounded by a coating substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of about 37° C; and

wherein said pharmaceutical composition in unit dose form reduces said patient's heartburn associated symptoms.

52. (Original) The method of claim 51, wherein administration of the unit dosage form reduces said patient's heartburn associated symptoms more than treating said patient with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

53. (Previously presented) The method of claim 51, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 1 month.

54. (Previously presented) The method of claim 51, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 3 months.

55. (Previously presented) The method of claim 51, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 6 months.

56. (Currently amended) A method ~~comprising: treating a disease or disorder in a patient at risk of developing an NSAID-associated ulcer by~~of reducing the incidence of NSAID-associated dyspepsia in patients at risk of developing such dyspepsia, wherein the method comprises administering to the patient a pharmaceutical composition in unit dosage form suitable for oral administration comprising:

(a) 20 mg of esomeprazole, or a pharmaceutically acceptable salt thereof, that is immediately soluble when the dosage form is placed in an aqueous medium, independent of pH, in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms, and

(b) 375 mg or 500 mg of naproxen, or a pharmaceutically acceptable salt thereof, wherein the naproxen or a pharmaceutically acceptable salt thereof is surrounded by a coating substantially insoluble in an aqueous medium at a pH below 3.5 and at a temperature of about 37° C; and

wherein the pharmaceutical composition reduces said patient's dyspepsia associated symptoms.

57. (Original) The method of claim 56, wherein administration of the unit dosage form to the patient reduces the patient's dyspepsia associated symptoms more than treating said patient with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

58. (Previously presented) The method of claim 56, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 1 month.

59. (Previously presented) The method of claim 56, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 3 months.

60. (Previously presented) The method of claim 56, wherein said pharmaceutical composition in unit dose form is administered to said patient twice a day for at least about 6 months.

61. (Original) The method according to claim 1, wherein said ulcer is a gastric ulcer, said patient is $\geq$ 60 years of age, and administration of said unit dose form to said patient results in an 70 to 100% relative risk reduction of said patient developing a gastric ulcer than a patient $\geq$ 60 years of age who is treated with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

62. (Original) The method according to claim 25, wherein said ulcer is a gastric ulcer, said patient is $\geq$ 60 years of age, and administration of said unit dosage form to said patient results in an 70 to 100% relative risk reduction of said patient developing a gastric ulcer than a patient $\geq$ 60 years of age who is treated with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

63. (Original) The method according to claim 61 or 62, wherein the administration of said unit dose form to said patient results in an 89.2% relative risk reduction of said patient developing a gastric ulcer than a patient $\geq$ 60 years of age who is treated with enteric coated naproxen, or a pharmaceutically acceptable salt thereof.

REMARKS

I. Status of the Claims

Claims 1-31 and 33-63 are pending in the application and stand rejected, variously, under 35 U.S.C. §112, first and second paragraphs, 35 U.S.C. §102, 35 U.S.C. §103, and for alleged obviousness-type double-patenting. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 1-31 and 33-63 are rejected as lacking enablement under the first paragraph of §112. Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended as suggested by the Action. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

III. Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1-31 and 33-63 are rejected as indefinite over the use of the term "NSAID-associated" as failing to describe a level of association. Applicants traverse.

The only stated basis for the rejection is that the ***level*** of association is not provided. However, there is no reason that this issue – truly one of breadth – raises indefiniteness concerns. Rather, it is quite clear on the face of the claim that ***any*** level of association is claimed. Moreover, the fact that this interpretation is quite clear to those of skill in the art can be ascertained simply by performing a Google search, which delivers several million hits for the term "NSAID associated ulcer." Thus, it is evident that the use of this term is pervasive, strongly refuting a suggestion that it is unclear.

Reconsideration and withdrawal of the rejection is therefore respectfully requested.

Claim 18 is rejected as indefinite in the use of the term "substantially" in light of the purported absence of a corresponding definition in the specification. Applicants traverse, but in the interest of advancing the prosecution, the claim is amended to recite that the tablet is at least about 95% free of sodium. The specification supports amendment this as follows:

> [0028] The phrase "substantially free" means from about 95% to about 99.99% free. In one embodiment, substantially free means about 95% free. In another embodiment, the term substantially free means about 96% free. In still another embodiment, the term substantially free means about 97% free. In yet another embodiment, the term substantially free means about 98% free. In a further embodiment, the term substantially free means about 99% free. In still a further embodiment, the term substantially free means about 99.99% free.

Reconsideration and withdrawal of the rejection is therefore respectfully requested.

IV. Rejection Under 35 U.S.C. §102(b)

Claims 1, 3, 6-9, 13-17, 19, 20, 22, 24, 25, 29, 30, 35, 37 38, 42, 44, 45, 48-52, 56 and 57 stand rejected as anticipated by U.S. Patent 6,926,907 ("the '907 patent"). Applicants traverse.

Applicants traverse, but in the interest of advancing the prosecution, the claims have been amended such that the recitations of claims 21 and 34 – 20 mg of esomeprazole – are incorporated into each of the independent claims. Since these claims were not rejected under §102(b) it is believed that the rejection is overcome.

Reconsideration and withdrawal of the rejection is therefore respectfully requested.

V. Rejection Under 35 U.S.C. §103

A. The '907 Patent

Claims 2, 4, 5, 10-12, 18, 21, 23, 26-28, 31, 33, 34, 36, 39-41, 43, 53-55 and 58-63 stand rejected as obvious over the '907 patent. Applicants traverse.

The Action argues that the '907 patent teaches pharmaceutical dosage forms, including those containing naproxen and omeprazole, for use in the raising gastric pH in chronic NSAID users. Ranges of 5-100 mg of esomeprazole and naproxen at 250 and 500 mg are said to be disclosed. However, it is acknowledged that the '907 patent fails to teach (a) specific time periods over a week or (b) administration to certain specific patient populations. Nonetheless, the Action considers the '907 patent to render the instant claims obvious as (a) the specific time periods are obvious in view of "chronic" administration, and (b) the specifically claimed subset of patients "are included in the group of patients needing prolonged NSAID treatment." It is also implied that the specific doses now claimed also are missing, but that they are encompassed in the ranges provided and hence *prima facie* obvious.

However, in point of fact, the '907 patent fails to teach or suggest more of what is presently claimed than the Action acknowledges. Furthermore, the lack of specific teachings in the '907 patent are not so easily swept away as "obvious" variations of the method.

1. Elements Missing from the '907 Patent

As stated above, the Action does concede that the specific duration of treatment and the particular patient subsets are missing from the '907 patent. It is also apparently acknowledged that specific dosages of both naproxen (375 mg) and esomeprazole (20 mg) are missing. Finally, the reference also lacks a specific teaching of the combination of naproxen with esomeprazole. Thus, in every sense, the present invention constitutes a 'selection invention' from among numerous different broader categories set forth in the '907 patent.

2. Lack of a *Prima Facie* Case

As explained above, to arrive at the presently claimed invention, the following selections from the '907 patent are required:

- select one NSAID among 24 of such agents; then
- select one gastric acid inhibitor among 12 such agents; then
- select one dosage for the gastric acid inhibitor and two for the NSAID; then
- select a duration of treatment; and then
- select patient subsets for treatment.

It must be appreciated, immediately, that the first two choices alone constitute some 288 options from which the skilled artisan must select just one to arrive at the claimed invention. And further, the choice of esomeprazole runs counter to the '907 patent's suggestion that famotidine was the most preferred gastric acid inhibitor[1]. In terms of dosage, naproxen was suggested at 275 mg and 550 mg, neither of which can be found in the claims above; similarly, esomeprazole was suggested at 40 mg, which is not presently claimed. Thus, this increases not only the sheer number of options, but the very nature applicants' selection of esomeprazole. Finally, both the duration and treatment population would have to be added into this calculus. Whatever the final number of options, they are ***at least*** in the many thousands.

Applicants acknowledge the Action's reliance on MPEP §2144.05, and cases cited therein such as *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) and *In re Geisler*, 116 F.3d 1465, 1469-71, 43 USPQ2d 1362, 1365-66 (Fed. Cir. 1997). However, if a reference's disclosed "range" is so broad as to encompass a very large number of possible distinct compositions – clearly the case here – this might present a situation more analogous to the

[1] "Preferably, the acid inhibitor is an H2 blocker and, in the most preferred embodiment, it is famotidine at a dosage of between 5 mg and 100 mg." '907 patent, col. 4, lines 42-45.

obviousness of a species when the prior art broadly discloses a genus. See *In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Indeed, there is specific instruction in MPEP §2144.05 to examine MPEP § 2144.08 when these facts exist, which applicants explain below as a more relevant guide for analyzing the inventiveness of the present claims.

MPEP §2144.08 addresses the situation of "when a single prior art reference which discloses a genus encompassing the claimed species or subgenus but does not expressly disclose the particular claimed species or subgenus." The MPEP instructs office personnel, in that situation, to find additional prior art to show that the differences between the prior art primary reference and the claimed invention as a whole would have been obvious. Where such additional prior art is not found, office personnel should determine whether the claimed species or subgenus would have been obvious to those of skill in the art. Further, a determination of patentability under 35 U.S.C. §103 should be made upon the facts of the particular case in view of the totality of the circumstances. See, *e.g.*, *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (*in banc*). The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) (Federal Circuit has "decline[d] to extract from *Merck* [*& Co. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989)] the rule that... regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it."). See also *In re Deuel*, 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995).

Like any proper obviousness analysis, a three-step process should be employed. First, Office personnel should establish a *prima facie* case of unpatentability considering the factors set out by the Supreme Court in *Graham v. John Deere*. See, e.g., *In re Bell*, 991 F.2d 781, 783, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993) ("The PTO bears the burden of establishing a case of *prima facie* obviousness."); *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), requires that to make out a case of obviousness, one must:

(A) determine the scope and contents of the prior art;

(B) ascertain the differences between the prior art and the claims in issue;

(C) determine the level of ordinary skill in the pertinent art; and

(D) evaluate any evidence of secondary considerations.

Only when a *prima facie* case is established does the burden shifts to applicant to come forward with rebuttal evidence or argument to overcome the *prima facie* case. See, *e.g.*, *Bell*, 991 F.2d at 783-84, 26 USPQ2d at 1531; *Rijckaert*, 9 F.3d at 1532, 28 USPQ2d at 1956; *Oetiker*, 977 F.2d at 1445, 24 USPQ2d at 1444.

As an initial matter, office personnel are instructed to determine the scope and content of the relevant prior art. In the case of a prior art reference disclosing a genus, Office personnel should make findings as to:

(A) the structure of the disclosed prior art genus and that of any expressly described species or subgenus within the genus;

(B) any physical or chemical properties and utilities disclosed for the genus, as well as any suggested limitations on the usefulness of the genus, and any problems alleged to be addressed by the genus;

(C) the predictability of the technology; and

(D) the number of species encompassed by the genus taking into consideration all of the variables possible.

Then the Action should then compare the prior art genus it to the claimed species or subgenus to determine the differences. Through this comparison, the closest disclosed species or subgenus in the prior art reference should be identified and compared to that claimed. In *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1537, 218 USPQ 871, 877 (Fed. Cir. 1983), the Court noted that "the question under 35 U.S.C. § 103 is not whether the differences [between the claimed invention and the prior art] would have been obvious" but "whether the claimed invention ***as a whole*** would have been obvious." (emphasis in original). Next, and this is highly relevant to the present situation, the Action should determine whether it would have been obvious to one of ordinary skill in the relevant art to make the claimed invention ***as a whole***, *i.e.*, to select the claimed species or subgenus from the disclosed prior art genus.

In determining whether the selection of the claimed species or subgenus, the Action is ***specifically directed to consider the size of the prior art genus***, bearing in mind that size alone cannot support an obviousness rejection. See, *e.g.*, *Baird*, 16 F.3d at 383, 29 USPQ2d at 1552 (observing that "it is not the mere number of compounds in this limited class which is significant here but, rather, the total circumstances involved"). There is no absolute correlation between the size of the prior art genus and a conclusion of obviousness. *Id.* Thus, the mere fact that a prior art genus contains a small number of members does not create a *per se* rule of obviousness.

However, a genus ***may*** be so small that, when considered in light of the totality of the circumstances, it would anticipate the claimed species or subgenus. For example, it has been held that a prior art genus containing only 20 compounds and a limited number of variations in the generic chemical formula inherently anticipated a claimed species within the genus because "one skilled in [the] art would ... envisage ***each member***" of the genus. *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962) (emphasis in original).

Here, referring again to the many thousands of options set out by the '907 patent, applicants submit that this case is far more like the facts of *In re Jones* or *In re Baird* than it is of *In re Petering*. Indeed, in making an obviousness determination, the Action should consider the number of variables which must be selected or modified, and the nature and significance of the differences between the prior art and the claimed invention. See, *e.g.*, *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992)

Also, if the prior art reference expressly teaches a particular reason to select the claimed species or subgenus, the Action should point out the express disclosure and explain why it would have been obvious to one of ordinary skill in the art to select the claimed invention. Other than noting that naproxen is used in some of the examples, nothing of the kind has been offered here. In addition, the Action must consider any teaching or suggestion in the reference of a preferred species or subgenus that is significantly different in structure from the claimed species or subgenus. Such a teaching may weigh against selecting the claimed species or subgenus and thus against a determination of obviousness. *Baird*, 16 F.3d at 382-83, 29 USPQ2d at 1552 (reversing obviousness rejection of species in view of large size of genus and disclosed "optimum" species which differed greatly from and were more complex than the claimed species). Here, the discussed preference for famotidine in the '907 patent would have steered the skilled artisan

towards famotidine rather than esomeprazole, presenting a factor that, according to *Baird*, argues in favor of non-obviousness.

Based on the evidence as a whole (*In re Bell*, 991 F.2d 781,784, 26 USPQ2d 1529, 1531 (Fed. Cir. 1993); *In re Kulling*, 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1057 (Fed. Cir. 1990)), the Action should make express fact-findings relating to the *Graham* factors, focusing primarily on the prior art teachings discussed above. Importantly, these fact-findings should ***specifically articulate what teachings or suggestions in the prior art would have motivated one of ordinary skill in the art to select the claimed species or subgenus***. *Kulling*, 897 F.2d at 1149, 14 USPQ2d at 1058; *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1579 n.42, 1 USQP2d 1593, 1606 n.42 (Fed. Cir. 1987). Here, the rejection simply posits that certain features of the present claims are generically described in the cited art. This is insufficient to establish obviousness, particularly where the claimed selection is one of thousands of options, and at least one of the features recited is considered less preferred. Thus, no *prima facie* case has been established, and the rejection should be withdrawn.

B. The '907 Patent in view of Phillips

Claims 46 and 47 are rejected over the '907 patent in view of Phillips (U.S. Patent Publn. 2004/0048896). Applicants traverse.

Here, the Action has cited the '907 patent exactly as above, and simply added the teachings of Phillips with respect to the inert, water-soluble coating of claims 46 and 47. As such, the rejection still suffers from the defects outline above – namely, that the'907 patent fails to specifically teach or suggest the very particular selection as now claimed from among the thousands of options offered by the '907 patent. Reconsideration and withdrawal of the rejection, for the reasons presented above, is therefore respectfully requested.

VI. Rejection for Obviousness-Type Double-Patenting

Claims 1-31 and 33-63 are rejected over claims 1-20 of copending application U.S. Serial No. 12/823,082 in view of the '907 patent. In light of the provisional nature of the rejection, applicants defer a response until one of the applications is in condition for allowance.

Claims 1-31 and 33-63 are rejected over claims 1-20 of copending application U.S. Serial No. 13/345,075 in view of the '907 patent. In light of the provisional nature of the rejection, applicants defer a response until one of the applications is in condition for allowance.

VII. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to the effect is earnestly solicited. The examiner is invited to contact the undersigned representative with any questions or concerns regarding this submission or the application.

Respectfully submitted,

Steven L. Highlander
Reg. No. 37,642

Date: March 14, 2013

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PTO/SB/22 (10-12)
Approved for use through 1/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number (Optional): PZAZ.P0002US

Application Number: 12/822,612

Filed: June 24, 2010

For: Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer

Art Unit: 1612

Examiner: Adam C. Milligan

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above-identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

	Fee	Small Entity Fee	
☐ One month (37 CFR 1.17(a)(1))	$150	$75	$
☐ Two months (37 CFR 1.17(a)(2))	$570	$285	$
☒ Three months (37 CFR 1.17(a)(3))	$1,290	$645	$ 1,290.00
☐ Four months (37 CFR 1.17(a)(4))	$2,010	$1,005	$
☐ Five months (37 CFR 1.17(a)(5))	$2,730	$1,365	$

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 50-5902/PZAZ.P0002US.

☒ Payment made via EFS-Web.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71. 37 CFR 3.73(b) statement is enclosed (Form PTO/SB/96).

☒ attorney or agent of record. Registration number 37,642.

☐ attorney or agent acting under 37 CFR 1.34. Registration number _____.

Signature

March 14, 2013
Date

Steve L. Highlander, Reg. No. 37,642
Typed or printed name

512-334-2900
Telephone Number

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.

☐ * Total of _____ forms are submitted.

MODIFIED PTO/SB/96 (04-07)

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Brian AULT, Clara HWANG, Everardus ORLEMANS, Mark SOSTEK and John R. PLACHETKA

Application No./Patent No. 12/822,612 Filed/Issue Date: June 24, 2010

Entitled: METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER

POZEN INC., a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☐ the assignee of the entire right, title, and interest;

2. ☐ an assignee of less than the entire right, title and interest.
The extent (by percentage) of its ownership interest is _____ %; or

3. ☒ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

in the patent application/patent identified above by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Everardus ORLEMANS and John R. PLACHETKA To: Pozen Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 028860, Frame 0880, or for which a copy thereof is attached.

2. From: Pozen Inc. To: AstraZeneca AB
The document was recorded in the United States Patent and Trademark Office at
Reel 028861, Frame 0035, or for which a copy thereof is attached.

3. From: AstraZeneca AB To: AstraZeneca AB and Pozen Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 028861, Frame 0066, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being submitted for recordation pursuant to 37 CFR 3.11.
[NOTE: A separate copy *(i.e.,* a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature	March 14, 2013 Date
Steven L. Highlander, Reg. No. 37,642 Printed or Typed Name	(512) 334-2900 Telephone Number
Attorney Title	PZAZ.P0002US File Code

Form PTO-1449 (modified)	Atty. Docket No.: PZAZ.P0002US	Serial No.: 12/822,612
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT (Use several sheets if necessary)	Applicant: **Brian AULT *et al.***	
	Filing Date: June 24, 2010	Group: 1612

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page2*	*See Pages 2-4*

U.S. Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Name	Class	Sub Class	Filing Date of App.
	A1	2001-0036473	11/01/01	Scott *et al.*	424	463	04/17/01
	A2	2001-0044410	11/22/01	Gelber *et al.*	514	27	01/05/01
	A3	2002-0111370	08/15/02	Bergman *et al.*	514	338	12/20/01
	A4	2002-0155153	12/24/02	Depui *et al.*	424	452	03/04/02
	A5	2002-0160046	10/31/02	Robinson *et al.*	424	469	11/21/01
	A6	2003-0040537	02/27/03	Plachetka *et al.*	514	406	09/26/02
	A7	2003-0129235	07/10/03	Chen *et al.*	424	470	10/28/02
	A8	2003-0232876	12/18/03	Plachetka	514	419	04/16/03
	A9	2004-0022846	02/05/04	Depui *et al.*	424	452	07/17/03
	A10	2004-0180089	09/16/04	Plachetka *et al.*	424	4	12/22/03
	A11	2005-0249811	11/10/05	Plachetka	424	472	05/16/05
	A12	2006-0177504	08/10/06	Sudharadas	424	488	02/08/06
	A13	2007-0207200	09/06/07	Plachetka *et al.*	424	451	03/02/07
	A14	2009-0297594	12/03/09	Depui *et al.*	424	451	02/09/09
	A15	5,690,960	11/25/97	Bengtsson *et al.*	424	480	09/27/94
	A16	5,872,145	02/16/99	Plachetka	514	415	08/14/97
	A17	6,060,499	05/09/00	Plachetka	514	415	09/11/98
	A18	6,126,816	10/03/00	Ruiz Jr.	210	95	07/14/99
	A19	7,030,162	04/18/06	Plachetka *et al.*	514	619	09/26/02
	A20	7,060,694	06/13/06	Plachetka *et al.*	514	177	10/29/02
	A21	7,332,183	02/19/08	Plachetka *et al.*	424	472	12/22/03

EXAMINER:	DATE CONSIDERED:

EXAMINER: INITIAL IF REFERENCE CONSIDERED, WHETHER OR NOT CITATION IS IN CONFORMANCE WITH MPEP609; DRAW LINE THROUGH CITATION IF NOT IN CONFORMANCE AND NOT CONSIDERED. INCLUDE COPY OF THIS FORM WITH NEXT COMMUNICATION TO APPLICANT.

Form PTO-1449 (modified)	Atty. Docket No.: PZAZ.P0002US	Serial No.: 12/822,612
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT	Applicant: Brian AULT *et al.*	
(Use several sheets if necessary)	Filing Date: June 24, 2010	Group: 1612

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page2*	*See Pages 2-4*

Foreign Patent Documents

Exam. Init.	Ref. Des.	Document Number	Date	Country	Language
	B1	EP 0 005 129 A1	10/31/79	Europe	English
	B2	EP 0 124 495 A2	11/07/84	Europe	English
	B3	EP 0 166 287 A1	01/02/86	Europe	German (English Abstract)
	B4	EP 0 167 958 A2	01/15/86	Europe	English
	B5	EP 0 174 726 A1	03/19/86	Europe	English
	B6	EP 0 244 380 A2	11/04/87	Europe	English
	B7	EP 0 244 380 B1	11/04/87	Europe	English
	B8	EP 0 426 479 A1	05/08/91	Europe	English
	B9	EP 0 550 083 A1	07/07/93	Europe	English
	B10	EP 1 020 461 A2	07/19/00	Europe	English
	B11	EP 1 068 867 A2	01/17/01	Europe	English
	B12	WO 2002/98352	12/12/02	WIPO	English

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C1	"Astrazeneca AB, Astrazeneca LP, KBI-E Inc., and Pozen, Inc. v Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd.: Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratories Ltd's. Invalidity contentions pursuant to L. Pat. R. 3.6(c)," dated November 23, 2011.
	C2	"Astrazeneca AB, Astrazeneca LP, KBI-E Inc., and Pozen, Inc. V Lupin Ltd. And Lupin Pharmaceuticals, Inc.: Defendants Lupin Ltd. And Lupin Pharmaceuticals, Inc's Amended Invalidity Contentions Pursuant to L. PAT. R. 3.3 and 3.6(c)," dated April 20, 2012.
	C3	"Astrazeneca AB, Astrazeneca LP, KBI-E Inc., and Pozen, Inc. v Lupin Ltd. And Lupin Pharmaceuticals Inc.: Defendants Lupin Ltd. And Lupin Pharmaceuticals, Inc.'s Invalidity Contentions Pursuant to L. Pat. R. 3.3 and 3.6(c)," dated November 23, 2011.
	C4	"Astrazeneca AB, Astrazeneca LP, KBI-E Inc., and Pozen, Inc. v. Anchen Pharmaceuticals, Inc.: Anchen's Initial Invalidity Contentions," dated May 11, 2012.

Form PTO-1449 (modified)	Atty. Docket No.: PZAZ.P0002US	Serial No.: 12/822,612
List of Patents and Publications for Applicant's INFORMATION DISCLOSURE STATEMENT	Applicant: Brian AULT *et al.*	
(Use several sheets if necessary)	Filing Date: June 24, 2010	Group: 1612

U.S. Patent Documents	Foreign Patent Documents	Other Art
See Page 1	*See Page2*	*See Pages 2-4*

Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C5	"Astrazeneca AB, Astrazeneca LP, KBI-E Inc., and Pozen, Inc. v. Dr. Reddy's Laboratories Inc. and Dr. Reddy's Laboratoriese Ltd.: Plaintiffs' Response to DRL's First Set of Interrogatories to Plaintiffs (Nos. 1-5)," dated March 5, 2012.
	C6	"Notice of Paragraph IV Certification Re: Dr. Reddy's Laboratories, Ltd.'s and Dr. Reddy's Laboratories, Inc.'s Naproxen and Esomeprazole Magnesium Delayed Release Tablets; U.S. Patent No. 6,926,907, from Dr. Reddy's Laboratories, Ltd./Dr. Reddy's Laboratories, Inc., dated March 11, 2011.
	C7	European Search Report issued in European Patent Application No. 09178773, dated February 11, 2010.
	C8	Jacques *et al.*, "Final purification, enrichment, of partially resolved enantiomer mixtures," In: *Enantiomers, Racemates, and Resolutions*, 423-434, 1981.
	C9	Letter to European Patent Office for European Application No. 02 734 602.2, regarding Oral Proceedings dated December 18, 2009.
	C10	Notice of Opposition to a European Patent, submitted against European Patent Publication No. EP 1 411 900 on April 15, 2011.
	C11	Notice of Opposition to a European Patent, submitted against European Patent Publication No. EP 1 411 900 on April 20, 2011.
	C12	Office Communication issued in European Patent Application 10177150.9, dated November 12, 2010.
	C13	Office Communication issued in European Patent Application No. 02734602.2, dated February 22, 2010.
	C14	Office Communication issued in European Patent Application No. 02734602.2, dated April 29, 2010.
	C15	Office Communication issued in European Patent Application No. 0273602.2, dated June 21, 2010.
	C16	PCT International Preliminary Report on Patentability issued in International Application No. PCT/US2009/003281 dated December 9, 2010.
	C17	PCT International Search Report and Written Opinion issued in International Application No. PCT/US2010/039864, dated August 30, 2010.
	C18	PCT International Search Report issued in International Application No. PCT/US2002/17105, dated March 14, 2003.

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Other Art (Including Author, Title, Date Pertinent Pages, Etc.)

Exam. Init.	Ref. Des.	Citation
	C19	Ramage *et al.*, "Inhibition of food stimulated acid secretion by misoprostol, an orally active synthetic E1 analogue prostaglandin," *Br. J. Clin Pharmac.*, 19:9-12, 1985.
	C20	*Remington's Pharmaceutical Sciences*, 17th ed., University of Sciences in Philadelphia, 1985.
	C21	Response to Office Communication filed in European Patent Application No. 02734602.2, dated May 10, 2010.
	C22	Takeuchi *et al.*, "Effects of topical application of acidified omeprazole on acid secretion and transmucosal potential difference in anesthetized rat stomachs," *Japan J. Pharmacol.*, 47:397-1988.
	C23	Wilson *et al.*, "Effects of misoprostol on gastric acid and mucus secretion in man," *Digestive Diseases and Sciences*, 31(2): 126S-129S, 1986.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 005 129
A1

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 79850022.9

(22) Date of filing: 03.04.79

(51) Int. Cl.²: C 07 D 403/12
A 61 K 31/44

(30) Priority: 14.04.78 SE 7804231

(43) Date of publication of application:
31.10.79 Bulletin 79/22

(84) Designated Contracting States:
BE CH DE FR GB IT LU NL SE

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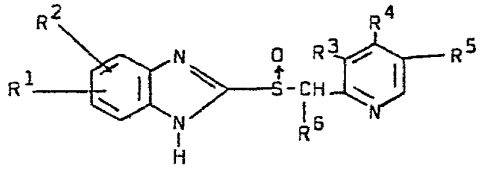
(54) **Substituted pyridylsulfinylbenzimidazoles having gastric acid secretion properties, pharmaceutical preparations containing same, and intermediates for their preparation.**

(57) The present invention relates to novel compounds of the formula



wherein R^1 and R^2 are same or different and are each hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, or alkanoyl, R^6 is hydrogen, methyl or ethyl, R^3, R^4 and R^5 are same or different and are each hydrogen, methyl, methoxy, ethoxy, methoxyethoxy or ethoxyethoxy whereby R^3, R^4 and R^5 are not all hydrogen, and whereby when two of R^3, R^4 and R^5 are hydrogen the third of R^3, R^4 and R^5 is not methyl. The compounds are potent gastric acid secretion inhibitors.

EP 0 005 129 A1

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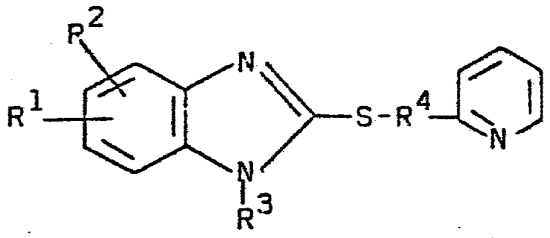
KH 575-1
79-03-07
UI/LB/EMH

Substituted pyridylsulfinylbenzimidazoles having gastric acid secretion properties, pharmaceutical preparations containing same, and intermediates for their preparation

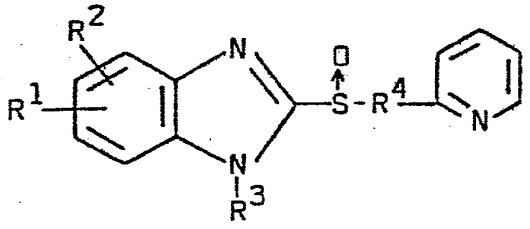
The present invention relates to new compounds having valuable properties in affecting gastric acid secretion in mammals, including man, as well as the process for their preparation, method of affecting gastric acid secretion and pharmaceutical preparations containing said novel compounds.

The object of the present invention is to obtain compounds which affect gastric acid secretion, and which inhibit exogenously or endogenously stimulated gastric acid secretion. These compounds can be used in the treatment of peptic ulcer disease.

It is previously known that compounds of the formulas I and II



(I)

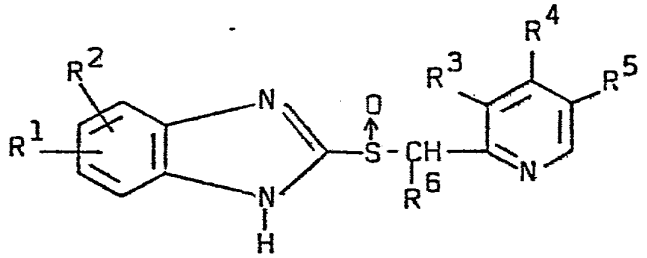


(II)

wherein R^1 and R^2 are each selected from the group consisting of hydrogen, alkyl, halogen, cyano, carboxy, carboxyalkyl, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoyloxy, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl and acyl in any position, R^3 is selected from the group consisting of hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl, and alkylsulphonyl, and R^4 is selected from the group consisting of straight and branched alkylene groups having 1 to 4 carbon atoms, whereby at most one methylene group is present between S and the pyridyl group, and whereby the pyridyl group may be further substituted with alkyl or halogen, possess inhibiting effect of gastric acid secretion.

It has now, however, surprisingly been found that the compounds defined below possess a still greater inhibiting effect than those given above.

Compounds of the invention are those of the general formula III



(III)

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, and R^3, R^4 and R^5 are same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4 and R^5 is not methyl.

Alkyl R^1 and R^2 of formula III are suitably alkyl having up to 7 carbon atoms, preferably up to 4 carbon atoms. Thus, alkyl R may be methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl.

Halogen R^1 and R^2 is chloro, bromo, fluoro, or iodo.

Alkoxy R^1 and R^2 are suitably alkoxy groups having up to 5 carbon atoms, preferably up to 3 carbon atoms, as methoxy, ethoxy, n-propoxy, or isopropoxy.

Alkanoyl R^1 and R^2 have preferably up to 4 carbon atoms and are e.g. formyl, acetyl, or propionyl, preferably acetyl.

A preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, alkoxy, and alkanoyl, whereby R^1 and R^2 are not both hydrogen, R^6 is hydrogen, and R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, and ethoxy, whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen the third of R^3, R^4, and R^5 is not methyl.

A second preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, R^3 is methyl, R^4 is methoxy, and R^5 is methyl.

A third preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 is hydrogen, R^4 is methoxy and R^5 is methyl or R^3 is methyl, R^4 is methoxy and R^5 is hydrogen.

A fourth preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, R^3 and R^5 are hydrogen and R^4 is methoxy.

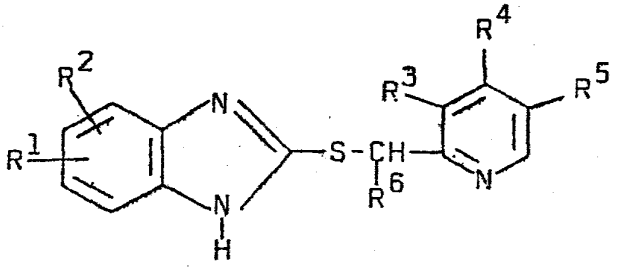
A fifth preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 and R^5 are methyl and R^4 is hydrogen.

A sixth preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, R^3 and R^5 are hydrogen and R^4 is ethoxy, methoxyethoxy or ethoxyethoxy.

A seventh preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, R^3, R^4, and R^5 are all methyl.

Compounds of formula III above may be prepared according to the following methods:

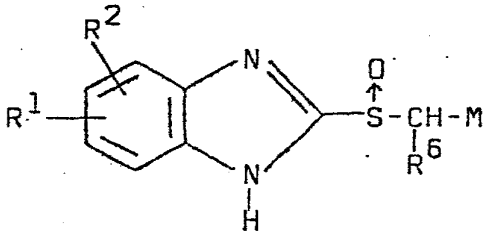
a) oxidizing a compound of formula IV



(IV)

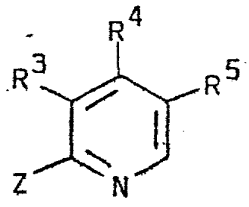
wherein R^1, R^2, R^6, R^3, R^4, and R^5 have the meanings given, to the formation of a compound of formula III.

b) reacting a compound of the formula V



(V)

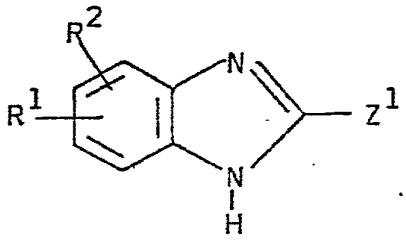
wherein R^1, R^2, and R^6 have the meanings given above and M is a metal selected from the group consisting of K, Na and Li, with a compound of formula VI.



(VII)

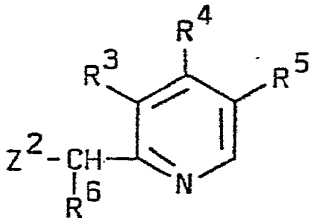
wherein R^3, R^4, and R^5 have the same meanings as given above, Z is a reactive esterified hydroxy group, to the formation of a compound of formula III;

c) reacting a compound of the formula VII



(VII)

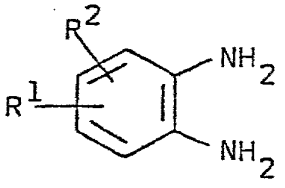
wherein R^1, and R^2 have the same meanings as given above and Z^1 is SH or a reactive esterified hydroxy group, with a compound of the formula VIII



(VIII)

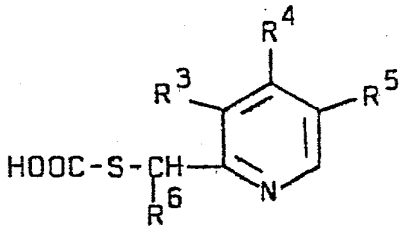
wherein R^6, R^3, R^4, and R^5 have the same meanings as given above, and Z^2 is a reactive esterified hydroxy group or SH, to the formation of an intermediate of formula IV above, which then is oxidized to give a compound of formula III;

d) reacting a compound of the formula IX



(IX)

wherein R^1 and R^2 have the same meanings as given above with a compound of the formula X



(X)

wherein R^6, R^3, R^4, and R^5 have the same meanings as given above, to the formation of an intermediate of formula IV above, which then is oxidized to give a compound of formula III, which compound may be converted to its therapeutically acceptable salts, if so desired.

In the reactions above, Z, Z^1, and Z^2 may be a reactive, esterified hydroxy group which is a hydroxy group esterified with strong, inorganic or organic acid, preferably a hydrohalogen acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid, also sulfuric acid or a strong organic sulfonic acid as a strong aromatic acid, e.g. benzenesulfonic acid, 4-bromobenzenesulfonic acid or 4-toluenesulfonic acid.

The oxidation of the sulfur atom in the chains above to sulfinyl (S→O) takes place in the presence of an oxidizing agent selected from the group consisting of nitric acid, hydrogen peroxide, peracids, peresters, ozone, dinitrogentetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite, diazobicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, cericammonium nitrate, bromine, chlorine, and sulfuryl chloride. The oxidation usually takes place in a solvent wherein the oxidizing agent is present in some excess in relation to the product to be oxidized.

Depending on the process conditions and the starting materials, the end product is obtained either as the free base or in the acid addition salt, both of which are included within the scope of the invention. Thus, basic, neutral or or mixed salts may be obtained as well as hemi,. mono, sesqui

or polyhydrates. The acid addition salts of the new compounds may in a manner known per se be transformed into free base using basic agents such as alkali or by ion exchange. On the other hand, the free bases obtained may form salts with organic or inorganic acids. In the preparation of acid addition salts preferably such acids are used which form suitable therapeutically acceptable salts. Such acids include hydrohalogen acids, sulfonic, phosphoric, nitric, and perchloric acids; aliphatic, alicyclic, aromatic, heterocyclic carboxy or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, antranilic, p-hydroxybenzoic, salicylic or p-aminosalicylic acid, embonic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogenbenzenesulfonic, toluenesulfonic, naphtylsulfonic or sulfanilic acids; methionine, tryptophane, lysine or arginine.

These or other salts of the new compounds, as e.g. picrates, may serve as purifying agents of the free bases obtained. Salts of the bases may be formed, separated from solution, and then the free base can be recovered from a new salt solution in a purer state. Because of the relationship between the new compounds in free base form and their salts, it will be understood that the corresponding salts are included within the scope of the invention.

Some of the new compounds may, depending on the choice of starting materials and process, be present as optical isomers or racemate, or if they contain at least two asymmetric carbon atoms, be present as an isomer mixture (racemate mixture).

The isomer mixtures (racemate mixtures) obtained may be separated into two stereoisomeric (diastereomeric) pure racemates by means of chromatography or fractional crystal-

lization.

The racemates obtained can be separated according to known methods, e.g. recrystallization from an optically active solvent, use of microorganisms, reactions with optically active acids forming salts which can be separated, separation based on different solubilities of the diastereomers. Suitable optically active acids are the L- and D-forms of tartaric acid, di-o-tolyl-tartaric acid, malic acid, mandelic acid, camphorsulfonic acid or quinic acid, Preferably the more active part of the two antipodes is isolated.

The starting materials are known or may, if they should be new, be obtained according to processes known per se.

In clinical use the compounds of the invention are administered orally, rectally or by injection in the form of a pharmaceutical preparation which contains an active component either as a free base or as a pharmaceutically acceptable, non-toxic acid addition salt, such as hydrochloride, lactate, acetate, sulfamate, in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semisolid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1 to 95 % by weight of the preparation, between 0.5 to 20 % by weight in preparations for injection and between 2 and 50 % by weight in preparations for oral administration.

In the preparation of pharmaceutical preparations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as with an antifriction agent such as magnesium stearate, calcium stearate, and polyethyleneglycol waxes. The mixture is then pressed

into tablets. If coated tablets are desired, the above prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide or with a lacquer dissolved in volatile organic solvent or mixture of solvents. To this coating various dyes may be added in order to distinguish among tablets with different active compounds or with different amounts of the active compound present.

Soft gelatin capsules may be prepared which capsules contain a mixture of the active compound or compounds of the invention and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance in a mixture with a neutral fat base, or they may be prepared in the form of gelatin-rectal capsules which contain the active substance in a mixture with a vegetable oil or paraffin oil.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions containing from 0.2 % to 20 % by weight of the active ingredient and the remainder consisting of sugar and a mixture of ethanol, water, glycerol and propylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharin and carboxymethylcellulose as a thickening agent.

Solutions for parenteral administration by injection may be prepared as an aqueous solution of a watersoluble pharmaceutically acceptable salt of the active compound, preferably in a concentration from 0.5 % to 10 % by weight. These solutions may also contain stabilizing agents and/or

buffering agents and may be manufactured in different dosage unit ampoules.

Pharmaceutical tablets for oral use are prepared in the following manner: The solid substances are ground or sieved to a certain particle size, and the binding agent is homogenized and suspended in a suitable solvent. The therapeutically active compounds and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension having the consistency of wet snow. The moistening causes the particles to aggregate slightly, and the resulting mass is pressed through a stainless steel sieve having a mesh size of approximately 1 mm. The layers of the mixture are dried in carefully controlled drying cabinets for approximately ten hours to obtain the desired particle size and consistency. The granules of the dried mixture are sieved to remove any powder. To this mixture, disintegrating, antifriction and antiadhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The pressure applied affects the size of the tablet, its strength and its ability to dissolve in water. The compression pressure used should be in the range 0.5 to 5 tons. Tablets are manufactured at the rate of 20.000 to 200.000 per hour. The tablets, especially those which are rough or bitter, may be coated with a layer of sugar or some other palatable substance. They are then packaged by machines having electronic counting devices. The different types of packages consist of glass or plastic gallipots, boxes, tubes and specific dosage adapted packages.

The typical daily dose of the active substance varies according to the individual needs and the manner of administration. In general, oral dosages range from 100 to 400 mg/day of active substance and intravenous dosages range from 5 to 20 mg/day.

The following illustrates a preferred embodiment of the invention without being limited thereto. Temperature is given in degrees Centigrade.

The starting materials in the examples found below were prepared in accordance with the following methods:
(1) a 1,2-diamino compound, such as o-phenylenediamine was reacted with potassium ethylxanthate (according to Org. Synth. Vol. 30, p. 56) to form a 2-mercaptobenzimidazole;
(2) the compound 2-chloromethylpyridine was prepared by reacting 2-hydroxymethylpyridine with thionylchloride (according to Arch. Pharm. Vol. 26, pp. 448-451 (1956));
(3) the compound 2-chloromethylbenzimidazole was prepared by condensing o-phenylenediamine with chloroacetic acid.

Example 1

28.9 g of 2-[2-(4,5-dimethyl)pyridylmethylthio]-(5-acetyl--6-methyl)-benzimidazole were dissolved in 160 ml of $CHCl_3$, 24.4 g of m-chloroperbenzoic acid were added in portions while stirring and cooling to 5°C. After 10 minutes, the precipitated m-chlorobenzoic acid was filtered off. The filtrate was diluted with CH_2Cl_2, washed with Na_2CO_3 solution, dried over Na_2SO_4 and evaporated in vacuo. The residue crystallized when diluted with CH_3CN, and 2-[2-(4,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole was recrystallized from CH_3CN. Yield 22.3 g; m.p. 158°C.

Examples 2-30

The preparation of compounds of formula III labelled 2-26 was carried out in accordance with Example 1 above. The compounds prepared are listed in Table 1 which identifies the substituents for these compounds.

Example 31 (method c)

0.1 moles of 4-6-dimethyl-2-mercaptobenzimidazole were dissolved in 20 ml of water and 200 ml of ethanol containing 0.2 moles of sodium hydroxide. 0.1 moles of 2-chloromethyl-(3,5-dimethyl)pyridine hydrochloride were added and the mixture was refluxed for two hours. The sodium chloride formed was filtered off and the solution was evaporated in vacuo. The residue was dissolved in acetone and was treated with active carbon. An equivalent amount of concentrated hydrochloric acid was added, whereupon the mono-hydrochloride of 2-[2-(3,5-dimethyl)pyridylmethylthio]-(4,6-dimethyl)benzimidazole was isolated. Yield 0.05 moles.

This compound was then oxidized in accordance with Example 1 above to give the corresponding sulfinyl compound, melting point 50-55°C.

Example 32 (method b)

0.1 moles of 2-[Li-methylsulfinyl](5-acetyl-6-methyl)-benzimidazole were dissolved in 150 mls of benzene. 0.1 moles 2-chloro-(3,5-dimethyl)pyridine were added and the mixture was refluxed for two hours. The lithiumchloride formed was filtered off, and the solution was evaporated in vacuo. The residue was crystallized from CH_3CN, and recrystallized from the same solvent. Yield 0.82 moles of 2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole melting at 171°C.

Example 33 (method d)

23.4 g of 2-[2-(3,4,5-trimethyl)pyridylmethylthio] formic acid and 16.6 g of o-(5-acetyl-6-methyl)phenylenediamine were boiled for 40 minutes in 100 ml of 4N HCl. The mixture was cooled and neutralized with ammonia. The neutral solution was then extracted with ethyl acetate. The organic phase was

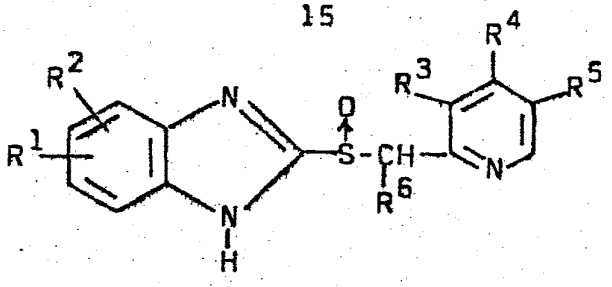
treated with active carbon and evaporated in vacuo. The residue was dissolved in acetone whereupon an equivalent of concentrated HCl was added. The precipitated hydrochloride was filtered off after cooling and the salt was recrystallized from absolute ethanol and some ether. Yield of 2-[2-(3,4,5-trimethylpyridyl)methylthio]-(5-acetyl-6-methyl)benzimidazole was 6.5 g.

This compound was then oxidized in accordance with Example 1 above, to give the corresponding sulfinyl derivative. M.p. 190°C.

Example 34 (method c)

22.0 g of 2-mercapto-(5-acetyl-6-methyl)benzimidazole and 19.5 g of chloromethyl(4,5-dimethyl)pyridine hydrochloride were dissolved in 200 ml of 95 % ethanol. 8 g of sodium hydroxide in 20 ml of water were added, whereupon the solution was refluxed for two hours. The sodium chloride formed was filtered off and the solution was evaporated in vacuo. The residue, 2-[2-(4,5-dimethyl)pyridylmethylthio]-(5-acetyl-6-methyl)benzimidazole, was recrystallized from 70 % ethanol. Yield 10.6 g.

This compound was then oxidized in accordance with Example 1 above, to give the corresponding sulfinyl derivative. M.p. 158°C.



Ex.	R^1	R^2	R^6	R^3	R^4	R^5	M.p. °C
1	5-$COCH_3$	6-CH_3	H	H	CH_3	CH_3	158
2	5-$COOCH_3$	6-CH_3	H	H	CH_3	CH_3	163
3	5-$COOCH_3$	H	H	H	CH_3	CH_3	141
4	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	H	160
5	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	H	163
6	4-CH_3	6-CH_3	H	CH_3	H	CH_3	50-55
7	5-$COCH_3$	6-CH_3	H	CH_3	H	CH_3	171
8	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	190
9	5-$COCH_3$	6-CH_3	H	H	OCH_3	H	165
10	4-CH_3	6-CH_3	H	H	OCH_3	H	122
11	5-$COCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	156
12	5-$COOCH_3$	6-CH_3	H	CH_3	H	CH_3	144
13	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	185
14	5-$COOCH_3$	6-CH_3	H	H	OCH_3	H	169
15	5-$COOCH_3$	6-CH_3	H	H	OC_2H_5	H	148
16	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	H	175
17	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	155
18	5-$COOCH_3$	6-CH_3	H	H	OCH_3	CH_3	158
19	5-$COOCH_3$	H	H	CH_3	H	CH_3	141
20	5-$COOCH_3$	H	H	CH_3	OCH_3	CH_3	142
21	5-$COCH_3$	H	H	CH_3	OCH_3	CH_3	162
22	5-OCH_3	H	H	H	OCH_3	CH_3	178
23	5-OCH_3	H	H	CH_3	OCH_3	CH_3	156
24	5-CH_3	H	H	CH_3	OCH_3	CH_3	181
25	H	H	H	CH_3	OCH_3	CH_3	165
26	5-Cl	H	H	CH_3	OCH_3	CH_3	185
27	5-CH_3	H	H	H	$OC_2H_4OCH_3$	H	119
28	5-$COOC_2H_5$	H	H	CH_3	OCH_3	CH_3	150-5
29	5-$COOCH_3$	H	CH_3	CH_3	H	CH_3	130
30	5-CH_3	H	CH_3	CH_3	H	CH_3	152

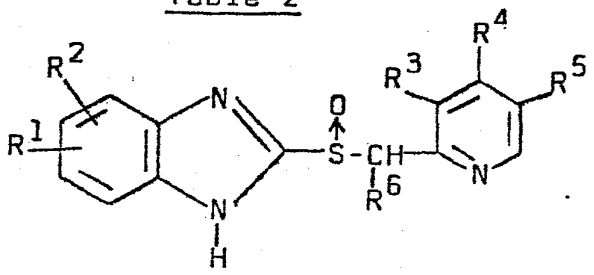
Biological effect

The compounds of the invention possess worthwhile therapeutic properties as gastric acid secretion inhibitors as demonstrated by the following tests. To determine the gastric acid secretion inhibitory properties, experiments have been performed on conscious dogs provided with gastric fistulas of conventional type and duodenal fistulas, the latter ones used for direct intraduodenal administration of the test compounds. After 18 hours starvation and deprivation of water the dogs were given a subcutaneous infusion of pentagastrin (1-4 nmol/kg, h) lasting for 6-7 hours. Gastric juice was collected in consecutive 30 minutes samples. An aliquot of each sample was titrated with 0.1 N NaOH to pH 7.0 for titrable acid concentration using an automatic titrator and pH-meter (Radiometer, Copenhagen, Denmark). Acid output was calculated as mmol H^+/60 minutes. The percent inhibition compared to control experiments was calculated for each compound and the peak inhibitory effect is given in Table 2 below. The test compounds, suspended in 0.5 % Methocel® (methyl cellulose), were given intraduodenally in doses from 4-20 µmol/kg when the secretory response to pentagastrin has reached a steady level.

In the test prior known compounds were compared with the compounds of the present invention as will be evident from the Table 2 below.

The following gastric acid inhibiting effect data were obtained for a number of compounds tested according to the method described.

Table 2



Ex.	R^1	R^2	R^6	R^3	R^4	R^5	Dose µmol/kg	Effect % inhibition
1	5-$COCH_3$	6-CH_3	H	H	CH_3	CH_3	2	90
4	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	H	1	60
7	5-$COCH_3$	6-CH_3	H	CH_3	H	CH_3	2	100
8	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	4	100
9	5-$COCH_3$	6-CH_3	H	H	OCH_3	H	2	95
11	5-$COCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	0.5	70
×	5-$COCH_3$	6-CH_3	H	H	CH_3	H	20	30
×	5-$COCH_3$	6-CH_3	H	H	H	CH_3	8	80
2	5-$COOCH_3$	6-CH_3	H	H	CH_3	CH_3	2	60
5	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	H	2	90
12	5-$COOCH_3$	6-CH_3	H	CH_3	H	CH_3	2	70
13	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	4	80
14	5-$COOCH_3$	6-CH_3	H	H	OCH_3	H	2	100
15	5-$COOCH_3$	6-CH_3	H	H	OC_2H_5	H	4	75
16	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	H	0.5	65
17	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	0.5	90
18	5-$COOCH_3$	6-CH_3	H	H	OCH_3	CH_3		
×	5-$COOCH_3$	6-CH_3	H	H	H	CH_3	4	50
×	5-$COOCH_3$	6-CH_3	H	Br	H	H	4	0
6	4-CH_3	6-CH_3	H	CH_3	H	CH_3	4	40
10	4-CH_3	6-CH_3	H	H	OCH_3	H	2	40
×	4-CH_3	6-CH_3	H	H	H	H	4	30
×	4-CH_3	6-CH_3	H	H	H	CH_3	12	50

cont.

Ex	R^1	R^2	R^6	R^3	R^4	R^5	Dose µmol/kg	Effect % inhibition
3	5-$COOCH_3$	H	H	H	CH_3	CH_3	4	100
19	5-$COOCH_3$	H	H	CH_3	H	CH_3	2	60
20	5-$COOCH_3$	H	H	CH_3	OCH_3	CH_3	0.5	65
x	5-$COOCH_3$	H	H	H	H	CH_3	20	90
x	5-$COOCH_3$	H	H	H	H	H	20	50
21	5-$COCH_3$	H	H	CH_3	OCH_3	CH_3	0.5	60
x	5-$COCH_3$	H	H	H	H	C_2H_5	20	40
22	5-OCH_3	H	H	H	OCH_3	CH_3		
23	5-OCH_3	H	H	CH_3	OCH_3	CH_3	0.5	65
x	5-OCH_3	H	H	H	CH_3	H	20	10
24	5-CH_3	H	H	CH_3	OCH_3	CH_3	0.5	50
x	5-CH_3	H	H	H	H	CH_3	4	50
25	H	H	H	CH_3	OCH_3	CH_3	0.5	60
x	H	H	H	H	H	H	4	50
28	5-$COOC_2H_5$	H	H	CH_3	OCH_3	CH_3	0.5	50
26	5-Cl	H	H	CH_3	OCH_3	CH_3	0.5	25
27	5-CH_3	H	H	H	$OC_2H_4OCH_3$	H	0.5	30
29	5-$COOCH_3$	H	CH_3	CH_3	H	CH_3	0.5	40

x denotes a previously known compound

Example 35

A syrup containing 2 % (weight per volume) of active substance was prepared from the following ingredients:

2-[2-(4,5-dimethyl)pyridylmethylsulfinyl]--(5-acetyl-6-methyl)benzimidazole · HCl	2.0 g
Saccharin	0.6 g
Sugar	30.0 g
Glycerin	5.0 g
Flavouring agent	0.1 g
Ethanol 96 %	10.0 ml
Distilled water (sufficient to obtain a final volume of 100 ml)	

Sugar, saccharin and the acid addition salt were dissolved in 60 g of warm water. After cooling, glycerin and a solution of flavouring agents dissolved in ethanol were added. To the mixture water was added to obtain a final volume of 100 ml.

The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

Example 36

2-[2-(3,4-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6--methyl)benzimidazole . HCl (250 g) was mixed with lactose (175.8 g), potato starch (169.7 g) and colloidal silicic acid (32 g). The mixture was moistened with 10 % solution of gelatin and was ground through a 12-mesh sieve. After drying, potato starch (160 g), talc (50 g) and magnesium stearate (5 g) were added and the mixture thus obtained was pressed into tablets (10.000), with each tablet containing 25 mg of active substance. Tablets can be prepared that contain any desired amount of the active ingredient.

Example 37

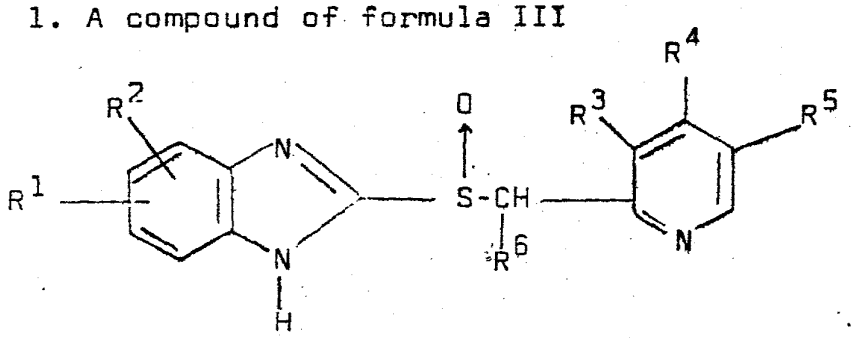
Granules were prepared from 2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole-p-hydroxybenzoate (250 g), lactose (175.9 g) and an alcoholic solution of polyvinylpyrrolidone (25 g). After drying, the granules were mixed with talc (25 g), potato starch (40 g), and magnesium stearate (2.50 g) and were pressed into 10.000 tablets. These tablets are first coated with a 10 % alcoholic solution of shellac and thereupon with an aqueous solution containing saccharose (45 %), gum arabic (5 %), gelatin (4 %), and dyestuff (0.2 %). Talc and powdered sugar were used for powdering after the first five coatings. The coating was then covered with a 66 % sugar syrup and polished with a solution of 10 % carnauba wax in carbon tetrachloride.

Example 38

2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6--methyl)benzimidazole hydrochloride (1 g), sodium chloride (0.6 g) and ascorbic acid (0.1 g) were dissolved in sufficient amount of distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance for each ml, was used in filling ampoules, which were sterilized by heating at 120°C for 20 minutes.

Claims

1. A compound of formula III



(III)

or a therapeutically acceptable salt thereof in which R^1 and R^2 are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl in any position, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxy-ethoxy and ethoxy-ethoxy whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4, and R^5 is not methyl.

2. A compound according to claim 1, wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, alkoxy, and alkanoyl in any position, whereby R^1 and R^2 are not both hydrogen, R^6 is hydrogen, and R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, and ethoxy, whereby R^3, R^4, and R^5 are not all hydrogen and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4, and R^5 are not methyl.

3. A compound according to claim 1, wherein R^1, R^2, and R^6 have the meanings given and R^3 and R^5 are methyl and R^4 is methoxy.

4. A compound according to claim 1, wherein R^1, R^2, and R^6 have the meanings given, R^4 is methoxy, and R^3 is hydrogen and R^5 is methyl, or R^5 is hydrogen and R^3 is methyl.

5. A compound according to claim 1 or a therapeutically acceptable salt thereof in which R^1, R^2, and R^6 have the meanings given, R^3 and R^5 are hydrogen, and R^4 is methoxy, ethoxy, methoxyethoxy or ethoxy-ethoxy.

6. A compound according to claim 1 or a therapeutically acceptable salt thereof in which R^1, R^2, and R^6 have the meanings given, and R^3, and R^5 are methyl and R^4 is hydrogen.

7. A compound according to claim 1 and selected from the group consisting of

2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6--methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(4,6-dimethyl)--benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)--benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6--methyl)-benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy--6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6--methyl)-benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)--benzimidazole

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(4,6-dimetnyl)-benzimidazole

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy--6-methyl)-benzimidazole,

2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy--6-methyl)-benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-ethoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3-methyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)--benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl)-benzimidazole,

2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-methoxy)--benzimidazole,

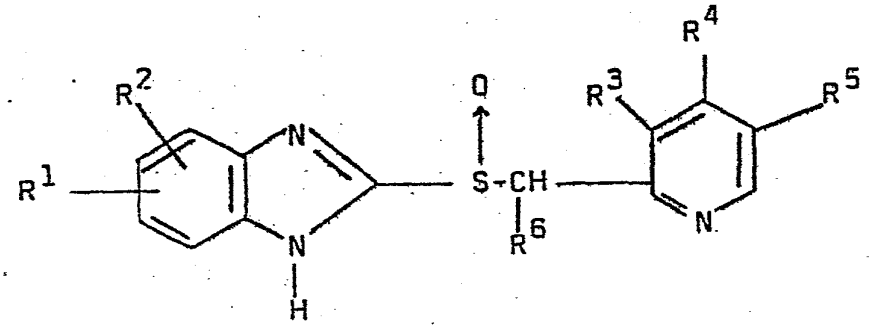
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5--methoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methyl)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-chloro)-benzimidazole

8. A pharmaceutical preparation for inhibiting gastric acid secretion, characterized in that it contains as active agent a compound of formula III



(III)

or a pharmaceutically acceptable non-toxic acid addition salt thereof in a therapeutically effective amount in which R^1 and R^2 are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl in any position, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxy-ethoxy, and ethoxy-ethoxy whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4, and R^5 is not methyl.

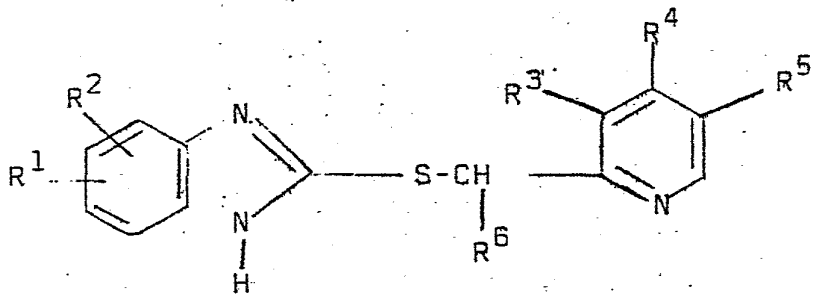
9. A pharmaceutical preparation according to claim 8 wherein the active ingredient is selected from the group consisting of

2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(4,6-dimethyl)-benzimidazole,
2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,
2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(4,6-dimethyl)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
2-[2-(4-ethoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
2-[2-(3-methyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl)-benzimidazole,
2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy]-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methyl)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-chloro)-benzimidazole,

or a pharmaceutically acceptable non-toxic addition salt thereof.

10. Intermediates of the formula



wherein R^1 and R^2, preferably in 3 to 5 position, are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, and R^3, R^4, and R^5 are the same or different and are selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxy-ethoxy, and ethoxy-ethoxy whereby R^3, R^4, and R^5

are not all hydrogen when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4, and R^5 is not methyl.

European Patent Office

EUROPEAN SEARCH REPORT

0005129
Application number

EP 79 85 0022

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
A	DE - A - 2 548 340 (AB HÄSSLE) * pages 1 to 12 *	1, 24

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 D 403/12
A 61 K 31/44

TECHNICAL FIELDS SEARCHED (Int.Cl.³)

C 07 D 403/12
A 61 K 31/44

CATEGORY OF CITED DOCUMENTS

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P: Intermediate document
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☒ The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	18-07-1979	DE BUYSER

EPO Form 1503.1 06.78

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 124 495**
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **84850066.6**

(22) Date of filing: **28.02.84**

(51) Int. Cl.³: **C 07 D 401/12**, A 61 K 31/44

(30) Priority: **04.03.83 SE 8301182**

(43) Date of publication of application: **07.11.84**
Bulletin 84/45

(84) Designated Contracting States: **AT BE CH DE FR GB IT LI LU NL SE**

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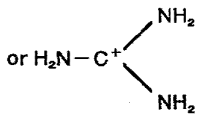
(54) Omeprazole salts.

(57) Novel salts of omeprazole with Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ti^{4+}, $N^+(R^1)_4$



as cation; processes for their preparation thereof, pharmaceutical compositions containing such salts and their use in medicine.

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TITLE MODIFIED
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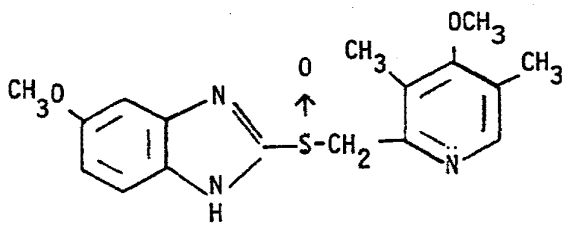
Novel compounds

Field of the invention

The invention relates to novel salts of the known compound omeprazole.

Background of the invention

The compound known under the generic name omeprazole, having the structural formula



(i)

which is described i.a. in European patent specification 0005129, is being extensively investigated clinically as a gastric acid secretion inhibiting agent.

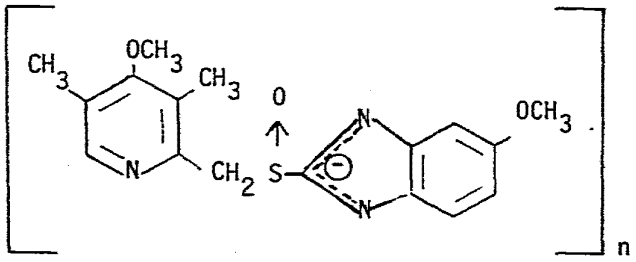
Omeprazol is useful for inhibiting gastric acid secretion as well as for providing gastrointestinal cytoprotective effects in mammals and man. In a more general sense, omeprazole may be used for prevention and treatment of gastrointestinal inflammatory diseases in mammals and man, including e.g. gastritis, gastric ulcer, and duodenal ulcer. Furthermore, omeprazole may be used for prevention and treatment of other gastrointestinal disorders where cytoprotective and/or gastric antisecretory effect is desirable, e.g. in patients with gastrinomas, in patients with acute upper gastrointestinal bleeding, and in patients with a history of chronic and excessive alcohol consumption.

The term "omeprazole" as used in this specification designates the neutral form of the compound of the formula (i), that is the form as given in the formula (i) without salt forming components present.

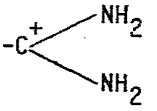
A problem with omeprazole is its stability characteristics. Upon storage without any special precautions being taken, it is degraded at a rate which is higher than desired. At storage during accelerated conditions, that is at +37°C and at a relative humidity of 80% for a period of 6 months, about 6% of the substance is converted to degradation products. While the rate of decomposition of omeprazole at normal storage conditions is lower, it is nevertheless desirable to obtain physical forms of omeprazole which exhibit improved stability. This need for more stable forms of omeprazole is apparent when considering the often considerable time periods involved from the synthesis of the active substance through its incorporation in pharmaceutical preparations, distribution of the finished product to pharmacies etc. up to the consumption of the preparation by the patient. The present invention provides such new forms of omeprazole which exhibit improved storage stability.

The invention

It has been found that the novel alkaline salts of omeprazole with the structural formula



A^{n+} I

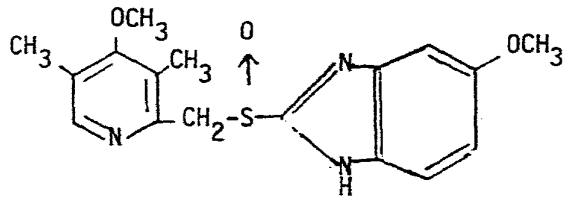
wherein n is 1,2, or 4; A^{n+} is Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ti^{4+}, $N^+(R^1)_4$ or  , wherein R^1 is an alkyl group containing 1-4 carbon atoms are more stable during storage than the corresponding neutral form of omeprazole. The salts of the formula I are also easier to handle than the neutral form in the manufacture of pharmaceutical dosage units.

A preferred group of omeprazole salts of the formula I are those wherein A^{n+} is Na^+, K^+, Mg^{2+} and Ca^{2+}.

Further preferred salts are those wherein A^{n+} is Na^+, Mg^{2+} and Ca^{2+}. The Na^+-salt is especially preferred for the preparation of liquid pharmaceutical formulations, e.g. solutions for intravenous administration. The $Mg^{2+}$and Ca^{2+}salts are especially preferred for the preparation of tablets. The Mg^{2+} salt is particularly preferred.

Illustrative examples of the alkyl group R^1 are CH_3, C_2H_5, n-C_3H_7, and n-C_4H_9.

The novel salts I of the invention are prepared by reacting omeprazole of the formula

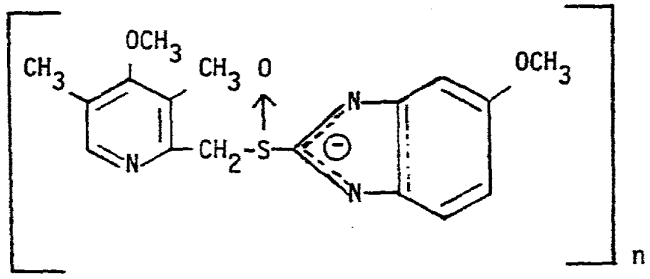


(i)

with a base capable of releasing the cation

$$A^{n+} \qquad \text{(ii)}$$

wherein A^{n+} is as defined above,
to give a salt of the formula



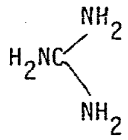
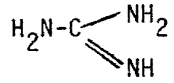
A^{n+} I

which salt is thereafter isolated.

Examples of bases capable of releasing the cation A^{n+}, and examples of reaction conditions are given below.

a) Salts of the formula I wherein A is Li, Na or K are prepared by treating omeprazole with LiOH, NaOH or KOH in an aqueous or nonaqueous medium or with LiOR, $LiNH_2$, $LiNR_2$, NaOR, $NaNH_2$, $NaNR_2$, KOR, KNH_2 or KNR_2, wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous medium.

b) Salts of the formula I wherein A is Mg, Ca, or Ti are prepared by treating omeprazole with $Mg(OR)_2$, $Ca(OR)_2$, CaH_2, $Ti(OR)_4$ or TiH_4, wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous solvent such as an alcohol (only for the alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran.

c) Salts of the formula I wherein A is  are prepared by treating omeprazole with the strong base  dissolved in a solvent, for example an alcohol.

d) A salt of formula I may be converted to another salt of the same formula by exchanging the cation. When both the starting material and the salt obtained as final product are sufficiently soluble, such an exchange may be performed by using a cation-exchange resin saturated with the cation desired in the product. The exchange may also be performed by utilizing the low solubility of a desired salt. By this principle, for example, Na^+ as a counter ion may be exchanged for Ca^{2+} or Mg^{2+}.

e) The reaction between the compounds (i) and (ii) may also be carried out by ion-pair extraction.For example, tetrabutylammonium salts of the invention may be prepared by dissolving the Na^+-salt in water containing tetrabutylammonium sulfate followed by extraction of the tetrabutylammonium salt I into a methylene chloride phase, and subsequent isolation of the tetrabutylammonium salt I. In this manner also other tetraalkylammonium salts I may be prepared.

Illustrative examples of the radical R are CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, i-C_4H_9, sec.-C_4H_9 and tert.-C_4H_9.

The invention also relates to pharmaceutical compositions containing a novel salt of omeprazole as active ingredient; to the use of the novel omeprazolesalts for providing gastrointestinal cytoprotective effects in mammals and man; to the use of the novel omeprazole salts in the prevention and treatment of gastrointestinal inflammatory diseases in mammals and man; to the use of the novel omeprazole salts for inhibiting gastric acid secretion in mammals and man; to a method for inhibiting gastric acid secretion in mammals and man by administering a compound of the formula I; to a method for the treatment of gastrointesti-

nal inflammatory diseases in mammals and man by administering a compound of the formula I; and to a method for providing gastrointestinal cytoprotective effects in mammals and man by administering a compound of the formula I.

For clinical use the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. The pharmaceutical formulation contains a compound of the invention in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1 and 50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, powdered carrier, e.g. lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as with lubricating agents e.g. magnesium stearate, calcium stearate, sodium steryl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets. Since the compounds of the invention are susceptible to degradation in acid to neutral media, the above-mentioned granules or tablets are preferably coated with an enteric coating which protects the active compound from acid degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers such as cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, partly methyl esterified methacrylic acid polymers and the like, if preferred in combination with a suitable plasticizer. To this coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules are preferably enteric coated as described above. Hard gelatine capsules may contain enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier e.g. lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatine; the hard gelatine capsules are preferably enteric coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose and thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1% to 10% by weight. These solutions may also contain stabilising agents and/or buffering agents and may be manufactured in unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

Sodium salts of the invention are preferably used in the preparation of parenteral formulations.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the manner of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 400 mg per day of active substance.

The following examples will further illustrate the invention.

Example 1. Preparation of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole sodium salt (omeprazole sodium salt).

Omeprazole (1000g, 2.90 mol) was added to a solution of NaOH (116g, 2.90 mol) in deionized water (25l). After stirring for 5 min methylene chloride (5l) was added and stirring was continued for 10 min. The two phases were separated. The aqueous phase was washed with methylene chloride (5l), filtered clear (Celite) and concentrated by evaporation under reduced pressure to about 2 l total volume. Absolute ethanol (6l) was added and the evaporation was continued until dryness. Ethyl acetate (7l) was added, the mixture was stirred under reflux for 30 min. After cooling and standing over night the resulting slurry was stirred with an additional amount (2l) of ethyl acetate and filtered. The filter cake was washed with diethyl ether and dried under reduced pressure at 40°C over night giving omeprazole sodium salt (975g, 92%), mp 208-210°C, NMR: $\delta(D_2O)$: 1.85(s,3H), 2.1(s,3H), 3.5(s,3H), 3.85(s,3H), 4.75(s,2H), 6.85 (dd,1H), 7.2(d,1H), 7.55(d,1H), 8.15(d,1H).

Example 2. Preparation of omeprazole sodium salt.
Omeprazole (1300g, 3.77 mol) was added under vigorous mechanic stirring to a mixture of tetrahydrofuran (13l) and 50% aqueous NaOH (296g, 3.7 mol) and stirring was then continued for 45 min. Trichloroethylene (5.7l) was added and stirring was continued over night at room temperature. The mixture was cooled to +5°C and then stirred for 3h. The precipitate was filtered off and the filter cake was washed with trichloroethylene (5l) and dried under reduced pressure at 50°C giving omeprazole

sodium salt (1314g, 95%), mp 208-210°C.

Example 3. Preparation of omeprazole potassium salt.
Omeprazole (10.0g, 0.0290 mol) was added to a solution of KOH (1.60g. 0.0285 mol) in deionized water and then methylene chloride (50ml) was added. The mixture was stirred vigorously for 15 min. The phases were separated and the aqueous phase was washed with methylene chloride (50ml) and filtered clear (Celite). Evaporation to dryness gave a crystalline residue. Recrystallisation from ethyl acetate yielded omeprazole patassium salt, mp. 148-150°C (soluble in water).

Example 4. Preparation of di-omeprazole calcium salt dihydrate.
Anhydrous $CaCl_2$ (17.9g, 0.161 mol) dissolved in deionized water (200 ml) was added dropwise under viogorous stirring to a solution of omeprazole sodium salt (125g, 0.340 mol) in deionized water (1250 ml) and then stirring was continued for 1h at room temperature. The precipitate was centrifugated down and washed with deionized water until no Cl^- was detectable ($AgNO_3$). After drying in the air and grinding, the crystals were dried in vacuum at 40° for 20h yielding omeprazole calcium salt dihydrate (104g, 80%), mp 182-184°C, NMR: δ(CDCl$_3$+1 drop of DMSO-d$_6$) 2.0(s,3H), 2.15(s,3H), 3.6(s,3H), 3.7(s,3H), 4.5(s,2H), 6.7(dd,1H), 7.1(d,1H), 7.6(d,1H, 8.15(s,1H).

Example 5. Preparation of di-omeprazole magnesium salt dihydrate.
Anhydrous $MgCl_2$ (16.2g, 0.17 mol) dissolved in deionized water (625 ml) was added dropwise under vigorous stirring to a solution of omeprazole sodium salt (125g, 0.340 mol) in deionized water(1560ml) and then the stirring was continued for 1h at room temperature. The precipitate was centrifugated down and then washed with deionized water until no Cl^- was detectable ($AgNO_3$). Drying in the air, grinding and drying in vacuum at 40° for 24h yielded omeprazole magnesium salt dihydrate (111g, 87%) mp 177-178°C.

Example 6. Preparation of di-omeprazole magnesium salt.
Magnesium (0.35g, 0.0145 mol) was reacted with absolute methanol (10ml) (in the presence of one drop of CCl_4) to give a solution of $Mg(OCH_3)_2$ in methanol solution. More methanol (10ml) was added and the solution

was added dropwise to a solution of omeprazole (10 g, 0.029 m) in methanol (200 ml) and the mixture was then stirred for 30 min at room temperature. Evaporation gave a crystalline solid of the di-omeprazole magnesium salt, mp. 178-180°.

Example 7. Preparation of omeprazole tetrabutylammonium salt. Omeprazole sodium salt (3.8g, 0.010 mol) was added to a mixture of tetrabutylammonium hydrogensulphate (3.5g, 0.010 mol) and NaOH (0.42 g, 0.0105 mol) in deionized water (15ml). Methylene chloride (10ml) was added and the mixture was shaken in a separatory funnel. After separation of the phases the organic phase was dried and the solvent evaporated off giving omeprazole tetrabutylammonium salt (3.5g, 60%), NMR: $\delta(CDCl_3)$: 0.8-1.15(m,12H), 1.15-1.6(m,16H), 2.25(s,3H), 2.3(s,3H), 2.75-3.15(m,8H), 3.75(s,3H), 3.9(s,3H), 4.7(d,1H), 5.05(d,1H), 6.8 (dd,1H), 7.3(d,1H), 7.7(d,1H), 8.35(s,1H).

Example 8. Preparation of omeprazole guanidinium $[C^+(NH_2)_3]$ salt. A solution of guanidine (0.0029 mol)[prepared from guanidinium nitrate and KOH] in ethanol (50ml) was added to a solution of omeprazole (1.0g, 0.0029 mol) and the resulting solution was stirred for 15 min. The solvent was evaporated giving omeprazole guanidinium salt, mp 110-112°C (soluble in water).

Example 9. Preparation of tetra-omeprazole titanium salt. Titanium tetraisopropylate (1.03g, 0.0036 mol) was added to a solution of omeprazole in dry isopropanol (250ml) and the mixture was stirred under N_2 at room temperature for 4h. (A white precipitate was formed). Evaporation of the solvent followed by washing 3 times with light petroleum and drying in vacuum gave a white crystalline powder of tetra-omeprazole titanium salt, mp >260°C.

Example 10. Preparation of omeprazole litium salt. Omeprazole (3.0 g, 0.0087 mol) was added to a solution of LiOH (0.207 g, 0.00865 mol) in deionized water and then methylene chloride (25 ml) was added. The mixture was stirred vigorously for 15 min. The phases were separated and the aqueous phase was washed with methylene chloride (25 ml) and filtered clear (Celite). Evaporation to dryness gave a crystalline omeprazole litium salt, mp. 198-200°C (soluble in water).

NMR: δ ($CDCl_3$) 1.65 (s,3H), 1.8 (s,3H), 3.45 (s,3H), 3.4 (s,3H), 4.2 (s,2H), 6.6 (dd,1H), 6.95 (d,1H), 7.45 (d,1H), 7.75 (s,1H).

The NMR data given in the examples are measured at 90 MHz.

Incorporation of the novel omeprazole salts of the present invention in pharmaceutical preparations is exemplified in the following examples.

Example 11. Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

I	Omeprazole sodium salt	1.0 g
	Sugar, powder	30.0 g
II	Saccharine	0.6 g
	Glycerol	5.0 g
	Flavouring agent	0.05g
	Ethanol	5.0 g
	Sorbic acid	0.5 g
	Sodium dihydrogen phosphate q.s. to pH=	9.0 g
	Distilled water q.s. to a final volume of	100 ml

I Powdered omeprazole sodium salt was carefully dry mixed with powdered sugar, dried in a vacuum oven over-night and dispensed into bottles each containing 31.0 gram of the powder mixture.

II A solution of saccharine, glycerol, flavouring agent, ethanol, sodium dihydrogen phosphate, sorbic acid and water was prepared, and dispensed into vials. When mixed with the powder mixture of omeprazole sodium salt and sugar the final volume was 100 ml.

Solvent vial II is to be added to powder mixture vial I just prior to use. The formed suspension is stable for ten days when stored at refrigerator temperature.

The salt given above may be replaced with another salt of the invention.

Example 12. Enteric-coated tablets

An enteric-coated tablet containing 20 mg of active compound was prepared from the following ingredients:

I	Omeprazole magnesium salt	200 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Distilled water	q.s.
II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

I Omeprazole magnesium salt, powder, was mixed with lactose, and granulated with a water solution of methyl cellulose. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 20 mg of active substance, in a tabletting machine using 6 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota®, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Example 13. Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

I	Omeprazole sodium salt	4.26 g
	Sterile water	200 ml
II	Polyethylene glycol 400 for injection	400 g
	Sodium dihydrogen phosphate	1.5 g
	Sterile water to a final volume of	1000 ml

I Omeprazole sodium salt 4.26 g, corresponding to 4.0 g of omeprazole, was dissolved in sterile water to a final volume of 200 ml. The solution was filtered through a 0.22 μ filter and dispensed into sterile vials, each vial containing 2.0 ml. The vials were placed in a freeze drier with a shelf temperature of -40°C. When the solution in the vials had frozen, the solution was freeze dried. After drying the vials were stoppered.

II A solution of polyethylene glycol and sodium dihydrogen phosphate in sterile water was prepared, filtered through a 0.22 μ filter, dispensed into sterile vials and the vials closed with a rubber stopper. The vials were sterilised in an autoclave at +120°C for twenty minutes. Immediately before use 10.0 ml of solvent II is added to vial I. The clear solution contains 4 mg of omeprazole per millilitre.

Test of the stability of omeprazole salts of the invention

The stability of omeprazole sodium salt, of the invention, obtained according to Example 1, was compared with the stability of the neutral form of omeprazole. Both test compounds were stored for six months at + 37°C and at a relative humidity of 80%. Thereafter, the amount of degradation products which had formed was measured. The result is given in Table 1 below.

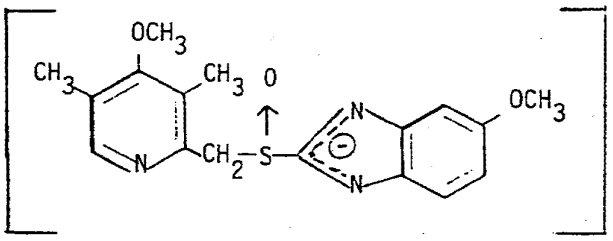
Table 1. Stability of neutral omeprazole and of omeprazole sodium salt after six months storage at + 37°C and 80% relative humidity

Test compound	Amount of degradation products formed (per cent calculated on original amount of omeprazole)
neutral omeprazole	6
omeprazole sodium salt	0.4

As is seen in Table 1 the omeprazole sodium salt of the invention gave rise to substantially lower amounts of degradation products than the neutral form of omeprazol. This shows the improved stability of the novel omeprazole salts of the invention.

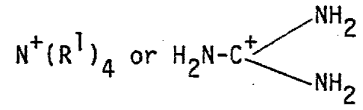
What we claim is:

1. A compound of the formula



A^{n+} I

wherein n is 1, 2, or 4; and A^{n+} is Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ti^{4+}, $N^+(R^1)_4$ or



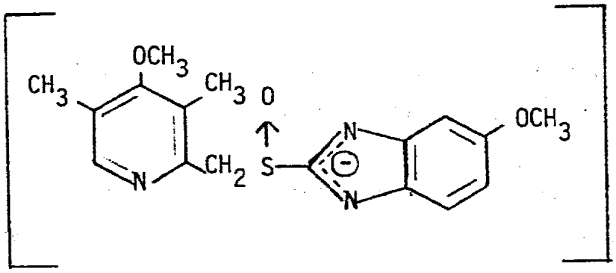
wherein R^1 is an alkyl group containing 1-4 carbon atoms.

2. A compound according to claim 1 wherein A^{n+} is Na^+, K^+, Mg^{2+} or Ca^{2+}.

3. A compound according to claim 1 wherein A^{n+} is Na^+.

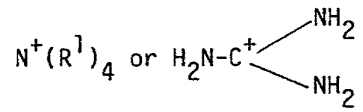
4. A compound according to claim 1 wherein A^{n+} is Mg^{2+}.

5. A process for the preparation of a compound of the formula

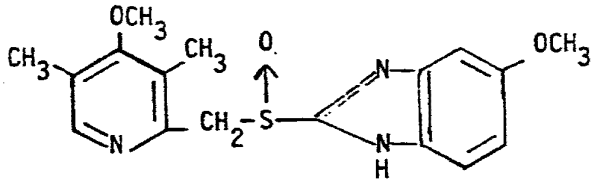


A^{n+} I

wherein n is 1, 2, or 4; and A^{n+} is Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ti^{4+}, $N^+(R^1)_4$ or



wherein R^1 is an alkyl group containing 1-4 carbon atoms characterized by reacting omeprazole of the formula



(i)

with a base capable of releasing the cation

$$A^{n+} \qquad \text{(ii)}$$

to give a salt of the formula I, which salt is thereafter isolated.

6. A process according to claim 5 wherein the base releasing the cation A^{n+} is NaOH, $NaNH_2$, or $NaNR_2$ wherein R is an alkyl group containing 1-4 carbon atoms.

7. A process according to claim 5 wherein the base releasing the cation A^{n+} is $Mg(OR)_2$ wherein R is an alkyl group containing 1-4 carbon atoms.

8. A pharmaceutical composition containing as active ingredient a compound according to any of claims 1-4.

9. A compound as defined in any of claims 1-4, for use in inhibiting gastric acid secretion in mammals and man.

10. A compound as defined in any of claims 1-4, for use as gastrointestinal cytoprotecting agent in mammals and man.

11. A compound as defined in any of claims 1-4, for use in the treatment of gastrointestinal inflammatory diseases in mammals and man.

B3

Notice

ABSTRACT EP0166287

Dialkoxypyridine the general formula I <IMAGE> wherein R1 is a completely or predominantly substituted by fluorine 1-3C-alkyl radical or a chlorofluorocarbon methyl radical and R1 'represents hydrogen, halogen, trifluoromethyl, a 1-3C-alkyl radical or an optionally fully or predominantly fluorine-substituted 1-3C-alkoxy, or R1 and R1 'together and with inclusion of the oxygen atom bound to the R1 is an optionally fully or partially substituted by fluorine is 1-2C-alkylenedioxy group or represent a Chlortrifluorethylendioxyrest, R3 a 1-3C-alkoxy, one of R2 and R4 is a 1-3C alkoxy and the other is a hydrogen atom or a 1-3C-alkyl radical and n represents the number 0 or 1, and salts thereof are novel compounds with interesting pharmacological properties.

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(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Veröffentlichungsnummer: **0 166 287**
A1

(12) EUROPÄISCHE PATENTANMELDUNG

(21) Anmeldenummer: **85107104.3**

(22) Anmeldetag: **10.06.85**

(51) Int. Cl.⁴: **C 07 D 401/12**, C 07 D 491/04, A 61 K 31/44

(30) Priorität: **16.06.84 CH 2899/84**
16.06.84 CH 2901/84

(43) Veröffentlichungstag der Anmeldung: **02.01.86**
Patentblatt 86/1

(84) Benannte Vertragsstaaten: **AT BE CH DE FR GB IT LI LU NL SE**

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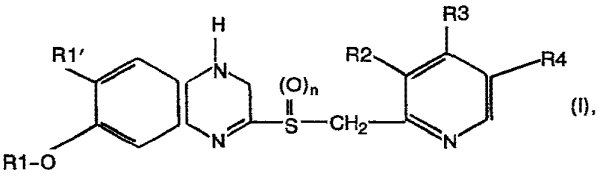
Erfinder: **Senn-Bilfinger, Jörg, Dr., Säntisstrasse 7, D-7750 Konstanz (DE)**

(54) Dialoxypyridine, Verfahren zu ihrer Herstellung, ihre Anwendung und sie enthaltende Arzneimittel.

(57) Dialkoxypyridine der allgemeinen Formel I



(I),

sowie deren Salze sind neue Verbindungen mit interessanten pharmakologischen Eigenschaften.

worin
R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chloridfluormethylrest und
R1′ Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest oder
R1 und R1′ gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2C-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest darstellen,
R3 einen 1-3C-Alkoxyrest,
einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und
n die Zahlen 0 oder 1 darstellt,

EP 0 166 287 A1

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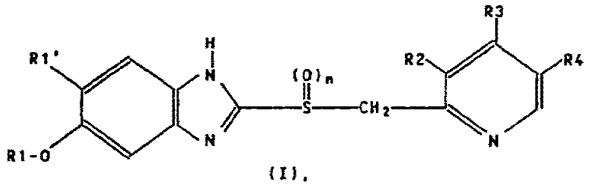
(54) Dialkoxypyridine, Verfahren zu ihrer Herstellung, ihre Anwendung und sie enthaltende Arzneimittel.

(57) Dialkoxypyridine der allgemeinen Formel I



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worin
R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chloridfluormethylrest und
R1′ Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest oder
R1 und R1′ gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2C-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest darstellen,
R3 einen 1-3C-Alkoxyrest,
einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und
n die Zahlen 0 oder 1 darstellt,

sowie deren Salze sind neue Verbindungen mit interessanten pharmakologischen Eigenschaften.

Dialkoxypyridine, Verfahren zu ihrer Herstellung, ihre Anwendung und sie enthaltende Arzneimittel

Anwendungsgebiet der Erfindung

Die Erfindung betrifft neue Dialkoxypyridine, Verfahren zu ihrer Herstellung, ihre Anwendung und sie enthaltende Arzneimittel. Die erfindungsgemäßen Verbindungen werden in der pharmazeutischen Industrie als Zwischenprodukte und zur Herstellung von Medikamenten verwendet.

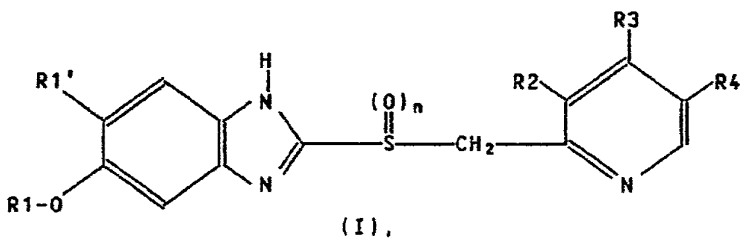
Stand der Technik

In der europäischen Patentanmeldung 0 005 129 werden substituierte Pyridylsulfinylbenzimidazole beschrieben, die magensäuresekretionshemmende Eigenschaften besitzen sollen. - In der europäischen Patentanmeldung 0 074 341 wird die Verwendung einer Reihe von Benzimidazolderivaten zur Magensäuresekretionshemmung beschrieben. In der britischen Patentanmeldung GB 2 082 580 werden tricyclische Imidazolderivate beschrieben, die die Magensäuresekretion hemmen und die Entstehung von Ulcera verhindern sollen.

Es wurde nun überraschenderweise gefunden, daß die unten näher beschriebenen Dialkoxypyridine interessante und unerwartete Eigenschaften aufweisen, durch die sie sich in vorteilhafter Weise von den bekannten Verbindungen unterscheiden.

Beschreibung der Erfindung

Gegenstand der Erfindung sind neue Dialkoxypyridine der allgemeinen Formel I



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worin

R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chlordifluormethylrest und

R1' Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest, oder

R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2C-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest darstellen,

R3 einen 1-3C-Alkoxyrest,

einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und

n die Zahlen 0 oder 1 darstellt,

sowie die Salze dieser Verbindungen.

Als ganz oder überwiegend durch Fluor substituierte 1-3C-Alkylreste seien beispielsweise der 1,1,2-Trifluorethylrest, der Perfluorpropylrest, der Perfluorethylrest und insbesondere der 1,1,2,2-Tetrafluorethylrest, der Trifluormethylrest, der 2,2,2-Trifluorethylrest und der Difluormethylrest genannt.

Halogen im Sinne der vorliegenden Erfindung ist Brom, Chlor und insbesondere Fluor.

1-3C-Alkylreste sind der Propyl-, Isopropyl-, Ethyl- und insbesondere der Methylrest.

1-3C-Alkoxyreste enthalten neben dem Sauerstoffatom die vorstehend genannten 1-3C-Alkylreste. Bevorzugt ist der Methoxyrest.

Ganz oder überwiegend durch Fluor substituierte 1-3C-Alkoxyreste enthalten neben dem Sauerstoffatom die vorstehend aufgeführten ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylreste. Beispielsweise seien der

1,1,2,2-Tetrafluorethoxy-, der Trifluormethoxy-, der 2,2,2-Trifluorethoxy- und der Difluormethoxyrest genannt.

Als gegebenenfalls ganz oder teilweise durch Fluor substituierte 1-2C-Alkylendioxyreste seien beispielsweise der 1,1-Difluorethylendioxyrest ($-O-CF_2-CH_2-O-$), der 1,1,2,2-Tetrafluorethylendioxyrest ($-O-CF_2-CF_2-O-$), der 1,1,2-Trifluorethylendioxyrest ($-O-CF_2-CHF-O-$) und insbesondere der Difluormethylendioxyrest ($-O-CF_2-O-$) als substituierte, und der Ethylendioxyrest und der Methylendioxyrest als unsubstituierte Reste genannt.

Als Salze kommen für Verbindungen der Formel I, in denen n die Zahl 0 bedeutet (Sulfide), bevorzugt alle Säureadditionssalze in Betracht. Besonders erwähnt seien die pharmakologisch verträglichen Salze der in der Galenik üblicherweise verwendeten anorganischen und organischen Säuren. Pharmakologisch unverträgliche Salze, die beispielsweise bei der Herstellung der erfindungsgemäßen Verbindungen im industriellen Maßstab als Verfahrensprodukte zunächst anfallen können, werden durch dem Fachmann bekannte Verfahren in pharmakologisch verträgliche Salze übergeführt. Als solche eignen sich beispielsweise wasserlösliche und wasserunlösliche Säureadditionssalze, wie das Hydrochlorid, Hydrobromid, Hydroiodid, Phosphat, Nitrat, Sulfat, Acetat, Citrat, Gluconat, Benzoat, Hibenzat, Fendizoat, Butyrat, Sulfosalicylat, Maleat, Laurat, Malat, Fumarat, Succinat, Oxalat, Tartrat, Amsonat, Embonat, Metembonat, Stearat, Tosilat, 2-Hydroxy-3-naphthoat, 3-Hydroxy-2-naphthoat oder Mesilat.

Für Verbindungen der Formel I, in denen n die Zahl 1 bedeutet (Sulfoxide), kommen als Salze bevorzugt basische Salze in Betracht, insbesondere pharmakologisch verträgliche Salze mit in der Galenik üblicherweise verwendeten anorganischen und organischen Basen. Als Beispiele für basische Salze seien Natrium-, Kalium-, Calcium- oder Aluminiumsalze erwähnt.

Eine Ausgestaltung (Ausgestaltung a) der Erfindung sind Verbindungen der Formel I, worin R1' Wasserstoff darstellt und R1, R2, R3, R4 und n die oben angegebenen Bedeutungen haben, und ihre Salze.

Eine weitere Ausgestaltung (Ausgestaltung b) der Erfindung sind Verbin-

dungen der Formel I, worin R1' Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest darstellt und R1, R2, R3, R4 und n die oben angegebenen Bedeutungen haben, und ihre Salze.

Eine weitere Ausgestaltung (Ausgestaltung c) der Erfindung sind Verbindungen der Formel I, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen 1-2C-Alkylendioxyrest darstellen und R2, R3, R4 und n die oben angegebenen Bedeutungen haben, und ihre Salze.

Eine weitere Ausgestaltung (Ausgestaltung d) der Erfindung sind Verbindungen der Formel I, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen ganz oder teilweise durch Fluor substituierten 1-2C-Alkylendioxyrest darstellen und R2, R3, R4 und n die oben angegebenen Bedeutungen haben, und ihre Salze.

Eine weitere Ausgestaltung (Ausgestaltung e) der Erfindung sind Verbindungen der Formel I, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen Chlortrifluorethylendioxyrest darstellen und R2, R3, R4 und n die oben angegebenen Bedeutungen haben, und ihre Salze.

Bevorzugte Verbindungen der Ausgestaltung a sind solche der Formel I, worin R1 1,1,2,2-Tetrafluorethyl, Trifluormethyl, 2,2,2-Trifluorethyl, Difluormethyl oder Chlordifluormethyl, R1' Wasserstoff, R3 Methoxy, einer der Reste R2 und R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

Bevorzugte Verbindungen der Ausgestaltung b sind solche der Formel I, worin R1 Difluormethyl, R1' Difluormethoxy oder Methoxy, R3 Methoxy, einer der Reste R2 und R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

Bevorzugte Verbindungen der Ausgestaltung c sind solche der Formel I, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das

R1 gebunden ist, einen Methylen- oder Ethylendioxyrest darstellen, R3 Methoxy, einer der Reste R2 und R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

Bevorzugte Verbindungen der Ausgestaltung d sind solche der Formel I, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen Difluormethylendioxyrest oder einen 1,1,2-Trifluorethylendioxyrest darstellen, R3 Methoxy, einer der Reste R2 und R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

Bevorzugte Verbindungen der Ausgestaltung e sind solche der Formel I, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen Chlortrifluorethylendioxyrest darstellen, R3 Methoxy, einer der Reste R2 und R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

Als erfindungsgemäße Verbindungen seien beispielsweise genannt:
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol,

5-Chlordifluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,

5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
2-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,
2-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
2-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
5-Difluormethoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-benzimidazol
5-Difluormethoxy-6-methoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-benzimidazol,
2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol,
2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol,
2-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-

benzimidazol,
2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
2-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol,
2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol,
2,2-Difluor-6-[(3-methyl-4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
2,2-Difluor-6-[(3-methyl-4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol,
6-[(4,5-Diethoxy-3-methyl-2-pyridyl)methylthio]-2,2-difluor-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
6-[(4,5-Diethoxy-3-methyl-2-pyridyl)methylsulfinyl]-2,2-difluor-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(4,5-Diethoxy-2-pyridyl)methylthio]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(4,5-Diethoxy-2-pyridyl)methylsulfinyl]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(4,5-Diethoxy-3-methyl-2-pyridyl)methylthio]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(4,5-Diethoxy-3-methyl-2-pyridyl)methylsulfinyl]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7,7-Tetrafluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7,7-Tetrafluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7,7-Tetrafluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7,7-Tetrafluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

2,2-Difluor-6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
2,2-Difluor-6-[(3,4-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol,
2,2-Difluor-6-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
2,2-Difluor-6-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
6-[(3,4-Diethoxy-5-methyl-2-pyridyl)methylthio]-2,2-difluor-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
6-[(3,4-Diethoxy-5-methyl-2-pyridyl)methylsulfinyl]-2,2-difluor-5H-[1,3]-dioxolo[4,5-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6,7-Trifluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(3,4-Diethoxy-2-pyridyl)methylthio]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(3,4-Diethoxy-2-pyridyl)methylsulfinyl]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(3,4-Diethoxy-5-methyl-2-pyridyl)methylthio]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
2-[(3,4-Diethoxy-5-methyl-2-pyridyl)methylsulfinyl]-6,6,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,6-Difluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6,6,7,7-Tetrafluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6,6,7,7-Tetrafluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6,6,7,7-Tetrafluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6,6,7,7-Tetrafluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)-methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]-benzimidazol,

6-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol,

6-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,

6-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,

6-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,

6-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol,

6-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]-benzimidazol,

6-[(3,4-Dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol,

6,7-Dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6,7-Dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

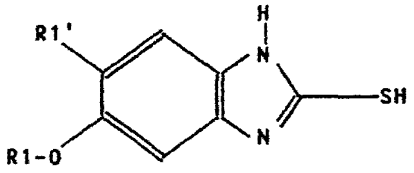
6,7-Dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,7-Dihydro-2-[(3,4-dimethoxy-5-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6,7-Dihydro-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino-[2,3-f]benzimidazol,
6,7-Dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino-[2,3-f]benzimidazol
und die Salze dieser Verbindungen.

Bedingt durch die Tautomerie im Imidazolring ist die 5-Substitution im Benzimidazol mit der 6-Substitution identisch. Entsprechend ist bei den Verbindungen, in denen R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen substituierten Ethylendioxyrest darstellen, die 6-Position im [1,4]-Dioxino[2,3-f]benzimidazolteil mit der 7-Position identisch.

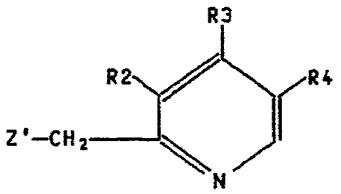
Ein weiterer Gegenstand der Erfindung ist ein Verfahren zur Herstellung der Dialkoxypyridine der Formel I, worin R1, R1', R2, R3. R4 und n die oben angegebenen Bedeutungen haben, und ihrer Salze.

Das Verfahren ist dadurch gekennzeichnet, daß man

a) Mercaptobenzimidazole der Formel II mit Picolinderivaten III,



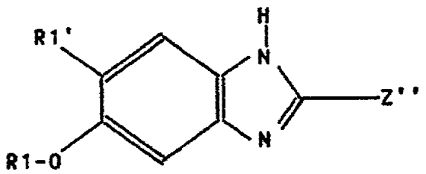
(II)



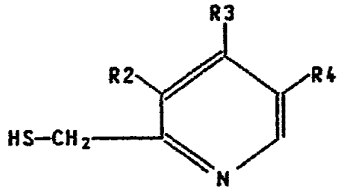
(III),

oder

b) Benzimidazole der Formel IV mit Mercaptopicolinen V,



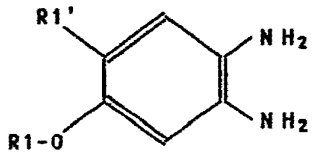
(IV)



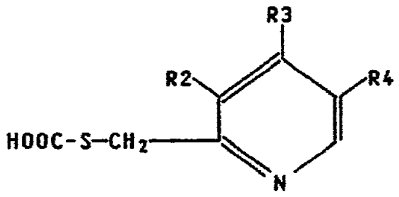
(V),

oder

c) o-Phenylendiamine der Formel VI mit Ameisensäurederivaten VII

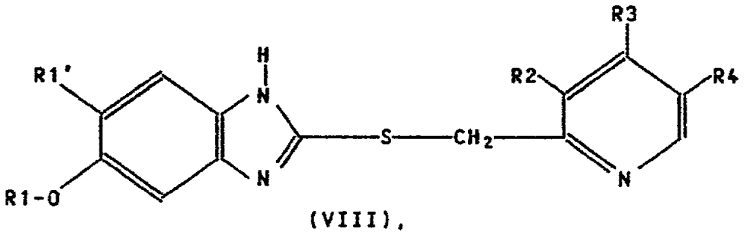


(VI)



(VII),

umsetzt und gegebenenfalls anschließend die nach a), b) oder c) erhaltenen 2-Benzimidazolyl-2-pyridylmethyl-sulfide der Formel VIII

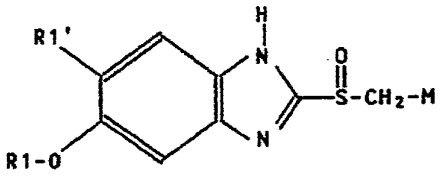


(VIII),

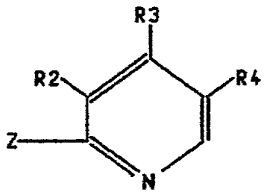
oxidiert und/oder in die Salze überführt,

oder daß man

d) Benzimidazole der Formel IX mit Pyridinderivaten X



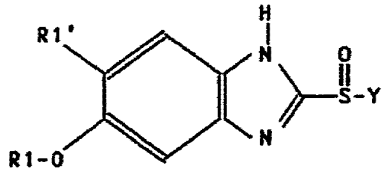
(IX)



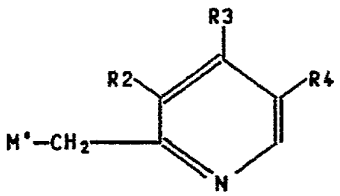
(X),

oder

e) Sulfinylderivate der Formel XI mit 2-Picolinderivaten XII



(XI)



(XII),

umsetzt und gegebenenfalls anschließend in die Salze überführt, wobei Y, Z, Z' und Z'' geeignete Abgangsgruppen darstellen, M für ein Alkalimetallatom (Li, Na oder K) steht, M' für das Äquivalent eines Metallatoms steht und R1, R1', R2, R3, R4 und n die oben angegebenen Bedeutungen haben.

Bei den vorstehend aufgeführten Umsetzungen können die Verbindungen II-XII als solche oder gegebenenfalls in Form ihrer Salze eingesetzt werden.

Die Herstellungsverfahren a), b) und c) führen zu den erfindungsgemäßen Sulfiden, die Oxidation der Verbindungen VIII und die Verfahren d) und e) liefern die erfindungsgemäßen Sulfoxide.

Welche Abgangsgruppen Y, Z, Z' bzw. Z'' geeignet sind, ist dem Fachmann

aufgrund seines Fachwissens geläufig. Eine geeignete Abgangsgruppe Y ist beispielsweise eine Gruppe, die zusammen mit der Sulfinylgruppe, an die sie gebunden ist, ein reaktives Sulfinsäurederivat bildet. Als geeignete Abgangsgruppen Y seien beispielsweise Alkoxy-, Dialkylamino- oder Alkylmercaptogruppen genannt. Als geeignete Abgangsgruppen Z, Z' bzw. Z'' seien beispielsweise Halogenatome, insbesondere Chloratome, oder durch Veresterung (z.B. mit p-Toluolsulfonsäure) aktivierte Hydroxylgruppen genannt. Das Äquivalent eines Metallatoms M' ist beispielsweise ein Alkalimetall- (Li, Na oder K), oder ein Erdalkalimetallatom (z.B. Mg), das durch ein Halogenatom (z.B. Br, Grignard-Reagenz) substituiert ist, oder irgendein anderes, gegebenenfalls substituiertes Metallatom, von dem bekannt ist, daß es bei Substitutionsreaktionen metallorganischer Verbindungen wie die obenerwähnten Metalle reagiert.

Die Umsetzung von II mit III erfolgt in an sich bekannter Weise in geeigneten, vorzugsweise polaren protischen oder aprotischen Lösungsmitteln (wie Methanol, Isopropanol, Dimethylsulfoxid, Aceton, Dimethylformamid oder Acetonitril) unter Zusatz oder unter Ausschluß von Wasser. Sie wird beispielsweise in Gegenwart eines Protonenakzeptors durchgeführt. Als solche eignen sich Alkalimetallhydroxide, wie Natriumhydroxid, Alkalimetallcarbonate, wie Kaliumcarbonat, oder tertiäre Amine, wie Pyridin, Triethylamin oder Ethyldiisopropylamin. Alternativ kann die Umsetzung auch ohne Protonenakzeptor durchgeführt werden, wobei - je nach Art der Ausgangsverbindungen - gegebenenfalls zunächst die Säureadditionssalze in besonders reiner Form abgetrennt werden können. Die Reaktionstemperatur kann zwischen 0^0 und 150^0C liegen, wobei in Gegenwart von Protonenakzeptoren Temperaturen zwischen 20^0 und 80^0C und ohne Protonenakzeptoren zwischen 60^0 und 120^0C - insbesondere die Siedetemperatur der verwendeten Lösungsmittel - bevorzugt sind. Die Reaktionszeiten liegen zwischen 0,5 und 24 Stunden.

Bei der Umsetzung von IV mit V, die in an sich bekannter Weise erfolgt, kommen ähnliche Reaktionsbedingungen wie bei der Umsetzung von II mit III zur Anwendung.

Die Reaktion von VI mit VII wird bevorzugt in polaren, gegebenenfalls was-

serHaltigen Lösungsmitteln in Gegenwart einer starken Säure, z.B. Salzsäure, insbesondere bei der Siedetemperatur des verwendeten Lösungsmittels durchgeführt.

Die Oxidation der Sulfide VIII erfolgt in an sich bekannter Weise und unter den Bedingungen, wie sie dem Fachmann für die Oxidation von Sulfiden zu Sulfoxiden geläufig sind [siehe hierzu z.B. J. Drabowicz und M. Mikolajczyk, Organic preparations and procedures int. 14(1-2), 45-89(1982) oder E. Block in S. Patai, The Chemistry of Functional Groups, Supplement E. Part 1, S. 539-608, John Wiley and Sons (Interscience Publication), 1980]. Als Oxidationsmittel kommen alle für die Oxidation von Sulfiden zu Sulfoxiden üblicherweise verwendeten Reagenzien in Frage, z.B. Hypohalogenite, insbesondere Peroxysäuren, wie z.B. Peroxyessigsäure, Trifluorperoxyessigsäure, 3,5-Dinitroperoxybenzoesäure, Peroxymaleinsäure oder bevorzugt m-Chlorperoxybenzoesäure.

Die Reaktionstemperatur liegt (je nach Reaktivität des Oxidationsmittels und Verdünnungsgrad) zwischen -70°C und der Siedetemperatur des verwendeten Lösungsmittels, bevorzugt jedoch zwischen -50° und +20°C. Die Oxidation wird zweckmäßigerweise in inerten Lösungsmitteln, z. B. aromatischen oder chlorierten Kohlenwasserstoffen, wie Benzol, Toluol, Dichlormethan oder Chloroform, oder in Estern, wie Essigsäureethylester oder Essigsäureisopropylester, oder in Ethern, wie Dioxan, mit Zusatz von Wasser oder ohne Wasser durchgeführt.

Die Umsetzung von IX mit X erfolgt bevorzugt in inerten Lösungsmitteln, wie sie auch für die Reaktion von Enolationen mit Alkylierungsmitteln üblicherweise verwendet werden. Beispielsweise seien aromatische Lösungsmittel wie Benzol oder Toluol genannt. Die Reaktionstemperatur liegt (je nach Art des Alkalimetallatoms M und der Abgangsgruppe Z) in der Regel zwischen 0° und 120°C, wobei die Siedetemperatur des verwendeten Lösungsmittels bevorzugt ist. Beispielsweise [wenn M Li(Lithium) und Z Cl(Chlor) darstellt und die Umsetzung in Benzol durchgeführt wird] ist die Siedetemperatur von Benzol (80°C) bevorzugt.

Die Verbindungen XI werden mit den Verbindungen XII in an sich bekannter

Weise umgesetzt, wie sie dem Fachmann für die Reaktion metallorganischer Verbindungen geläufig ist.

Je nach Art der Ausgangsverbindungen, die gegebenenfalls auch in Form ihrer Salze eingesetzt werden können, und in Abhängigkeit von den Reaktionsbedingungen werden die erfindungsgemäßen Verbindungen zunächst entweder als solche oder in Form ihrer Salze gewonnen.

Im übrigen erhält man die Salze durch Auflösen der freien Verbindungen in einem geeigneten Lösungsmittel, z.B. in einem chlorierten Kohlenwasserstoff, wie Methylenchlorid oder Chloroform, einem niedermolekularen aliphatischen Alkohol (Ethanol, Isopropanol), einem Ether (Diisopropylether), Keton (Aceton) oder Wasser, das die gewünschte Säure bzw. Base enthält, oder dem die gewünschte Säure bzw. Base - gegebenenfalls in der genau berechneten stöchiometrischen Menge anschließend zugegeben wird.

Die Salze werden durch Filtrieren, Umfällen, Ausfällen oder durch Verdampfen des Lösungsmittels gewonnen.

Erhaltene Salze können durch Alkalisieren bzw. Ansäuern, z.B. mit wäßrigem Natriumhydrogencarbonat bzw. mit verdünnter Salzsäure, in die freien Verbindungen umgewandelt werden, welche wiederum in die Salze übergeführt werden können. Auf diese Weise lassen sich die Verbindungen reinigen, oder es lassen sich pharmakologisch nicht verträgliche Salze in pharmakologisch verträgliche Salze umwandeln.

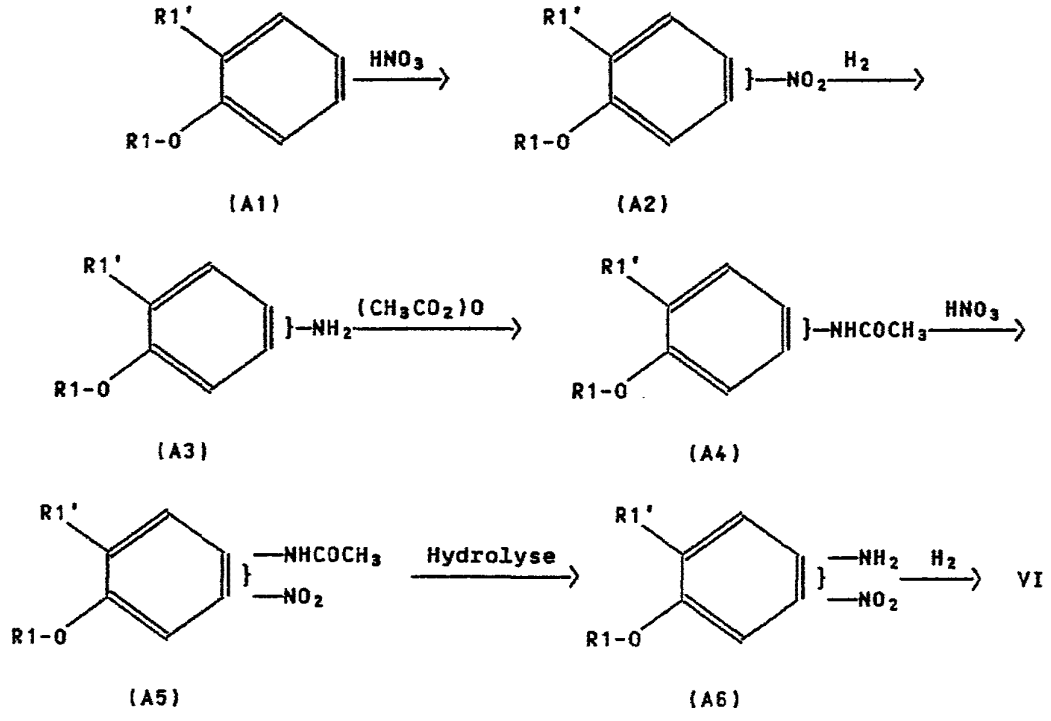
Die erfindungsgemäßen Sulfoxide sind optisch aktive Verbindungen. Die Erfindung umfaßt daher sowohl die Enantiomeren als auch ihre Mischungen und Racemate. Die Enantiomeren können in an sich bekannter Weise (beispielsweise durch Herstellung und Trennung entsprechender diastereoisomerer Verbindungen) separiert werden. Die Enantiomeren können aber auch durch asymmetrische Synthese, beispielsweise durch Reaktion optisch aktiver reiner Verbindungen XI oder diastereoisomer reiner Verbindungen XI mit Verbindungen XII hergestellt werden [siehe hierzu K.K. Andersen, Tetrahedron Lett., 93 (1962)].

Die erfindungsgemäßen Verbindungen werden bevorzugt durch Umsetzung von II mit III und gegebenenfalls anschließende Oxidation des entstandenen Sulfids VIII synthetisiert.

Die Verbindungen der Formel II sind teils bekannt (DE-OS 31 32 613), oder sie können nach bekannten Vorschriften analog hergestellt werden. Verbindungen II erhält man beispielsweise durch Umsetzen von Verbindungen VI mit Kohlendisulfid in Gegenwart von Alkalihydroxiden oder mit Alkali-O-ethyldithiocarbonaten.

Die Verbindungen VI können nach der im folgenden Reaktionsschema A angegebenen allgemeinen Herstellungsmethode synthetisiert werden:

Reaktionsschema A:



Die Ausgangsverbindungen A1 - A3 können nach bekannten Methoden oder analog zu diesen [z.B. J.Org.Chem. 44, 2907-2910 (1979); J.Org.Chem. 29, 1-11 (1964); DE-OS 20 29 556; DE-OS 28 48 531; J.Fluorine Chem. 18, 281-91 (1981); Synthesis 1980, 727-8] hergestellt werden, wobei bei ungleichen Substituenten R1' und R1-O- auch Isomerengemische entstehen können.

Die Verbindungen IV, IX und XI können beispielsweise aus den Verbindungen II in für den Fachmann bekannter Weise hergestellt werden.

Die Verbindungen IX werden beispielsweise aus den Verbindungen II durch Methylierung, Oxydation und anschließende Deprotonierung - z.B. mit Alkalimetallhydriden oder -alkoholaten oder üblichen metallorganischen Verbindungen erhalten. Die Verbindungen X werden in Anlehnung an Z. Talik, Roczniki Chem. 35, 475 (1961) hergestellt.

Die Verbindungen III können - je nach Substitutionsmuster - auf verschiedene Weise hergestellt werden:

1. Verbindungen III mit R2 und R3 = 1-3C-Alkoxy und R4 = Wasserstoff oder 1-3C-Alkyl.

   Diese Verbindungen werden z.B. ausgehend von bekannten oder auf bekanntem Wege herstellbaren 3-Hydroxy- bzw. 3-Hydroxy-5-alkyl-pyridinen durch Benzylierung der Hydroxygruppe (z.B. mit Kaliumhydroxid und Benzylchlorid in Dimethylsulfoxid), N-Oxidation (z.B. mit 30 %-igem Wasserstoffperoxid), Nitrierung in 4-Position (z.B. mit Nitriersäure), Austausch der Nitrogruppe gegen die 1-3C-Alkoxygruppe (z.B. durch Umsetzung mit Alkali-alkoxid), reduktive Debenzylierung und gleichzeitige N-Deoxygenierung (z.B. mit Wasserstoff an Palladium/Kohle in saurem Medium), Einführung der Hydroxymethylgruppe in o-Position zum Pyridinstickstoff (z.B. durch Umsetzung mit alkalischer Formalinlösung), Umwandlung der 3-Hydroxy- in eine 1-3C-Alkoxygruppe (z.B. durch Alkylierung mit 1-3C-Alkyliodid in basischem Medium) und Einführung der Fluchtgruppe Z' (z.B. durch Umsetzung mit Thionylchlorid) hergestellt. In einer bevorzugten Alternative werden die Verbindungen ausgehend von bekannten oder auf bekanntem Wege herstellbaren

3-Hydroxy-2-alkyl- bzw. 3-Hydroxy-2,5-dialkyl-pyridinen durch Alkylierung der Hydroxygruppe (z.B. mit Kaliumhydroxid und Methyliodid in Dimethylsulfoxid), N-Oxidation (z.B. mit 30%igem Wasserstoffperoxid), Nitrierung in 4-Position (z.B. mit Salpetersäure), Austausch der Nitrogruppe gegen die 1-3C-Alkoxygruppe (z.B. durch Umsetzung mit Alkalialkoxid), Umwandlung in das 2-Acetoxymethylpyridin (z.B. mit heißem Essigsäureanhydrid), Verseifung (z.B. mit verdünnter Natronlauge) zur Hydroxymethylgruppe und Einführung der Fluchtgruppe Z' (z.B. durch Umsetzung mit Thionylchlorid) hergestellt.

2. Verbindungen III mit R3 und R4 = 1-3C-Alkoxy und R2 = Wasserstoff.

Diese Verbindungen werden z.B. ausgehend vom bekannten 5-Hydroxy-2-methylpyridinen durch Alkylierung der Hydroxygruppe (z.B. mit 1-3C-Alkyliodid und Kaliumhydroxid in Dimethylsulfoxid), N-Oxidation (z.B. mit 30 %-igem Wasserstoffperoxid), Nitrierung in 4-Position (z.B. mit Nitriersäure), Austausch der Nitrogruppe gegen die 1-3C-Alkoxygruppe (z.B. durch Umsetzung mit Alkali-alkoxid), Umwandlung in das 2-Acetoxymethylpyridin (z.B. mit heißem Essigsäureanhydrid), Verseifung (z.B. mit verdünnter Natronlauge) zur 2-Hydroxymethylgruppe und Einführung der Fluchtgruppe Z' (z.B. durch Umsetzung mit Thionylchlorid) hergestellt.

3. Verbindungen III mit R3 und R4 = 1-3C-Alkoxy und R2 = 1-3C-Alkyl.

Diese Verbindungen werden z.B. ausgehend von bekannten oder auf bekanntem Weg herstellbaren 2-Methyl-3-alkyl-4-alkoxypyridinen (siehe z.B. EP-A 0 080 602) durch N-Oxidation (z.B. mit 30 %-igem Wasserstoffperoxid), gezielte Acetoxylierung und anschließende Verseifung in 5-Postition (z.B. mit Essigsäureanhydrid und anschließend Natronlauge), Alkylierung der 5-Hydroxygruppe (z.B. mit 1-3C-Alkyliodid und Natronlauge in Dimethylsulfoxid), N-Oxidation (z.B. mit m-Chlorperoxibenzoesäure), Umwandlung in das 2-Acetoxymethylpyridin (z.B. mit heißem Essigsäureanhydrid), Verseifung (z.B. mit verdünnter Natronlauge) zur 2-Hydroxymethylgruppe und Einführung der Fluchtgruppe Z' (z.B. durch Umsetzung mit Thionylchlorid) hergestellt.

Welche Reaktionsbedingungen (Temperaturen, Reaktionszeiten, Lösungsmittel etc.) bei den oben skizzierten Synthesewegen für die Herstellung der Verbindungen III im einzelnen erforderlich sind, ist dem Fachmann aufgrund seines Fachwissens geläufig. Die genaue Herstellung einzelner Vertreter der Verbindungen III ist in den Beispielen angegeben. Die Herstellung weiterer Vertreter erfolgt in analoger Weise.

Verbindungen der Formel III, worin R3 einen 1-3C-Alkoxyrest darstellt, einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere einen 1-3C-Alklyrest darstellt sind neu und ebenfalls Gegenstand der Erfindung.

Die Verbindungen V, VII und XII werden beispielsweise ausgehend von den Verbindungen III auf für den Fachmann bekannten Wegen hergestellt.

Die folgenden Beispiele erläutern die Erfindung näher, ohne sie einzuschränken. Die in den Beispielen namentlich aufgeführten Verbindungen der Formel I sowie Salze dieser Verbindungen sind bevorzugter Gegenstand der Erfindung. In den Beispielen bedeutet F. Schmelzpunkt, Zers. steht für Zersetzung, Sdp. steht für Siedepunkt.

Beispiele

1. 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol

Zu einer Lösung von 1,64 g 2-Mercapto-5-trifluormethoxy-1H-benzimidazol in 40 ml Ethanol und 20 ml 1n Natronlauge werden 1,57 g 2-Chlormethyl-4,5-dimethoxypyridiniumchlorid zugegeben, 2 Stunden bei 20°C und anschließend noch 1 Stunde bei 40°C gerührt, Ethanol am Rotationsverdampfer (1 kPa/40°C) abdestilliert, der dabei ausfallende farblose Niederschlag über eine Nutsche filtriert, mit 1n Natronlauge und Wasser nachgewaschen und getrocknet. Man erhält 2,15 g (79 % d.Th.) der Titelverbindung vom F. 92-93°C.

Analog erhält man
5-Chlordifluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol (Öl),
5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol (F. 159-160°C) und
5-Difluormethoxy-6-fluor-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol
durch Umsetzung von
5-Chlordifluormethoxy-2-mercapto-1H-benzimidazol,
5-Difluormethoxy-2-mercapto-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-mercapto-1H-benzimidazol,
5-Difluormethoxy-2-mercapto-6-methoxy-1H-benzimidazol und
5-Difluormethoxy-6-fluor-2-mercapto-1H-benzimidazol
mit
2-Chlormethyl-4,5-dimethoxypyridiniumchlorid.

2. 2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol

Zu einer Lösung von 0,36 g 2-[4,5-Dimethoxy-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol in 10 ml Methylenchlorid tropft man bei -50°C 5,5 ml einer 0,2m Lösung von m-Chlorperoxibenzoesäure in Methylenchlorid zu und rührt weitere 30 Minuten bei der angegebenen Temperatur. Nach Zugabe von 0,3 ml Triethylamin wird die kalte Reaktionsmischung in 10 ml 5 %-ige Natriumthiosulfat- und 10 ml 5 %-ige Natriumcarbonatlösung eingerührt, nach Phasentrennung wird noch dreimal mit 10 ml Methylenchlorid extrahiert, die vereinigten organischen Phasen werden einmal mit 5 ml einer 5 %igen Natriumthiosulfatlösung gewaschen, getrocknet, vom Trockenmittel (Magnesiumsulfat) filtriert und eingeengt. Der Rückstand wird mit Diisopropylether zur Kristallisation gebracht und anschließend aus Methylenchlorid/Diisopropylether umgefällt. Man erhält 0,27 g (72 % d.Th.) der Titelverbindung als farblosen Feststoff vom F. 159-61°C (Zers.).

Analog erhält man
5-Chlordifluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol [F. 159°C (Zers.)],
5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol und
5-Difluormethoxy-6-fluor-2,2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol
durch Oxidation der weiteren Sulfide des Beispiels 1 mit m-Chlorperoxibenzoesäure.

3. 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol

Nach der in Beispiel 1 angegebenen Arbeitsweise erhält man durch Umsetzung von 1,07 g 2-Mercapto-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol mit

0,90 g 2-Chlormethyl-4,5-dimethoxypyridiniumchlorid in 15 ml Ethanol unter Zusatz von 17 ml 0,5 n Natronlauge 1,40 g der Titelverbindung als gelbes Öl. Umkristallisation aus Petrolether liefert das Produkt in Form farbloser Kristalle vom F. 125-127°C. Ausbeute: 1,20 g (72% d.Th).

4. 2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol

Nach der in Beispiel 2 angegebenen Arbeitsweise erhält man durch Oxidation von 0,76 g 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol mit 19 ml einer 0,1 m Lösung von m-Chlorperoxibenzoesäure in 30 ml Methylenchlorid bei -40°C nach Extraktion eine Lösung des Produktes in Methylenchlorid. Nach Trocknung über Magnesiumsulfat wird vom Trockenmittel filtriert, eingeengt und der Rückstand aus Methylenchlorid/Diisopropylether kristallisiert. Man erhält 0,64 g (82% d.Th.) der Titelverbindung in Form farbloser Kristalle vom F. 160-162°C (Zers.).

5. 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol

1,0 g 2-Mercapto-5-(2,2,2-trifluorethoxy)-1H-benzimidazol werden in 15 ml Ethanol und 8,5 ml 1n Natronlauge gelöst, mit 0,90 g 2-Chlormethyl-4,5-dimethoxypyridiniumchlorid versetzt und 20 Stunden gerührt. Nach Zugabe von 30 ml Wasser extrahiert man dreimal mit je 30 ml Methylenchlorid, wäscht die Methylenchloridphase einmal mit 5 ml 0,1 n Natronlauge, trocknet die vereinigten organischen Phasen über Magnesiumsulfat und engt nach Filtration des Trockenmittels vollständig ein. Man erhält 1,51 g (94% d.Th.) der Titelverbindung als amorphen, festen Rückstand vom F. 55-57°C.

6. 2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol

0,8 g 2-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol werden in 15 ml Dioxan und 2,5 ml 1 n Natronlauge gelöst. Innerhalb von 2 Stunden wird ein Gemisch von 3 ml 8-prozentiger Natriumhypochloritlösung und 3,5 ml 1n Natronlauge unter Kühlung auf 0-5°C zuge-

tropft. Nach Zugabe von 5 ml 5%iger Natriumthiosulfatlösung wird zur Trockene eingeengt, der Rückstand in Wasser aufgenommen und mit Phosphatpuffer auf pH7 gestellt. Man filtriert vom ausgefallenen Feststoff, trocknet und kristallisiert aus Essigester/Diisopropylether um. Man erhält 0,45 g (55% d.Th.) der Titelverbindung als farblose Kristalle vom F. 142-143°C (Zers.).

7. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol

Nach der in Beispiel 1 angegebenen Arbeitsweise erhält man durch Umsetzung von 1,07 g 2-Mercapto-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol mit 0,96 g 2-Chlormethyl-4,5-dimethoxy-3-methylpyridiniumchlorid in 12 ml Ethanol unter Zusatz von 17 ml 0,5 n Natronlauge 1,46 g (83% d.Th.) der Titelverbindung vom F. 127-128°C (farbloses Pulver).

8. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol

Nach der in Beispiel 2 angegebenen Arbeitsweise erhält man durch Oxidation von 0,99 g 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol mit 12 ml einer 0,2 m Lösung von m-Chlorperoxibenzoesäure in Methylenchlorid bei -40°C und einer Reaktionszeit von 1,5 Stunden 0,8 g eines blaßgelben Öls. Zweimalige Umkristallisation aus Methylenchlorid/Diisopropylether liefert 0,30 g (34% d.Th.) der Titelverbindung in Form farbloser Kristalle vom F. 125°C (Zers.).

9. 5-Difluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol

Nach der in Beispiel 1 angegebenen Arbeitsweise erhält man durch Umsetzung von 0,38 g (2 mMol) 5-Difluormethoxy-2-mercapto-1H-benzimidazol mit 0,48 g (2 mMol) 2-Chlormethyl-4,5-dimethoxy-3-methylpyridiniumchlorid in 10 ml Ethanol unter Zusatz von 8,8 ml 1n Natronlauge nach zwei Stunden bei 50°C 0,64 g (84% d.Th.) der Titelverbindung vom F. 100-102°C (farbloses Kristallpulver).

10. 2-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5-(1,1,2,2-tetrafluorethoxyl)-1H-benzimidazol

Zu einer Lösung von 0,46 g (1,7 mMol) 2-Mercapto-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol in 10 ml Ethanol, 10 ml Wasser und 1,8 ml 2n Natronlauge werden 0,38 g (1,7 mMol) 2-Chlormethyl-3,4-dimethoxy-pyridiniumchlorid zugegeben; nach einer Stunde Rühren bei 20°C werden erneut 10 ml Wasser zugetropft; anschließend wird bei 20°C nochmals vier Stunden gerührt. Man filtriert vom ausgefallenen Feststoff, wäscht mit 0,01 n Natronlauge und anschließend mit Wasser neutral und trocknet bis zur Gewichtskonstanz. Man erhält 0,63 g (90% d.Th.) der Titelverbindung als farbloses Kristallpulver vom F. 98-102°C.

Analog erhält man
5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol (F. 104-108°C) und
5-Difluormethoxy-6-methoxy-2-[(3,4-dimethoxy-2-pyridyl)methylthio]-1H-benzimidazol (F. 137-138°C) durch Umsetzung von
5-Difluormethoxy-2-mercapto-1H-benzimidazol und
5-Difluormethoxy-6-methoxy-2-mercapto-1H-benzimidazol mit
2-Chlormethyl-3,4-dimethoxypyriniumchlorid.

11. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol

Nach der in Beispiel 1 angegebenen Arbeitsweise erhält man durch Umsetzung von 1,15 g 2-Mercapto-5-trifluormethoxy-1H-benzimidazol mit 1,20 g 2-Chlormethyl-4,5-dimethoxy-3-methylpyridiniumchlorid in 20 ml Isopropanol unter Zusatz von 20,5 ml 0,5n Natronlauge 1,40 g (70 % d.Th) der Titelverbindung. Umkristallisation aus Diisopropylether/Petrolether liefert ein Produkt vom F. 94-97°C.

Analog erhält man
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol,

5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol und
5-Difluormethoxy-6-fluor-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-benzimidazol
durch Umsetzung von
2-Mercapto-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
5-Chlordifluormethoxy-2-mercapto-1H-benzimidazol,
5,6-Bis(difluormethoxy)-2-mercapto-1H-benzimidazol,
5-Difluormethoxy-2-mercapto-6-methoxy-1H-benzimidazol und
5-Difluormethoxy-6-fluor-2-mercapto-1H-benzimidazol
mit
2-Chlormethyl-4,5-dimethoxy-3-methyl-pyridiniumchlorid.

12. 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol

Nach der in Beispiel 2 angegebenen Arbeitsweise erhält man durch Oxidation von 0,24 g 2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5-trifluormethoxy-1H-benzimidazol mit 3,3 ml einer 0,2m Lösung von m-Chlorperoxibenzoesäure in Methylenchlorid bei -50°C und Umfällung aus Methylenchlorid/Diisopropylether 0,19 g (76 % d.Th.) der Titelverbindung als farbloses Pulver; 158-159°C Zers.

Analog erhält man
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-(2,2,2-trifluorethoxy)-1H-benzimidazol,
5-Chlordifluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol [F. 133-135 (Zers.)],
5,6-Bis(difluormethoxy)-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-benzimidazol,
5-Difluormethoxy-6-methoxy-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methyl-

sulfinyl]-1H-benzimidazol,
5-Difluormethoxy-6-fluor-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methyl-sulfinyl]-1H-benzimidazol
2-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol [F. 117-119°C (Zers.)] und
5-Difluormethoxy-2-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-1H-benzimidazol [F. 136°C (Zers.)]
durch Oxidation der Sulfide der obigen Beispiele 9 bis 11 mit m-Chlorperoxibenzoesäure.

13. 2,2-Difluor-6-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol

Zu einer Lösung von 0,92g 2,2-Difluor-5H-[1,3]-dioxolo[4,5-f]benzimidazol-6-thiol in 10 ml Ethanol und 10 ml 1n Natronlauge werden 0,96 g 2-Chlormethyl-4,5-dimethoxy-3-methylpyridiniumchlorid zugegeben. Man rührt die gelbe Reaktionsmischung 1 Stunde bei 20°C, setzt nochmals 10 ml Wasser zu, wobei ein farbloser Feststoff ausfällt, rührt weitere 5 Stunden, filtriert, wäscht mit 1n Natronlauge und Wasser nach und trocknet bis zur Gewichtskonstanz. Das amorphe Pulver wird aus Methylenchlorid/Diisopropylether umkristallisiert. Man erhält 1,5 g (93 % d.Th.) der Titelverbindung in Form farbloser Kristalle vom F. 160-61°C.

Analog erhält man
6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol und
6,7-Dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol
durch Umsetzung von
6,6,7-Trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol bzw.
6,7-Dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol mit
2-Chlormethyl-4,5-dimethoxy-3-methylpyridiniumchlorid.

14. 2,2-Difluor-6-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol

Zu einer auf -40°C gekühlten Suspension von 0,80 g 2,2-Difluor-6[(4,5-dimethoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol in 10 ml Methylenchlorid tropft man innerhalb von 10 Minuten 21 ml einer 0,1n Lösung von m-Chlorperoxibenzoesäure in Methylenchlorid zu. Man rührt weitere 20 Minuten und läßt die Temperatur dabei auf -20°C ansteigen, setzt 0,5 ml Triethylamin zu und gießt das Reaktionsgemisch in 40 ml einer jeweils 5 %-igen Natriumthiosulfat- und 5 %-igen Natriumcarbonatlösung ein. Nach Phasentrennung wird die Wasserphase noch zweimal mit je 20 ml Methylenchlorid extrahiert; die vereinigten organischen Phasen werden mit einem Gemisch aus jeweils 5 ml Natriumthiosulfat- und Natriumcarbonatlösung gewaschen, getrocknet und eingeengt. Der Rückstand wird aus Methylenchlorid/Diisopropylether umkristallisiert. Man erhält 0,62 g (75 % d.Th.) der Titelverbindung; Zers. 189-90°C.

Analog erhält man
6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol und
6,7-Dihydro-2-[(4,5-dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol
durch Oxidation der unter Beispiel 13 genannten weiteren Sulfide mit m-Chlorperoxibenzoesäure.

15. 6-[(4,5-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]-benzimidazol

Nach der in Beispiel 13 beschriebenen Arbeitsweise erhält man durch Umsetzung von 0,85 g 5H-[1,3]-dioxolo[4,5-f]-benzimidazol-6-thiol mit 0,98 g 2-Chlormethyl-4,5-dimethoxypyridiniumchlorid in 10 ml Ethanol und 10 ml Wasser unter Zusatz von 8,5 ml 1n Natronlauge nach einer Reaktionszeit von 20 Stunden und nach Einengen des Lösungsmittels im Vakumm auf ein Volumen von 10 ml einen bräunlichen Feststoff. Man löst das Rohprodukt in 30 ml

Methylenchlorid, klärt mit Bleicherde (z. B. Tonsil®), engt ein, kristallisiert durch Zugabe von Diisopropylether und kocht den nun blaßgelben Feststoff in 5 ml Methanol aus. Man erhält 0,90 g (60% d.Th.) der Titelverbindung als farblosen Feststoff vom F. 198-200°C.

16. 6-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]-benzimidazol

Nach der in Beispiel 14 beschriebenen Arbeitsweise erhält man durch Oxidation von 0,7 g 6-[4,5-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]-benzimidazol mit 23 ml einer 0,1 m Lösung von m-Chlorperoxibenzoesäure nach Umkristallisation aus Diethylether 0,27 g der Titelverbindung in Form farbloser Kristalle vom F. 199°C (Zers.).

17. 2,2-Difluor-6-[(3,4-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol

Nach der in Beispiel 13 angegebenen Arbeitsweise erhält man durch Umsetzung von 0,69 g (3 mMol) 2,2-Difluor-5H-[1,3]-dioxolo[4,5-f]-benzimidazol-6-thiol mit 0,67 g (3 mMol) 2-Chlormethyl-3,4-dimethoxypyridiniumchlorid in einem Gemisch von 10 ml Ethanol und 10 ml Wasser unter Zusatz von 3,3 ml 2n Natronlauge nach 10 Stunden Reaktionszeit 1,05 g (92% d.Th.) der Titelverbindung als feinkristallines, farbloses Pulver vom F. 185-187°C.

Analog erhält man
6-[(3,4-Dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol (F. 155-157°C)
durch Umsetzung von
5H-[1,3]-dioxolo[4,5-f]benzimidazol-6-thiol
mit
2-Chlormethyl-3,4-dimethoxypyridiniumchlorid.

18. 6-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol

0,78 g (4 mMol) 5H-[1,3]-dioxolo[4,5-f]benzimidazol-6-thiol werden mit 0,95 g (4 mMol) 2-Chlormethyl-4,5-dimethoxy-3-methylpyridiniumchlorid in

30 ml Isopropanol 15 Stunden unter Rückfluß zum Sieden erhitzt. Man filtriert vom ausgefallenen Feststoff, rührt mit Isopropanol aus, filtriert erneut und trocknet bis zur Gewichtskonstanz. Man erhält 1,0 g (59% d.Th.) des Dihydrochlorids der Titelverbindung als farblosen Feststoff vom F. 206°C (Zers.).

19. 2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol

Zu einer auf 50°C erwärmten Lösung von 0,69 g 2,2-Difluor-5H-[1,3]-dioxolo[4,5-f]benzimidazol-6-thiol und 0,67 g 2-Chlormethyl-4,5-dimethoxypyridiniumchlorid in 9 ml Ethanol und 4 ml Wasser tropft man innerhalb einer Minute 6,3 ml 1n Natronlauge zu. Beim Abkühlen der klaren Reaktionsmischung auf 20°C fällt nach kurzer Zeit ein farbloser Niederschlag aus. Man rührt weitere 5 Stunden bei 20°C, saugt über eine Nutsche ab, wäscht mit 1n Natronlauge und Wasser nach und trocknet bis zur Gewichtskonstanz. Der beige Feststoff wird in 10 ml Methylenchlorid gelöst, von unlöslichen Bestandteilen filtriert, das Filtrat eingeengt und durch Zugabe von Diisopropylether und nach Abkühlung zur Kristallisation gebracht. Man erhält 1,02 g (90 % d.Th.) der Titelverbindung vom F. 189-91°C.

Analog erhält man
6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino[2,3-f]benzimidazol und
6,7-Dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylthio]-1H-[1,4]-dioxino-[2,3-f]benzimidazol
durch Umsetzung von
6,6,7-Trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol,
6-Chlor-6,7,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol, bzw.
6,7-Dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol
mit
2-Chlormethyl-4,5-dimethoxy-pyridiniumchlorid.

20. 2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol

0,76 g 2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol werden in 10 ml Dioxan und 2 ml 1n Natronlauge gelöst. Unter Eiskühlung tropft man zuerst eine äquimolare Menge einer titrierten wäßrigen Natriumhypochloritlösung, die mit 1 Mol pro Liter Natronlauge versetzt ist, zu, und setzt nach einer Stunde nochmals 1 Äquivalent und nach 3 Stunden die halbe äquimolare Menge Natriumhypochlorit zur Erreichung einer vollständigen Umsetzung zu. Nach 4 Stunden Reaktionszeit werden 5 ml 5 %-ige Natriumthiosulfatlösung und weitere 25 ml Dioxan zugegeben, die obere Dioxanphase abgetrennt, einmal mit 5 ml Natriumthiosulfatlösung gewaschen und am Rotationsverdampfer eingeengt. Der ölige Rückstand wird in 20 ml Wasser und 10 ml Essigsäureethylester gelöst und mit ca. 100 ml einer Pufferlösung vom pH 6,8 auf pH 7 gestellt. Der ausgefallene Feststoff wird über eine Nutsche abgesaugt, mit Wasser gewaschen, bei 0°C mit Aceton ausgerührt und getrocknet. Man erhält 0,7 g (87 % d.Th.) der Titelverbindung in Form farbloser Kristalle; Zers. bei 211-213°C.

Analog erhält man

2,2-Difluor-6-[(3,4-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]-benzimidazol [F. 177-178°C (Zers.)]

6-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo-[4,5-f]-benzimidazol,

6,6,7-Trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol,

6-[(3,4-Dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol [F. 170-171°C (Zers.)],

6-Chlor-6,7,7-trifluor-6,7-dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol und

6,7-Dihydro-2-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-1H-[1,4]-dioxino[2,3-f]benzimidazol

durch Oxidation der in den Beispielen 17 bis 19 genannten weiteren Sulfide mit Natriumhypochloritlösung.

21. 2-Mercapto-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol

a) 55 g 1-Nitro-4-(1,1,2,2-tetrafluorethoxy)benzol werden in 300 ml Ethanol an 0,5 g 10%iger Palladiumkohle in einer Umlaufhydrierungsapparatur unter Atmosphärendruck 1 h bei 20-45°C hydriert, der Katalysator abfiltriert und die Lösung bei 40°C im Vakuum eingeengt. Man verdünnt das 4-(1,1,2,2-tetrafluorethoxy)anilin mit 100 ml Eisessig und tropft 23 ml Essigsäureanhydrid bei Raumtemperatur zu, versetzt nach 30 Min. mit 2 ml Wasser, engt nach kurzer Zeit die Lösung bei 50°C im Vakuum ein und versetzt mit 500 ml Eiswasser. Man erhält 56 g (97%) N-[4-(1,1,2,2-tetrafluorethoxy)phenyl]-acetamid vom Schmp. 121-122°C.

b) Man löst 55 g der vorstehenden Verbindung in 380 ml Dichlormethan, tropft 55 ml 100%ige Salpetersäure in 10 Min. bei Raumtemperatur zu und rührt noch 6 h. Die organische Lösung wird dann mit wäßriger Natriumcarbonatlösung und Wasser gewaschen, mit Magnesiumsulfat getrocknet und eingeengt. Man erhält 65 g (100%) N-[2-Nitro-4-(1,1,2,2-tetrafluorethoxy)phenyl]-acetamid vom Schmp. 80-81°C (aus Cyclohexan).

c) Man löst 63 g vorstehender Verbindung in 450 ml Methanol, tropft bei Raumtemperatur 106 ml 6 m Natronlauge zu, kühlt im Eisbad und fällt durch Zutropfen von 900 ml Wasser 53 g (98%) 2-Nitro-4-(1,1,2,2-tetrafluorethoxy)-anilin (Schmp. 85-86°C).

d) 33 g vorstehender Verbindung werden in ca. 600 ml Isopropanol an 1 g 10%iger Palladiumkohle in einer Umlaufhydrierungsapparatur drucklos bei Raumtemperatur hydriert. Man saugt den Katalysator ab und fällt mit 4 m Chlorwasserstoff in Ether 34 g (89%) 4-(1,1,2,2-Tetrafluorethoxy)-1,2-phenylendiamin-dihydrochlorid vom Schmp. 275-276°C (Zersetzung).

e) 33 g vorstehender Verbindung werden mit 330 ml Ethanol, 60 ml Wasser, 8,9 g Natriumhydroxid und 23 g Kalium-O-ethyldithiocarbonat (umkristallisiert aus Isopropanol) versetzt und 15 h unter Rückfluß zum Sieden erhitzt. Man versetzt mit 1,2 l Eiswasser, stellt mit Natronlau-

ge auf pH 13-14, klärt mit Aktivkohle und fällt mit verdünnter Salzsäure bis pH 3,5. Man erhält 27 g (91%) der Titelverbindung vom Schmp. 316-319°C (aus Isopropanol).

22. 2-Mercapto-5-trifluormethoxy-1H-benzimidazol

Analog Beispiel 21e) erhält man durch Umsetzen von 4-Trifluormethoxy-1,2-phenylendiamin-dihydrochlorid (vgl. C.A. 55, 23408d, 1961) mit Kalium-O-ethyldithiocarbonat und Natronlauge in Ethanol in 75 % Ausbeute die Titelverbindung vom Schmp. 305-307°C (Zersetzung, aus Toluol).

23. 2-Mercapto-5-(2,2,2-trifluorethoxy)-1H-benzimidazol

a) 50 g 1-(2,2,2-Trifluorethoxy)-4-nitrobenzol (Synthesis 1980, Seite 727) werden analog Beispiel 21a) hydriert und acetyliert. Man erhält 50 g (95 %) N-[4-(2,2,2-Trifluorethoxy)phenyl]acetamid (Schmp. 140-141°C).

b) Man rührt 42 g voranstehender Verbindung mit 9,7 ml 100% Salpetersäure in 290 ml Eisessig 18 h bei Raumtemperatur und fällt mit Wasser. Man erhält 47 g (94%) N-[2-Nitro-4-(2,2,2-trifluorethoxy)phenyl]-acetamid (Schmp. 117-118°C).

c) Man hydrolysiert 47 g voranstehender Verbindung analog Beispiel 21c und erhält 38,7 g (97%) 2-Nitro-4-(2,2,2-trifluorethoxy)-anilin (Schmp. 84-85°C).

d) Man hydriert 37 g voranstehender Verbindung analog Beispiel 21d) und erhält 41 g (94%) 4-(2,2,2-Trifluorethoxy)-1,2-phenylendiamin-dihydrochlorid vom Schmp. 230-233°C (Zersetzung).

e) Analog Beispiel 21e) erhält man aus 36 g voranstehender Verbindung 30 g (94%) der Titelverbindung (Schmp. 288-290°C).

24. 5-Chlordifluormethoxy-2-merkapto-1H-benzimidazol

a) 10,0 g N-[4-(Chlordifluormethoxy)phenyl]-acetamid (Schmp. 101-103°C, aus 4-Chlordifluormethoxyanilin und Essigsäureanhydrid) und 12,3 ml 100% Salpetersäure werden in 80 ml Dichlormethan 4 h bei 20°C gerührt. Man

neutralisiert mit wäßriger Kaliumhydrogencarbonatlösung, engt die organische Schicht ein und erhält 11,4 g (96%) N-(4-Chlordifluormethoxy-2-nitrophenyl)-acetamid (Schmp. 89-91°C).

b) Man tropft bei 5°C zu 10,5 g voranstehender Verbindung in 200 ml Methanol 8,6 ml einer 30%igen Lösung von Natriummethylat in Methanol, rührt 2 h ohne Kühlung, versetzt mit Eiswasser, stellt auf pH 8 und erhält 8,7 g (97%) 4-Chlordifluormethoxy-2-nitroanilin (Schmp. 40-42°C).

c) Man hydriert 8,5 g voranstehender Verbindung an 0,8 g 10%iger Palladiumkohle drucklos in 200 ml Methanol, versetzt mit konzentrierter Salzsäure, filtriert, engt ein und verrührt mit Diisopropylether. Man erhält 8,5 g (97%) 4-Chlordifluormethoxy-1,2-phenylendiamin-dihydrochlorid.

d) Aus 8,5 g voranstehender Verbindung werden analog Beispiel 21e) 6,3 g (72%) der Titelverbindung vom Schmp. 268-270°C (Zersetzung) erhalten.

25. 5-Difluormethoxy-2-merkapto-1H-benzimidazol

a) 11,8 g N-(4-Difluormethoxyphenyl)-acetamid [L.M.Jagupol'skii et al., J.General Chemistry (USSR) 39, 190 (1969)] werden in 200 ml Dichlormethan mit 12,1 ml 100%iger Salzsäure 1,5 h bei Raumtemperatur gerührt. Analog Beispiel 21b) erhält man 13,3 g (92%) N-[(4-Difluormethoxy--2-nitro)phenyl]-acetamid (Schmp. 71-73°C).

b) Analog Beispiel 24b erhält man daraus in 96%iger Ausbeute 4-Difluormethoxy-2-nitroanilin (Schmp. 68-70°C).

c) Analog Beispiel 24c erhält man in 94% Ausbeute 4-Difluormethoxy-1,2-phenylendiamin-dihydrochlorid.

d) Analog Beispiel 24e erhält man in 78% Ausbeute die Titelverbindung vom Schmp. 250-252°C (aus Isopropanol).

26. 5,6-Bis(difluormethoxy)-2-merkapto-1H-benzimidazol

a) In eine Lösung von 100 g Brenzkatechin, 220 g Natriumhydroxid und 60 g Natriumdithionit in 500 ml Wasser und 400 ml Dioxan leitet man bei 50-55°C 275 g Chlordifluormethan analog L.N. Sedova et al., Zh. Org. Khim. 6, 568 (1970) ein. Man erhält nach Destillation bei 61-62°C/1,0-1,1kPa eine Mischung von 1,2-Bis(difluormethoxy)benzol und 2-Difluormethoxyphenol, die durch Chromatographie an Kieselgel mittels Cyclohexan/Essigsäureethylester (4:1) getrennt werden.

b) Eine Lösung von 15 g 1,2-Bis(difluormethoxy)benzol und 15 ml 100 %iger Salpetersäure in 150 ml Dichlormethan wird 7 h bei Raumtemperatur gerührt. Man neutralisiert mit Kaliumhydrogencarbonatlösung, trennt die organische Schicht ab und chromatographiert an Kieselgel mittels Cyclohexan/Essigsäureethylester (4:1). Man erhält 1,2-Bis(difluormethoxy)-4-nitrobenzol. Dieses hydriert und acetyliert man analog Beispiel 21a zu N-[3,4-Bis(difluormethoxy)phenyl]acetamid (Schmp. 81-83°C). Analog Beispiel 21 erhält man ferner N-[4,5-Bis(difluormethoxy)-2-nitrophenyl]acetamid (Schmp. 65-67°C), N-[4,5-Bis(difluormethoxy)-2-nitro]anilin (Schmp. 107-109°C), 4,5-Bis(difluormethoxy)-1,2-phenylendiamin-dihydrochlorid und die Titelverbindung vom Schmp. 285-287°C (Zersetzung; aus Isopropanol).

27. 5-Difluormethoxy-2-merkapto-6-methoxy-1H-benzimidazol

a) In eine Lösung von 55,5 g Guajacol und 130 g Natriumhydroxid in 300 ml Wasser und 300 ml Dioxan werden bei 60°C ca. 58 g Chlordifluormethan eingeleitet. Man filtriert die Mischung bei 10°C, trennt die organische Schicht ab, trocknet mit wasserfreiem Kaliumcarbonat und destilliert. Man erhält 56 g (73%) 1-Difluormethoxy-2-methoxybenzol vom Siedepunkt 75-76°C/0,9kPa.

b) Zu einer Lösung von 47 g voranstehender Verbindung in 230 ml Dichlormethan wird bei 0-5°C eine Lösung von 33,8 ml 100%iger Salpetersäure in 90 ml Dichlormethan getropft, nach 30 Min. mit 250 ml Eiswasser versetzt und mit Kaliumhydrogencarbonat neutralisiert. Die getrocknete organische Phase wird im Vakuum eingeengt und der Rückstand aus Cyclohexan

umkristallisiert. Man erhält 53 g (90%) 1-Difluormethoxy-2-methoxy-5-nitrobenzol (Schmp. 48-49°C). Dieses wird analog Beispiel 21a hydriert und acetyliert. Man erhält in 90% Ausbeute N-(3-Difluormethoxy-4-methoxyphenyl)acetamid (Schmp. 129-130°C).

c) 46 g voranstehender Verbindung werden mit 33 ml 100%iger Salpetersäure in Dichlormethan analog voranstehender Vorschrift nitriert. Man erhält in 99% Ausbeute N-(5-Difluormethoxy-4-methoxy-2-nitrophenyl)acetamid (Schmp. 116-117°C).

d) 54 g voranstehender Verbindung werden in 810 ml Methanol 1 h mit 44,8 ml 30%iger methanolischer Natriummethylatlösung bei Raumtemperatur gerührt. Man engt im Vakuum ein, versetzt mit Eiswasser und Eisessig bis pH 8 und erhält in 99% Ausbeute 5-Difluormethoxy-4-methoxy-2-nitroanilin (Schmp. 144-145°C).

e) 25 g voranstehender Verbindung werden in 300 ml Methanol an 1,25 g 10%iger Palladiumkohle entsprechend Beispiel 21d hydriert. Man erhält 26 g (88%) 3-Difluormethoxy-4-methoxy-1,2-phenylendiamindihydrochlorid vom Schmp. 218-220°C (Zersetzung).

f) 25 g voranstehender Verbindung werden mit 19 g Kalium-O-ethyldithiocarbonat entsprechend Beispiel 21e umgesetzt. Man erhält 20 g (89%) der Titelverbindung vom Schmp. 280-282°C (Zersetzung; aus Isopropanol).

28. <u>5-Difluormethoxy-6-fluor-2-merkapto-1H-benzimidazol</u>

a) Analog Beispiel 27a erhält man aus 2-Fluorphenol und Chlordifluormethan 1-Difluormethoxy-2-fluorbenzol (Sdp. 76°C/10 kPa; n_D^{20} = 1,4340)

b) Zu 30 g der voranstehenden Verbindung in 300 ml Dichlormethan tropft man bei -10°C 38,4 ml 100%ige Salpetersäure, rührt 1 h bei -10°C und 2,5 h bei 0°C. Man versetzt mit Eiswasser, stellt neutral und chromatographiert über Kieselgel mit Essigester/Cyclohexan (4:1). Man erhält 34 g eines Öles, das ca. 90% 1-Difluormethoxy-2-fluor-4-nitrobenzol und 10% 1-Difluormethoxy-2-fluor-5-nitrobenzol (NMR-Spektrum) enthält.

c) 30 g voranstehender Mischung wird analog Beispiel 21a hydriert und acetyliert. Nach Umkristallisieren aus Toluol erhält man 21 g (65%) N-(4-Difluormethoxy-3-fluorphenyl)acetamid vom Schmp. 112-113°C.

d) Zu 20 g voranstehender Verbindung in 200 ml Dichlormethan werden bei 20°C 22,5 ml 100%ige Salpetersäure in 30 Min. zugetropft und 15 h bei Raumtemperatur nachgerührt. Analog Beispiel 27c erhält man in 89% Ausbeute N-(4-Difluormethoxy-5-fluor-2-nitrophenyl)acetamid vom Schmp. 72-74°C (aus Cyclohexan). Durch mehrstündiges Rühren mit 1 m Salzsäure in Methanol bei 60°C erhält man in 95% Ausbeute 4-Difluormethoxy-5-fluor-2-nitroanilin vom Schmp. 95-97,5°C und analog Beispiel 27e) in 85% Ausbeute 4-Difluormethoxy-5-fluor-1,2-phenylendiamin-dihydrochlorid. Zersetzung ab 210°C.

e) 15 g voranstehender Verbindung werden mit 11,8 g Kalium-O-ethyldithiocarbonat entsprechend Beispiel 21e umgesetzt. Man erhält 11,1 g (84%) der Titelverbindung vom Schmp. 275-276°C (Zersetzung, aus Isopropanol).

29. 2,2-Difluor-5H-[1,3]-dioxolo[4,5-f]benzimidazol-6-thiol

a) Man hydriert 30 g 4-Amino-2,2-difluor-5-nitro-1,3-benzodioxol in 300 ml Methanol an 0,5 g 10%iger Palladiumkohle in einer Umlaufhydrierungsappatur bei Atmosphärendruck und Raumtemperatur, versetzt mit 2,5 Äquivalenten methanolischer Chlorwasserstofflösung, filtriert, engt die Lösung im Vakuum ein, versetzt mit Isopropanol und Ether und erhält 35 g (97 %) 2,2-Difluor-1,3-benzodioxol-4,5-diamin-dihydrochlorid vom Schmp. 232-233°C (Zersetzung).

b) Man versetzt 30 g voranstehender Verbindung in 300 ml Ethanol mit 24 g Kalium-O-ethyldithiocarbonat (umkristallisiert aus Isopropanol) und 9,2 g Natriumhydroxid in 55 ml Wasser und erhitzt 15 h unter Rückfluß zum Sieden. Man gießt auf 1,5 l Wasser, stellt mit Natronlauge auf pH 14, klärt mit Aktivkohle, fällt mit konzentrierter Salzsäure in der Wärme und saugt den Niederschlag in der Kälte ab. Man erhält 24 g (91 %) der Titelverbindung vom Schmp. 365-370°C (Zersetzung).

30. 6,6,7-Trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol

a) Zu 50 g 2,2,3-Trifluor-2,3-dihydro-1,4-benzodioxin wird bei 5°C in 1 h eine Mischung von 39,5 ml 69%iger Salpetersäure und 46 ml 97%iger Schwefelsäure getropft. Man rührt 1 h bei 10°C, 1 h bei 20°C und 5 Min. bei 40°C und gießt auf 200 g Eis, extrahiert mit Dichlormethan, wäscht mit Wasser, trocknet mit Magnesiumsulfat und destilliert im Vakuum. Man erhält 58 g (94 %) einer Mischung von 2,2,3-Trifluor-2,3-dihydro-6-nitro-(und 7-nitro)-1,4-benzodioxin vom Sdp. 68,5°C (0,15 mbar) und n_D^{20} 1,5080. Ein Gaschromatogramm mit einer 10 m Fused Silica Säule (Fa. Chrompack) zeigt zwei Peaks im Verhältnis 2:3.

b) Man hydriert 35 g des Isomerengemisches in 400 ml Ethanol an 3 g 10 %-iger Palladiumkohle bei Atmosphärendruck und 20-30°C in einer Umlaufhydrierungsapparatur, filtriert und engt im Vakuum ein. Man erhält 30,5 g (100 %) einer flüssigen Mischung von 6-Amino-(und 7-Amino)-2,2,3-trifluor-2,3-dihydro-1,4-benzodioxin.

c) Zu 28 g der voranstehenden Isomerenmischung tropft man bei 20-30°C eine Mischung aus 15,3 g Essisäureanhydrid und 15 ml Eisessig, rührt 30 Min. bei 30°C, setzt 1 ml Wasser zu, rührt 30 Min. bei 30°C und destilliert das Lösungsmittel im Vakuum ab. Durch Umkristallisation aus Toluol erhält man 19 g einer Fraktion des Gemisches der isomeren Acetaminoderivate vom Schmp. 128-133°C.

d) Zu 17 g des Isomerengemisches der Acetaminoderivate, suspendiert in 200 ml Dichlormethan, tropft man bei -6° bis -8°C 14 ml 100%ige Salpetersäure, gelöst in 60 ml Dichlormethan, rührt 2 h bei 0°C und dann über Nacht bei Raumtemperatur. Man gießt auf 110 g Eis, trennt die organische Phase ab, wäscht mit Wasser und engt im Vakuum ein. Der Rückstand (19,8 g) wird aus 20 ml Ethanol umkristallisiert. Man erhält 15,5 g einer Mischung von 6-Acetamino-2,2,3-trifluor-2,3-dihydro-7-nitro-1,4-benzodioxin und 7-Acetamino-2,2,3-trifluor-2,3-dihydro-6-nitro-1,4-benzodioxin.

e) Man suspendiert 14,5 g des voranstehenden Produktgemisches in 80 ml Methanol und tropft unter Erwärmung auf 30°C 30 ml 5m Natronlauge zu. Man rührt noch 0,5 h bei Raumtemperatur, gießt auf 200 g Eis und erhält 11,7 g einer Mischung von 6-Amino-2,2,3-trifluor-2,3-dihydro-7-nitro-1,4-benzodioxin und 7-Amino-2,2,3-trifluor-2,3-dihydro-6-nitro-1,4-benzodioxin. Eine Probe wird an einer Kieselgelsäule mit Cyclohexan/Essigsäureethylester (4:1) in zwei reine Isomeren mit den Schmelzpunkten 110,5-111,5°C und 120-121°C getrennt, deren NMR-Spektren an einem 60 MHz-Gerät in Deuterochloroform praktisch identisch sind.

f) 10,9 g des voranstehenden Isomerengemisches werden in 300 ml Methanol bei Raumtemperatur und Atmosphärendruck an 1 g 10%iger Palladiumkohle in 2,5 h hydriert. Man setzt 30 ml 4 m Chlorwasserstoff in Methanol zu, filtriert, engt im Vakuum ein und verrührt mit 100 ml Ether. Man erhält 12,6 g (98 %) 2,2,3-Trifluor-2,3-dihydro-1,4-benzodioxin-6,7-diamin-dihydrochlorid (Schmp. >250°C).

g) 12 g voranstehender Verbindung und 8,5 g Kalium-O-ethyldithiocarbonat (umkristallisiert aus Isopropanol) werden in 120 ml Ethanol mit 20,5 ml 4 m wäßriger Kaliumhydroxidlösung versetzt und 17 h unter Rückfluß zum Sieden erhitzt. Man gießt auf 300 g Eis, stellt mit Kaliumhydroxidlösung auf pH 12-13, klärt mit Aktivkohle und fällt mit konzentrierter Salzsäure. Nach erneuter Fällung mit Säure aus alkalischer wäßrig-alkoholischer Lösung erhält man 10 g (93 %) der Titelverbindung vom Schmp. 309-310°C (Zersetzung).

31. 6-Chlor-6,7,7-trifluor-6,7-dihydro-1H-[1,4]-dioxino[2,3-f]benzimidazol-2-thiol

a) Zu 18 g 2-Chlor-2,3,3-trifluor-2,3-dihydro-1,4-benzodioxin tropft man bei 5°C eine Mischung von 18,3 ml 65%iger Salpetersäure und 15,4 ml 97%ige Schwefelsäure, rührt 2 h bei 5-10°C und gießt auf Eis. Man extrahiert mit Methylenchlorid und erhält 21,3 g einer Mischung von 2-Chlor-2,3,3-trifluor-2,3-dihydro-6-nitro-(und 7-nitro)-1,4-benzodioxin als Öl.

b) Analog Beispiel 30b) erhält man daraus in 95% Ausbeute eine ölige Mischung von 2-Chlor-2,3,3-trifluor-2,3-dihydro-1,4-benzodioxin-6-(und 7-)amin, welche entsprechend Beispiel 30c) zu einer Mischung der entsprechenden Acetaminoderivate quantitativ umgesetzt wird.

c) 19 g der voranstehenden Mischung wird in 190 ml Dichlormethan mit 16 ml 100%iger Salpetersäure gerührt und das Reaktionsprodukt durch Chromatographie an Kieselgel mittels Cyclohexan/Essigsäureethylester (4:1) gereinigt. Man erhält 15 g einer Mischung von 6-Acetamino-2-chlor-2,3,3-trifluor-6,7-dihydro-7-nitro-1,4-benzodioxin und 7-Acetamino-2-chlor-2,3,3-trifluor-6,7-dihydro-6-nitro-1,4-benzodioxin als hellgelbes Öl.

d) Zu 14,5 g der voranstehenden Mischung in 100 ml Methanol tropft man bei 5°C 10,2 ml einer 30%igen Lösung von Natriummethylat in Methanol, rührt 1,5 h ohne Kühlung, gießt auf Eis, neutralisiert mit verdünnter Salzsäure, extrahiert mit Dichlormethan und engt im Vakuum ein. Man erhält 12,7 g einer Mischung von 6-Amino-2-chlor-2,3,3-trifluor-2,3-dihydro-7-nitro-1,4-benzodioxin und 7-Amino-2-chlor-2,3,3-trifluor-2,3-dihydro-6-nitro-1,4-benzodioxin als orangefarbenes Öl.

e) 12,4 g der voranstehenden Mischung werden analog Beispiel 30f) hydriert. Man erhält 12,6 g (99%) 2-Chlor-2,3,3-trifluor-2,3-dihydro-1,4-benzodioxin-6,7-diamin-dihydrochlorid.

f) 12,4 g der voranstehenden Verbindung werden analog Beispiel 30g) mit 9,1 g Kalium-O-ethyldithiocarbonat und Kaliumhydroxidlösung in Ethanol umgesetzt. Man erhält 9,6 g (74%) der Titelverbindung vom Schmp. 288-290°C (Zersetzung).

32. <u>2-Chlormethyl-4,5-dimethoxy-pyridinium-chlorid</u>

a) 2-Chlormethyl-4,5-dimethoxy-pyridinium-chlorid

Zu einer auf 0°C gekühlten Lösung von 5 g 2-Hydroxymethyl-4,5-dimethoxypyridin in 40 ml Methylenchlorid tropft man innerhalb einer Stunde

3 ml Thionylchlorid, gelöst in 10 ml Methylenchlorid zu, rührt anschließend 4 Stunden bei 20°C, wobei sich die Reaktionsmischung rot färbt, setzt 5 ml Toluol zu und engt am Rotationsverdampfer vollständig ein (30°C / 5 mbar). Der ölige Rückstand wird in 50 ml warmem Isopropanol gelöst, mit wenig Tonsil® geklärt, filtriert und erneut eingeengt. Man nimmt in 10 ml Toluol auf und bringt die Lösung mit Petrolether zur Kristallisation. Nach Abkühlung im Eisbad wird abgesaugt, mit Petrolether gewaschen und getrocknet. Man erhält 4,6 g (70 % d.Th.) der Titelverbindung 2-Chlormethyl-4,5-dimethoxy-pyridinium-chlorid als farblosen Feststoff; Zers. bei 160-61°C.

b) 2-Hydroxymethyl-4,5-dimethoxy-pyridin

19 g 4,5-Dimethoxy-2-methylpyridin-1-oxid werden innerhalb von 30 Minuten in der Weise zu 60 ml auf 80°C erwärmten Essigsäureanhydrid zudosiert, daß die Temperatur nicht über 100°C steigt. Nach weiteren 45 Minuten bei 85°C wird überschüssiges Essigsäureanhydrid im Vakuum abdestilliert und der ölige dunkle Rückstand, der im wesentlichen aus dem Zwischenprodukt 2-Acetoxymethyl-4,5-dimethoxypyridin besteht, mit 80 ml 2n Natronlauge 1 Stunde lang bei 80°C gerührt. Nach Verdünnen mit 80 ml Wasser und Abkühlung wird achtmal mit je 100 ml Methylenchlorid extrahiert, die vereinigten organischen Phasen zweimal mit 1n Natronlauge gewaschen, getrocknet, eingeengt und der kristalline, bräunliche Rückstand aus Toluol umkristallisiert. Man erhält 14 g (74 % d.Th.) 2-Hydroxymethyl-4,5-dimethoxy-pyridin vom F. 122-24°C.

c) 4,5-Dimethoxy-2-methylpyridin-1-oxid

Zu einer Suspension von 16,9 g 5-Methoxy-2-methyl-4-nitropyridin-1-oxid in 170 ml trockenem Methanol werden 20 ml einer 30 %-igen Natriummethylatlösung zugetropft, 15 Stunden bei 20°C und anschließend 4 Stunden bei 50°C gerührt. Man stellt durch vorsichtige Zugabe von konzentrierter Schwefelsäure unter Eiskühlung auf pH 7, engt ein, rührt den Rückstand mit 200 ml Methylenchlorid aus, filtriert von unlöslichen Bestandteilen, versetzt mit 10 ml Toluol und engt erneut zur Trockne ein. Man erhält 15,2 g (98 % d.Th.) 4,5-Dimethoxy-2-methylpyridin-1-oxid als

farbloses Kristallisat vom F. 118-121°C.

d) 5-Methoxy-2-methyl-4-nitropyridin-1-oxid

Zu 35 ml auf 60°C erwärmte 65 %-ige Salpetersäure werden 21,2 g 5-Methoxy-2-methylpyridin-1-oxid in der Weise zudosiert, daß die Temperatur der Reaktionsmischung 80°C nicht übersteigt. Man rührt 1 Stunde bei 80°C, setzt zur vollständigen Umsetzung noch 13 ml 100 %-ige Salpetersäure zu und rührt weitere 2 Stunden bei 60-70°C. Zur Aufarbeitung gießt man auf 300 g Eis. Der ausgefallene gelbe Niederschlag wird über ein Nutsche filtriert, mit Wasser gewaschen und getrocknet. Der trockene Feststoff wird mit 200ml Methylenchlorid ausgekocht, filtriert und getrocknet. Durch Konzentrierung des Filtrats wird weiteres DC-reines Produkt isoliert. Man erhält 22,3 g (87 % d.Th.) 5-Methoxy-2-methyl-4-nitropyridin-1-oxid vom F. 201-202°C; gelbe Kristalle.

e) 5-Methoxy-2-methylpyridin-1-oxid

Zu einer Lösung von 60,9 g 5-Methoxy-2-methylpyridin in 300 ml Eisessig werden bei 60°C 120 g 30 %-ige Wasserstoffperoxidlösung innerhalb von 1 Stunde zugetropft und 3 Stunden nachgerührt. Nach Zerstörung von überschüssigen Perverbindungen durch Zugabe von aktivem Mangandioxid wird filtriert, eingeengt, der Rückstand in 500 ml Essigsäureethylester heiß geklärt, erneut eingeengt und bei 0,3 mbar destilliert. Man erhält 54 g (77 % d.Th.) 5-Methoxy-2-methylpyridin-1-oxid als rasch erstarrendes Öl (Sdp. 130°C); F. 80-84°C.

f) 5-Methoxy-2-methylpyridin

Zu einer Lösung von 84 g Kaliumhydroxid in 400 ml Methanol und 500 ml Dimethylsulfoxid werden innerhalb einer Stunde 150 ml 3-Hydroxy-6-methylpyridin zudosiert. Nach Entfernung des Methanols am Rotationsverdampfer tropft man unter Eiskühlung 213 g Methyliodid, gelöst in 100 ml Dimethylsulfoxid zu, rührt 15 Stunden bei 20°C und unterwirft das Reaktionsgemisch einer Wasserdampfdestillation. Das Destillat wird am Extraktor kontinuierlich mit Methylenchlorid extrahiert und der Extrakt

eingeengt. Man erhält 85 g (56 % d.Th.) 5-Methoxy-2-methylpyridin als farbloses Öl.

33. 2-Chlormethyl-4,5-dimethoxy-3-methylpyridinium-chlorid

a) 2-Chlormethyl-4,5-dimethoxy-3-methylpyridinium-chlorid

Nach der in Beispiel 32a) beschriebenen Arbeitsweise erhält man durch Umsetzung von 2,7 g 2-Hydroxymethyl-4,5-dimethoxy-3-methylpyridin mit 4 g Thionylchlorid in 25 ml Methylenchlorid nach 1 Stunde Reaktionszeit und nach einer vereinfachten Aufarbeitungsmethode, nämlich durch Zusatz von 10 ml Toluol, abdestillieren des Methylenchlorids und überschüssigen Thionylchlorids, Absaugung des ausgefallenen Kristallisats und Trocknung 3,45 g (99 % d.Th) der Titelverbindung als farblose Kristalle; Zers. bei 125-26°C.

b) 2-Hydroxymethyl-4,5-dimethoxy-3-methylpyridin

4,5 g 4,5-Dimethoxy-2,3-dimethylpyridin-1-oxid werden in 20 ml Essigsäureanhydrid 30 Minuten auf 110°C erwärmt und anschließend am Rotationsverdampfer eingeengt. Der ölige Rückstand, der aus dem Zwischenprodukt 2-Acetoxymethyl-4,5-dimethoxy-3-methylpyridin besteht, wird in 30 ml 3n Natronlauge 2 Stunden bei 80°C gerührt, nach Abkühlung fünfmal mit je 30 ml Methylenchlorid extrahiert, die vereinigten organischen Phasen zweimal mit 2n Natronlauge gewaschen, getrocknet, eingeengt, der Rückstand mit Petrolether verrührt, abgesaugt und getrocknet. Man erhält 4,0 g (89 % d.Th.) 2-Hydroxymethyl-4,5-dimethoxy-3-methylpyridin vom F. 91-92°C.

c) 4,5-Dimethoxy-2,3-dimethylpyridin-1-oxid

6,3 g 4,5-Dimethoxy-2,3-dimethylpyridin werden in 120 ml Methylenchlorid gelöst, sukzessive 20 g m-Chlorperoxibenzoesäure zugegeben, erst 2 Stunden bei 20°C und anschließend 4 Stunden bei 40°C gerührt. Nach Zusatz von 20 ml 5n Natronlauge wird dreimal mit einem Gemisch aus einer 5 %-igen Natriumthiosulfat- und 5 %-igen Natriumcarbonatlösung gewa-

schen, die Wasserphasen zweimal mit Methylenchlorid rückextrahiert, die vereinigten organischen Phasen über Magnesiumsulfat getrocknet und eingeengt. Man erhält 4,6 g (66 % d.Th.) 4,5-Dimethoxy-2,3-dimethylpyridin-1-oxid. Der Rf-Wert in Methylenchlorid/Methanol 19:1 beträgt 0,25.

d) 4,5-Dimethoxy-2,3-dimethylpyridin

Nach der in Beispiel 32f) beschriebenen Arbeitsweise erhält man durch Umsetzung von 9,18 g 5-Hydroxy-4-methoxy-2,3-dimethylpyridin in 50 ml Dimethylsulfoxid zuerst mit 3,6 g Natriumhydroxid, anschließend mit 8,95 g Methyliodid 7,4 g (74 % d.Th.) 4,5-Dimethoxy-2,3-dimethylpyridin als farbloses, allmählich kristallisierendes Öl, F. 36-38°C.

e) 5-Hydroxy-4-methoxy-2,3-dimethylpyridin

1000 g 4-Methoxy-2,3-dimethylpyridin-1-oxid werden bei 100°C unter Rühren innerhalb von 7 Stunden zu 3 l Essigsäureanhydrid zudosiert und weitere 3 Stunden bei 100°C nachgerührt. Man läßt abkühlen, engt bei 70°C/10 mbar vollständig ein und destilliert anschließend bei 10^{-2} mbar. Die Fraktion mit einem Siedeintervall von 95-145°C (Gemisch aus dem Zwischenprodukt 5-Acetoxy-4-methoxy-2,3-dimethylpyridin und 2-Acetoxymethyl-4-methoxy-3-methylpyridin) wird abgenommen (952 g) und zu 3,5 l auf 50°C erwärmte 2n Natronlauge innerhalb von 30 Minuten zugegeben.
Man rührt bei 50°C bis zur Bildung einer klaren Lösung (ca. 3 Stunden), läßt abkühlen und extrahiert dreimal mit je 1 l Methylenchlorid. Die vereinigten organischen Phasen werden zweimal mit je 0,5 l 1n Natronlauge rückextrahiert und anschließend die vereinigten Wasserphasen mit halbkonzentrierter Salzsäure unter Rühren auf pH 7,5 gestellt. Man filtriert vom ausgefallenen Feststoff, wäscht nach und trocknet bis zur Gewichtskonstanz. Man erhält 5-Hydroxy-4-methoxy-2,3-dimethylpyridin vom F. 274-76°C.

34. 2-Chlormethyl-3,4-dimethoxy-pyridinium-chlorid

a) 2-Chlormethyl-3,4-dimethoxy-pyridiniumchlorid

Nach der in Beispiel 32a beschriebenen Arbeitsweise erhält man durch Umsetzung von 3,38 g 2-Hydroxymethyl-3,4-dimethoxypyridin mit 2 ml Thionylchlorid in 30 ml Methylenchlorid nach 2,5 Stunden Reaktionszeit und nach der in Beispiel 33a beschriebenen Art der Aufarbeitung 4,2 g (93% d.Th.) der Titelverbindung als farblosen Feststoff vom F. 151-152°C (Zers.)

b) 2-Hydroxymethyl-3,4-dimethoxypyridin

4,8 g 2-Acetoxymethyl-3,4-dimethoxypyridin werden nach Zusatz von 15 ml 2n Natronlauge bei 80°C kräftig gerührt, wobei sich aus dem anfänglichen Zweiphasengemisch eine homogene Lösung bildet. Nach 2 h läßt man abkühlen, extrahiert fünfmal mit je 30 ml Methylenchlorid, wäscht die vereinigten organischen Phasen zweimal mit je 5 ml 0,3 n Natronlauge, trocknet über Kaliumcarbonat, filtriert, engt ein und verrührt den Destillationsrückstand mit Petrolether. Man erhält 3,6 g (96% d.Th.) 2-Hydroxymethyl-3,4-dimethoxypyridin als farblosen Feststoff vom F. 87-89°C.

c) 2-Acetoxymethyl-3,4-dimethoxypyridin

Zu 25 ml Essigsäureanhydrid werden bei 85°C innerhalb von einer Stunde 4,8 g (28 mMol) 3,4-Dimethoxy-2-methylpyridin-1-oxid zudosiert, eine Stunde bei der selben Temperatur gerührt, im Vakuum vollständig eingeengt und der braune, ölige Rückstand in einer Kugelrohrdestille bei 1 Pa destilliert. Man erhält 5,3 g (90% d.Th.) 2-Acetoxymethyl-3,4-dimethoxypyridin; Sdp. 125-130°C.

d) 3,4-Dimethoxy-2-methylpyridin-1-oxid

4,5 g (25 mMol) 3-Methoxy-2-methyl-4-nitropyridin-1-oxid werden in 75 ml trockenem Methanol nach Zusatz von 4,7 ml 30%iger Natriummethylatlösung 16 Stunden bei 40°C gerührt. Anschließend kühlt man ab, stellt mit konz. Schwefelsäure auf pH 7, filtriert, engt im Vakuum vollständig ein, nimmt den öligen, rötlichen Rückstand in 50 ml Toluol auf, filtriert erneut von unlöslichen Bestandteilen und engt das Filtrat zur Trockene ein. Der gelbe, ölige Rückstand kristallisiert im Eisbad und wird abschließend mit

30 ml Petrolether (50/70) bei 40°C ausgerührt. Nach Filtration und Trocknung im Exsiccator erhält man 5,2 g (88% d.Th.) 3,4-Dimethoxy-2-methylpyridin-1-oxid in Form blaßgelber Kristalle vom F. 111-113°C.

e) 3-Methoxy-2-methyl-4-nitropyridin-1-oxid

Zu 5,4 g 3-Methoxy-2-methylpyridin-1-oxid in 12 ml Eisessig werden bei 80°C innerhalb von 6h in vier Portionen von je 2 ml 8 ml konz. Salpetersäure zugegeben, über Nacht bei der selben Temperatur gerührt, nochmals in drei Portionen innerhalb von 6 Stunden 8 ml Salpetersäure zugegeben und weitere 15 Stunden gerührt. Nach Abkühlung gießt man auf Eis (40g), stellt mit 10n Natronlauge auf pH 6, filtriert vom ausgefallenen Nebenprodukt (3-Methoxy-2-methyl-4-nitropyridin) und extrahiert viermal mit 50 ml Methylenchlorid. Nach Trocknung werden die vereinigten organischen Phasen vollständig eingeengt und der Rückstand aus wenig Methylenchlorid/Petrolether umkristallisiert. Man erhält 4,2 g (57% d.Th.) der Titelverbindung in Form gelber Kristalle vom F. 103-104°C.

f) 3-Methoxy-2-methylpyridin-1-oxid

15,3 g (0,124 Mol) 3-Methoxy-2-methylpyridin werden in 100 ml Eisessig gelöst und bei 80°C in 4 Portionen 40 ml 30%iges Wasserstoffperoxid innerhalb von 6 Stunden zugegeben. Man rührt weitere drei Stunden und engt anschließend im Vakuum (1,5 kPa) ein, setzt zweimal je 50 ml Essigsäure zu und engt jeweils vollständig ein. Nach negativem Nachweis auf Perverbindungen wird im Kugelrohrofen destilliert. Die bei 120°C (1,5 Pa) destillierende Fraktion wird in wenig Diethylether ausgerührt, der Feststoff filtriert und getrocknet. Man erhält 12 g (60% d.Th.) 3-Methoxy-2-methylpyridin-1-oxid in Form farbloser Kristalle vom F. 72-78°C.

g) 3-Methoxy-2-methylpyridin

Nach der in Beispiel 32f beschriebenen Arbeitsweise erhält man durch Umsetzung von 13,7 g (125 mMol) 3-Hydroxy-2-methylpyridin mit 9,2 ml Methyliodid unter Zusatz von 46 ml 3m methanolischer Kaliumhydroxidlösung nach einer Reaktionszeit von 3 Stunden 15,5 g (90% d.Th.) 3-Methoxy-2-methylpyridin als farbloses Öl.

Gewerbliche Anwendbarkeit

Die Dialkoxypyridine der allgemeinen Formel I und ihre Salze besitzen wertvolle pharmakologische Eigenschaften, die sie gewerblich verwertbar machen. Sie hemmen deutlich die Magensäuresekretion von Warmblütern und weisen darüberhinaus eine ausgezeichnete Magen- und Darmschutzwirkung bei Warmblütern auf. Diese Magen- und Darmschutzwirkung wird bereits bei der Verabreichung von Dosen beobachtet, die unterhalb der säuresekretionshemmenden Dosen liegen. Darüberhinaus zeichen sich die erfindungsgemäßen Verbindungen durch das Fehlen wesentlicher Nebenwirkungen und eine große therapeutische Breite aus.

Unter "Magen- und Darmschutz" wird in diesem Zusammenhang die Verhütung und Behandlung gastrointestinaler Krankheiten, insbesondere gastrointestinaler entzündlicher Krankheiten und Läsionen (wie z.B. Ulcus ventriculi, Ulcus duodeni, Gastritis, hyperazider oder medikamentös bedingter Reizmagen) verstanden, die beispielsweise durch Mikroorganismen, Bakterientoxine, Medikamente (z.B. bestimmte Antiphlogistika und Antirheumatika), Chemikalien (z.B. Ethanol), Magensäure oder Streßsituationen verursacht werden können.

Ein weiterer Vorteil der erfindungsgemäßen Verbindungen ist ihre vergleichsweise große chemische Stabilität.

In ihren ausgezeichneten Eigenschaften erweisen sich die erfindungsgemäßen Verbindungen überraschenderweise den aus dem Stand der Technik bekannten Verbindungen deutlich überlegen. Aufgrund dieser Eigenschaften sind die Dialkoxypyridine und ihre pharmakologisch verträglichen Salze für den Einsatz in der Human- und Veterinärmedizin hervorragend geeignet, wobei sie insbesondere zur Behandlung und/oder Prophylaxe von Krankheiten des Magens und Darms und solcher Krankheiten, die auf einer überhöhten Magensäuresekretion beruhen, verwendet werden.

Ein weiterer Gegenstand der Erfindung sind daher die erfindungsgemäßen Verbindungen zur Anwendung bei der Behandlung und/oder Prophylaxe der vorstehend genannten Krankheiten.

Ebenso umfaßt die Erfindung die Verwendung der erfindungsgemäßen Verbindungen zur Herstellung von Arzneimitteln, die zur Behandlung und/oder Prophylaxe der vorstehend genannten Krankheiten eingesetzt werden.

Ein weiterer Gegenstand der Erfindung sind Arzneimittel, die ein oder mehrere Dialkoxypyridine der allgemeinen Formel I und/oder ihre pharmakologisch verträglichen Salze enthalten.

Die Arzneimittel werden nach an sich bekannten, dem Fachmann geläufigen Verfahren hergestellt. Als Arzneimittel werden die erfindungsgemäßen pharmakologisch wirksamen Verbindungen (=Wirkstoffe) entweder als solche, oder vorzugsweise in Kombination mit geeigneten pharmazeutischen Hilfs- oder Trägerstoffen in Form von Tabletten, Dragees, Kapseln, Suppositorien, Pflastern (z.B. als TTS), Emulsionen, Suspensionen oder Lösungen eingesetzt, wobei der Wirkstoffgehalt vorteilhafterweise zwischen 0,1 und 95% beträgt.

Welche Hilfs- bzw. Trägerstoffe für die gewünschten Arzneimittelformulierungen geeignet sind, ist dem Fachmann aufgrund seines Fachwissens geläufig. Neben Lösemitteln, Gelbildnern, Suppositoriengrundlagen, Tabletten-Hilfsstoffen und anderen Wirkstoffträgern können beispielsweise Antioxidantien, Dispergiermittel, Emulgatoren, Entschäumer, Geschmackskorrigentien, Konservierungsmittel, Lösungsvermittler, Farbstoffe oder insbesondere Permeationspromotoren und Komplexbildner (z.B. Cyclodextrine) verwendet werden.

Die Wirkstoffe können oral, parenteral oder percutan appliziert werden.

Im allgemeinen hat es sich in der Humanmedizin als vorteilhaft erwiesen, den oder die Wirkstoffe bei oraler Gabe in einer Tagesdosis von etwa 0,01 bis etwa 20, vorzugsweise 0,05 bis 5, insbesondere 0,1 bis

1,5 mg/kg Körpergewicht, gegebenenfalls in Form mehrerer, vorzugsweise 1 bis 4 Einzelgaben zur Erzielung des gewünschten Ergebnisses zu verabreichen. Bei einer parenteralen Behandlung können ähnliche bzw. (insbesondere bei der intravenösen Verabreichung der Wirkstoffe) in der Regel niedrigere Dosierungen zur Anwendung kommen. Die Festlegung der jeweils erforderlichen optimalen Dosierung und Applikationsart der Wirkstoffe kann durch jeden Fachmann aufgrund seines Fachwissens leicht erfolgen.

Sollen die erfindungsgemäßen Verbindungen und/oder Salze zur Behandlung der oben genannten Krankheiten eingesetzt werden, so können die pharmazeutischen Zubereitungen auch einen oder mehrere pharmakologisch aktive Bestandteile anderer Arzneimittelgruppen, wie Antacida, beispielsweise Aluminiumhydroxyd, Magnesiumaluminat; Tranquilizer, wie Benzodiazpine, beispielsweise Diazepam; Spasmolytika, wie z.B. Bietamiverin, Camylofin; Anticholinergica, wie z.B. Oxyphencyclimin, Phencarbamid; Lokalanaesthetika, wie z.B. Tetracain, Procain; gegebenenfalls auch Fermente, Vitamine oder Aminosäuren enthalten.

Hervorzuheben ist in diesem Zusammenhang insbesondere die Kombination der erfindungsgemäßen Verbindungen mit anderen, die Säuresekretion hemmenden Pharmaka, wie beispielsweise H_2-Blockern (z.B. Cimetidin, Ranitidin), ferner mit sogenannten peripheren Anticholinergika (z.B. Pirenzepin, Telenzepin, Zolenzepin) sowie mit Gastrin-Antagonisten, mit dem Ziel, die Hauptwirkung in additivem oder überadditivem Sinn zu verstärken und/oder die Nebenwirkungen zu eliminieren oder zu verringern.

Pharmakologie

Die ausgezeichnete Magenschutzwirkung und die magensekretionshemmende Wirkung der erfindungsgemäßen Verbindungen läßt sich tierexperimentell am Modell Shay-Ratte nachweisen. Die untersuchten erfindungsgemäßen Verbindungen sind wie folgt mit Nummern versehen worden:

Lfd. Nr.	Name der Verbindung
1	2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol
2	2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol
3	2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol
4	2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo[4,5-f]benzimidazol
5	2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylsulfinyl]-5H-[1,3]-dioxolo[4,5-f]benzimidazol

Der Einfluß der untersuchten Verbindungen auf die durch Pylorusligatur (4h; sog. Shay-Ratte) und orale Gabe von 100 mg/kg Acetylsalicylsäure ausgelöste Magenläsionsbildung sowie die Magensekretion (HCl) während 4 h bei der Ratte, ist in der folgenden Tabelle dargestellt.

Magenschutzwirkung und Magensekretionshemmung

Lfd. Nr.	n [Anzahl d.Tiere]	Magenschutzwirkung (Ratte) Hemmung d. Läsionsindexes, ED50+) [mg/kg, p.o.]	Hemmung der HCl-Sekretion d. Magens (Ratte; Summe 4 h) % Hemmung der HCl-Sekretion ++)	ED25+) [mg/kg, p.o.]	ED50+) [mg/kg, p.o.]
1	40	0,6	15	1,0	~ 3
2	48	0,8	25	0,7	1,7
3	56	0,6	18	~ 1	3,4
4	40	3,5	28	3,0	6,5
5	72	~ 1	25	1,0	3,0

+) ED25 bzw. ED50 = Dosis, die den Läsionsindex bzw. die HCl-Sekretion (4h) des Rattenmagens bei der behandelten Gruppe gegenüber der Kontrollgruppe um 25 bzw. 50 % mindert.

++) nach Gabe der antiulcerösen ED50

Die Prüfung der antiulcerogenen Wirkung erfolgte nach der Methode der sogenannten Shay-Ratte:

Die Ulcusprovokation erfolgt bei 24 Stunden nüchtern gehaltenen Ratten (weiblich, 180-200 g, 4 Tiere je Käfig auf hohem Gitterrost) durch Pylorusligatur (unter Diethylethernarkose) und orale Applikation von 100 mg/10 ml/kg Acetylsalicylsäure. Die zu prüfenden Substanzen werden oral (10 ml/kg) eine Stunde vor der Pylorusligatur verabreicht. Der Wundverschluß wird mittels Michelklammern vorgenommen. 4 Stunden danach erfolgt die Tötung der Tiere im Etherrausch durch Atlas-Dislokation und die Resektion des Magens. Der Magen wird längs eröffnet und auf einer Korkplatte fixiert, nachdem zuvor die Menge

des sezernierten Magensaftes (Volumen) und später sein HCl-Gehalt (Titration mit Natronlauge) bestimmt wurde; mit einem Stereomikroskop werden bei 10-facher Vergrößerung Anzahl und Größe (=Durchmesser) vorhandener Ulcera ermittelt. Das Produkt aus Schweregrad (gemäß nachfolgender Punkteskala) und Anzahl der Ulcera dient als individueller Läsionsindex.

Punkteskala:

keine Ulcera		0
Ulcusdurchmesser	0,1 - 1,4 mm	1
	1,5 - 2,4 mm	2
	2,5 - 3,4 mm	3
	3,5 - 4,4 mm	4
	4,5 - 5,4 mm	5
	> 5,5 mm	6

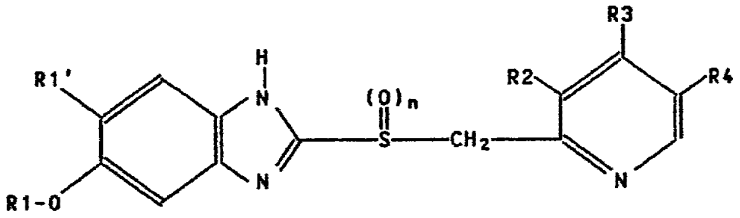
Als Maß für den antiulcerogenen Effekt dient die Minderung des mittleren Läsionsindex jeder behandelten Gruppe gegenüber dem der Kontrollgruppe (=100%). Die ED25 bzw. ED50 bezeichnen diejenigen Dosen, die den mittleren Läsionsindex bzw. die HCl-Sekretion gegenüber der Kontrolle um 25% bzw. 50% mindern.

Toxizität

Die LD50 aller geprüften Verbindungen liegt oberhalb von 1000 mg/kg [p.o.] bei der Maus.

Patentansprüche

1. Dialkoxypyridine der allgemeinen Formel I



(I),

worin

R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chlordifluormethylrest und

R1' Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest oder

R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest darstellen,

R3 einen 1-3C-Alkoxyrest,

einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und

n die Zahlen 0 oder 1 darstellt,

sowie die Salze dieser Verbindungen.

2. Verbindungen der Formel I nach Anspruch 1,

worin

R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chlordifluormethylrest,

R1' Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen

gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest,

R3 einen 1-3C-Alkoxyrest,

einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und

n die Zahlen 0 oder 1 darstellt,

sowie die Salze dieser Verbindungen.

3. Verbindungen der Formel I nach Anspruch 1,

worin

R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2C-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest,

R3 einen 1-3C-Alkoxyrest,

einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und

n die Zahlen 0 oder 1 darstellt,

sowie die Salze dieser Verbindung.

4. Verbindungen der Formel I nach Anspruch 2, worin R1 1,1,2,2-Tetrafluorethyl, Trifluormethyl, 2,2,2-Trifluorethyl oder Difluormethyl, R1' Wasserstoff, R3 Methoxy, einer der Reste R2 oder R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

5. Verbindungen der Formel I nach Anspruch 3, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen Difluormethylendioxyrest oder einen Methylendioxyrest darstellen, R3 Methoxy, einer der Reste R2 oder R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt, und die Salze dieser Verbindungen.

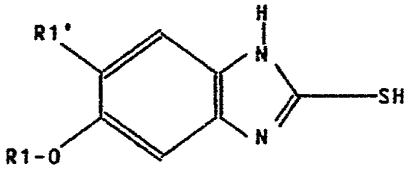
6. Verbindungen der Formel I nach einem der Ansprüche 1 bis 5, worin n die Zahl 0 bedeutet, und ihre Säureadditionssalze.

7. Verbindungen der Formel I nach einem der Ansprüche 1 bis 5, worin n die Zahl 1 bedeutet, und ihre Salze mit Basen.

8. Verbindung ausgewählt aus der Gruppe bestehend aus
2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(4,5-Dimethoxy-3-methyl-2-pyridyl)methylsulfinyl]-5-trifluormethoxy-1H-benzimidazol,
2-[(4,5-Dimethoxy-2-pyridyl)methylsulfinyl]-5-(1,1,2,2-tetrafluorethoxy)-1H-benzimidazol
2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylthio]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol und
2,2-Difluor-6-[(4,5-dimethoxy-2-pyridyl)methylsulfiyl]-5H-[1,3]-dioxolo-[4,5-f]benzimidazol
und ihren Salzen.

9. Verfahren zur Herstellung von Dialkoxypyridinen der Formel I nach Anspruch 1 und ihren Salzen, dadurch gekennzeichnet, daß man

a) Mercaptobenzimidazole der Formel II mit Picolinderivaten III,



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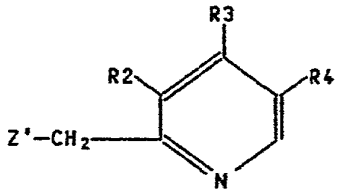
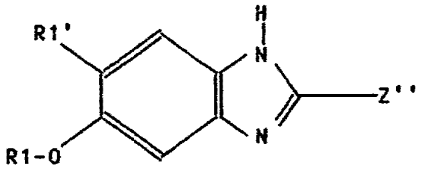


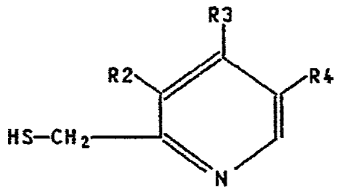
(III),

oder

b) Benzimidazole der Formel IV mit Mercaptopicolinen V,



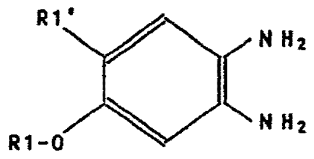
(IV)



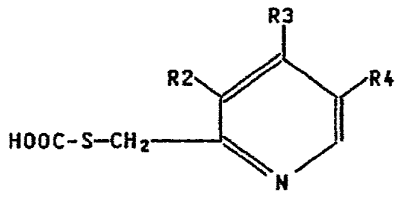
(V),

oder

c) o-Phenylendiamine der Formel VI mit Ameisensäurederivaten VII

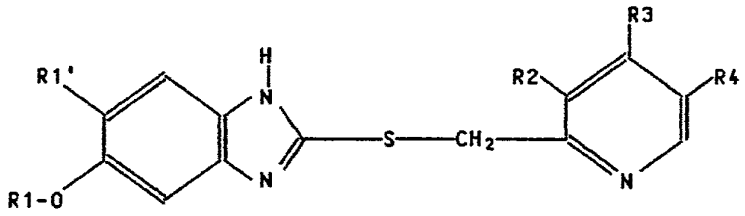


(VI)



(VII),

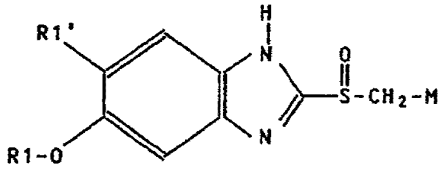
umsetzt und gegebenenfalls anschließend die nach a), b) oder c) erhaltenen 2-Benzimidazolyl-2-pyridylmethyl-sulfide der Formel VIII



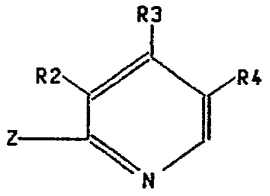
(VIII),

oxidiert und/oder in die Salze überführt,
oder daß man

d) Benzimidazole der Formel IX mit Pyridinderivaten X



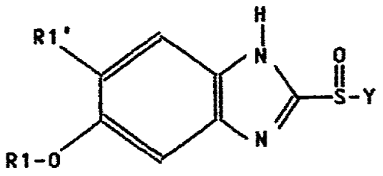
(IX)



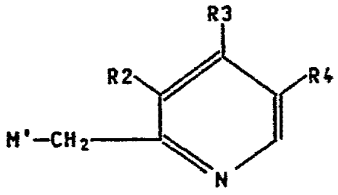
(X),

oder

e) Sulfinylderivate der Formel XI mit 2-Picolinderivaten XII



(XI)



(XII),

umsetzt und gegebenenfalls anschließend in die Salze überführt, wobei Y, Z, Z' und Z'' geeignete Abgangsgruppen darstellen, M für ein Alkalimetallatom (Li, Na oder K) steht, M' für das Äquivalent eines Metallatoms steht und R1, R1', R2, R3, R4 und n die in Anspruch 1 angegebenen Bedeutungen haben.

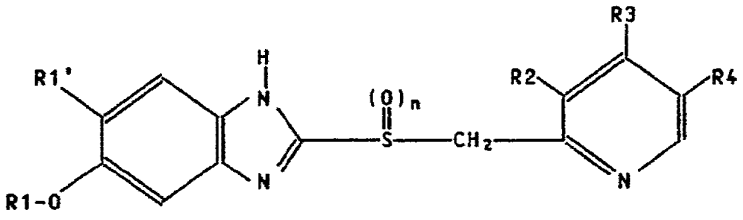
10. Arzneimittel enthaltend ein oder mehrere Dialkoxypyridine nach einem oder mehreren der Ansprüche 1 bis 8 und/oder ihre pharmakologisch verträglichen Salze.

11. Dialkoxypyridine nach einem der Ansprüche 1 bis 8 und ihre pharmakologisch verträglichen Salze zur Anwendung bei der Behandlung und/oder Prophylaxe von Krankheiten des Magens und/oder Darms und solcher Krankheiten, die auf einer erhöhten Magensäuresekretion beruhen.

12. Verwendung von Dialkoxypyridinen nach einem der Ansprüche 1 bis 8 und ihren pharamkologisch verträglichen Salzen zur Herstellung von Arzneimitteln für die Behandlung und/oder Prophylaxe von Krankheiten des Magens und/oder Darms und solchen Krankheiten, die auf einer erhöhten Magensäuresekretion beruhen.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung von Dialkoxypyridinen der allgemeinen Formel I



(I),

worin

R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chlordifluormethylrest und

R1' Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest oder

R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest darstellen,

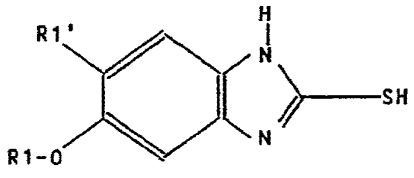
R3 einen 1-3C-Alkoxyrest,

einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und

n die Zahlen 0 oder 1 darstellt,

und ihren Salzen, dadurch gekennzeichnet, daß man

a) Mercaptobenzimidazole der Formel II mit Picolinderivaten III,



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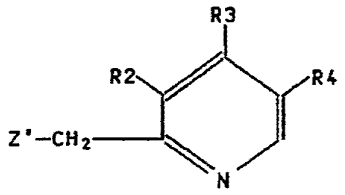
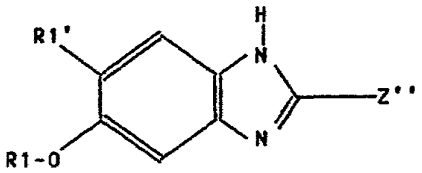


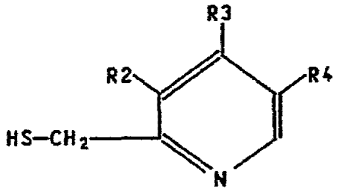
(III),

oder

b) Benzimidazole der Formel IV mit Mercaptopicolinen V,



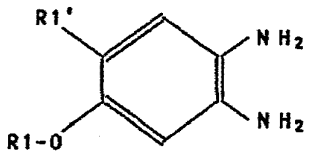
(IV)



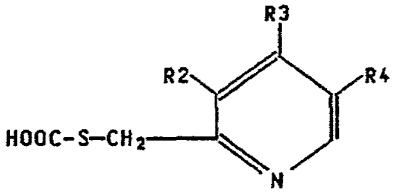
(V),

oder

c) o-Phenylendiamine der Formel VI mit Ameisensäurederivaten VII

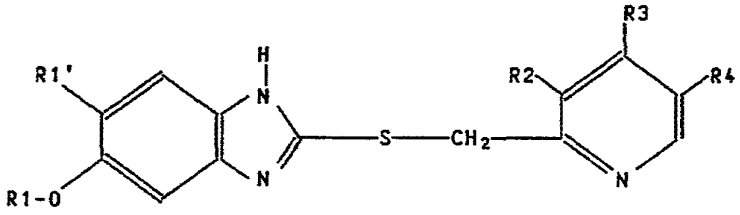


(VI)



(VII),

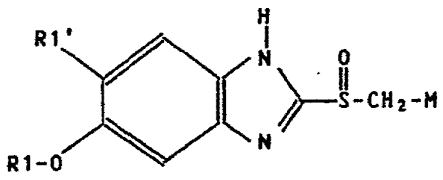
umsetzt und gegebenenfalls anschließend die nach a), b) oder c) erhaltenen 2-Benzimidazolyl-2-pyridylmethyl-sulfide der Formel VIII



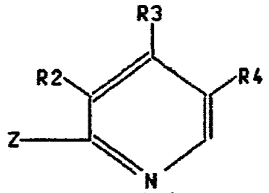
(VIII),

oxidiert und/oder in die Salze überführt,
oder daß man

d) Benzimidazole der Formel IX mit Pyridinderivaten X



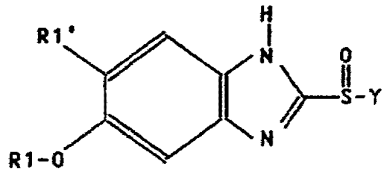
(IX)



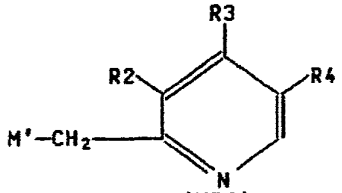
(X),

oder

e) Sulfinylderivate der Formel XI mit 2-Picolinderivaten XII



(XI)



(XII),

umsetzt und gegebenenfalls anschließend in die Salze überführt, wobei Y, Z, Z' und Z'' geeignete Abgangsgruppen darstellen, M für ein Alkalimetallatom (Li, Na oder K) steht, M' für das Äquivalent eines Metallatoms steht und R1, R1', R2, R3, R4 und n die oben angegebenen Bedeutungen haben.

2. Verfahren nach Anspruch 1,
worin
R1 einen ganz oder überwiegend durch Fluor substituierten 1-3C-Alkylrest oder einen Chlordifluormethylrest,
R1' Wasserstoff, Halogen, Trifluormethyl, einen 1-3C-Alkylrest oder einen gegebenenfalls ganz oder überwiegend durch Fluor substituierten 1-3C-Alkoxyrest,
R3 einen 1-3C-Alkoxyrest,
einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und
n die Zahlen 0 oder 1 darstellt.

3. Verfahren nach Anspruch 1,
worin
R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1

gebunden ist, einen gegebenenfalls ganz oder teilweise durch Fluor substituierten 1-2C-Alkylendioxyrest oder einen Chlortrifluorethylendioxyrest,

R3 einen 1-3C-Alkoxyrest,

einer der Reste R2 und R4 einen 1-3C-Alkoxyrest und der andere ein Wasserstoffatom oder einen 1-3C-Alkylrest und

n die Zahlen 0 oder 1 darstellt.

4. Verfahren nach Anspruch 1, worin R1 1,1,2,2-Tetrafluorethyl, Trifluormethyl, 2,2,2-Trifluorethyl oder Difluormethyl, R1' Wasserstoff, R3 Methoxy, einer der Reste R2 oder R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt.

5. Verfahren nach Anspruch 1, worin R1 und R1' gemeinsam und unter Einschluß des Sauerstoffatoms, an das R1 gebunden ist, einen Difluormethylendioxyrest oder einen Methylendioxyrest darstellen, R3 Methoxy, einer der Reste R2 oder R4 Methoxy und der andere Wasserstoff oder Methyl und n die Zahlen 0 oder 1 darstellt.

6. Verfahren zur Herstellung von Verbindungen der Formel I nach Anspruch 1, worin R1, R1', R2, R3 und R4 die in Anspruch 1 angegebenen Bedeutungen haben und n die Zahl 0 bedeutet, dadurch gekennzeichnet, daß man Mercaptobenzimidazole der Formel II mit Picolinderivaten III umsetzt und gegebenenfalls anschließend in die Säureadditionssalze überführt.

7. Verfahren zur Herstellung von Verbindungen der Formel I nach Anspruch 1, worin R1, R1', R2, R3 und R4 die in Anspruch 1 angegebenen Bedeutungen haben und n die Zahl 1 bedeutet, dadurch gekennzeichnet, daß man die 2-Benzimidazolyl-2-pyridylmethyl-sulfide der Formel VIII oxidiert und gegebenenfalls anschließend in die Salze mit Basen überführt.

8. Verfahren zur Herstellung von Arzneimitteln, dadurch gekennzeichnet, daß man eine Verbindung der Formel I nach Anspruch 1 oder ein pharmakologisch verträgliches Salz davon mit einem pharmazeutischen Hilfs- und/oder Trägerstoff vermischt.

0166287
Nummer der Anmeldung

Europäisches Patentamt

EUROPÄISCHER RECHERCHENBERICHT

EP 85 10 7104

EINSCHLÄGIGE DOKUMENTE

Kategorie	Kennzeichnung des Dokuments mit Angabe, soweit erforderlich, der maßgeblichen Teile	Betrifft Anspruch	KLASSIFIKATION DER ANMELDUNG (Int. Cl.4)
D,A	EP-A-0 074 341 (HÄSSLE) -----		C 07 D 401/12 C 07 D 491/04 A 61 K 31/44

RECHERCHIERTE SACHGEBIETE (Int. Cl.4)

C 07 D 401/00
C 07 D 491/00
A 61 K 31/00

Der vorliegende Recherchenbericht wurde für alle Patentansprüche erstellt.

Recherchenort	Abschlußdatum der Recherche	Prüfer
DEN HAAG	17-09-1985	DE BUYSER F.A.F.

KATEGORIE DER GENANNTEN DOKUMENTEN

X : von besonderer Bedeutung allein betrachtet
Y : von besonderer Bedeutung in Verbindung mit einer anderen Veröffentlichung derselben Kategorie
A : technologischer Hintergrund
O : nichtschriftliche Offenbarung
P : Zwischenliteratur
T : der Erfindung zugrunde liegende Theorien oder Grundsätze

E : älteres Patentdokument, das jedoch erst am oder nach dem Anmeldedatum veröffentlicht worden ist
D : in der Anmeldung angeführtes Dokument
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& : Mitglied der gleichen Patentfamilie, übereinstimmendes Dokument

EPA Form 1503 03.82

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 167 958**
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **85108146.3**

(22) Date of filing: **01.07.85**

(51) Int. Cl.⁴: **A 61 K 9/24**

(30) Priority: **12.07.84 IT 2187484**

(43) Date of publication of application:
15.01.86 Bulletin 86/3

(84) Designated Contracting States:
AT CH DE FR LI

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(54) Oral solid pharmaceutical form with sequential action for the administering of drugs with ulcerogenic side effect.

(57) Oral solid pharmaceutical form with antiinflammatory and analgesic activity, with sequential action, with protective effect on the gastric and duodenal mucosa against the action of the active principles having ulcerogenic effect, contained in the same pharmaceutical form.

Said pharmaceutical form is constituted by a tablet comprising: (a) a centre core containing an active principle provided with antiinflammatory and analgesic activity, with ulcerogenic side effects; (b) a layer coating of said core, containing a second active principle provided with protective action for said gastric and duodenal mucosa, which is immediately released.

EP 0 167 958 A2

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ORAL SOLID PHARMACEUTICAL FORM WITH SEQUENTIAL ACTION FOR THE ADMINISTERING OF DRUGS WITH ULCEROGENIC SIDE EFFECT.

The present invention relates to a new pharmaceutical form with antiinflammatory and analgesic activity, avoiding the ulcerogenic side effect of the antiinflammatory and analgesic active principle.

More particularly, the present invention relates to an oral solid pharmaceutical form with antiinflammatory and analgesic activity, with sequential action, showing an effect of protection of the gastric and duodenal mucosa against the action of the active principles having ulcerogenic side effect.

It is known that during these last years several non-steroidic drugs with antiinflammatory and analgesic action, denominated as FANS (Non Steroidic Antiinflammatory Drugs, NSAD) have been prepared and tested.

It is known too that for all these drugs as a side effect a damaging action on the gastric and duodenal mucosa has been evidenced, which makes unadvisable the prolonged use thereof.

In order to overcome this problem, several modifications and administering forms have been suggested for these drugs, e.g., the formation of salts with alkaline metals, the formation of complexes with Al, Mg or Cu, the prepara-

tion of inclusion compounds with B-cyclodextrins and the like.

Notwithstanding the attention devoted to this problem, and the large number of solutions proposed, the problem of the ulcerogenic action of antiinflammatory drugs is to be considered as being still open, and always of great interest in the pharmaceutical field.

A noticeable step forward has been done with the contemporary administering, in the 1 : 1 ratio, of FANS and sucralfate, which allows an antiinflammatory activity similar to that exerted by the same FANS alone to be obtained, with a considerable reduction in the damaging effects on the gastric and duodenal mucosa (Italian Patent Application Nr. 23205 A.83).

Sucralfate [3,4,5,6-tetra-(polyhydroxyalumino)-α-D-glucopyranosyl sulphate - 2,3,4,5-tetra-(polyhydroxyalumino)-β-D-fructofuranoside sulphate] is a product prepared during these last years, and successfully tested in the management of gastric and duodenal ulcer (R. Nagashima et al., Arzneim. Forsch., 1980: 30: 84/8; 1980: 30: 88/91 "Selective Binding of Sucralfate to Ulcer Lesion").

We have now found that if, instead of contemporaneously administering the mixture of the two active principles, the administering in sequence of sucralfate first, and of FANS then is carried out, a more efficacious protection of the mucosa is obtained. The result in practice is such as to allow the same protection level with lower amounts of sucralfate to be obtained. This administering form causes however the drawback that a double administering is to be carried out, with a suitable time interval.

Purpose of the present invention is to provide a solid pharmaceutical form which allows the contemporary admin-

istering of the two drugs above mentioned, or of other similar drugs, and the release of them in a sequential fashion.

This purpose is achieved by means of the pharmaceutical form sequentially relasing the active principles according to the present invention, which is characterized in that it is constituted by a tablet comprising:

a) a centre core containing an active principle providing an anti-inflammatory and analgesic activity with side ulcerogenic effects;

b) a layer coating for said core, containing a second active principle, providing a protective action of the gastric and duodenal mucosa, which is released immediately.

These and other characteristics and advantages of the pharmaceutical form according to the present invention shall be evidenced in greater detail by the following detailed disclosure, and by the related Figure 1, which are reported to the purpose of illustrating and not of limiting the invention itself.

Referring to the numerical indices of fig. 1, the centre core (1) of the pharmaceutical form according to the present invention is prepared by making into a paste the antiinflammatory and analgesic active principle, suitably formulated, with an alcoholic solution of ethylcellulose; the paste is granulated, dried, blended with lubricating and disintegrating substances, and then transformed into tablets.

The coating layer (2) is prepared by mixing sucralfate in suitable formulations, and is applied to the core (1) by means of the double-compression technique, i.e., by compressing two coating layers respectively positioned on and under the core.

The coating layer can contain as mucose protecting ac-

tive principles, in addition to sucralfate, also mucin, cellulose derivatives, natural or synthetic polymeric materials, alone, or as different combinations with each other.

The coating layer is so formulated, as to release an extremely subdivided dispersion of sucralfate before that the FANS composing the core comes in contact with the gastric and duodenal mucosa.

The action of this farmaceutical form is hence developed in two sequential steps, whose sequence is evidenced by observations related to tests carried out on animal. The steps of this action are:

A) Disintegration quick and of microgranular type, in the acidic medium of the stomach, of the coating layer, with formation of a wide dispersion of the protective agent composing it. The active principle of the coating has hence the time and the possibility of lining the gastric and intestinal mucosa, protecting it from the subsequent contact with the ulcerogenic drug contained in the core.

B) Slow disintegration of the core in a medium wherein the protective active substance has already lined the mucosa.

In this way, the lesioning action of the drug contained in the core is limited by the action of the protective drug.

Several compositions containing sucralfate : FANS in weight ratios comprised within the range of from 1: 4 to 8 : 1 have been tested on rats by means of the test of pylorus ligature according to the technique Linda J. et al., J. Pharmac., 1978, 30, 244 - 246 "Inhibitors of Gastric Lesions in the Rat".

The testing has been carried out on Charles River Wistar rats of 230 - 270 g of weight and in the number of 8 rats per each group. The rats, fasting from 15 hours, have been submitted to etheric anesthesia and then to the liga

ture of the pylorus. The rats have been treated, immediately after the recovery, by means of gastric probe, with the FANS alone, with the FANS in the sucralfate-FANS form with sequential action according to the present invention, and by means of the administering of sucralfate first, and then, after a 10 minutes interval, of FANS.

The single active principles have been administered as aqueous suspension in sodium-CMC at 0.5% p.o.

Six hours later than the intervention, the rats have been sacrificed and the stomach, after having been withdrawn, has been cut along the line of the greater curvature. The stomach, after having been slightly washed with bidistilled water has been spread out and mounted on a support for the evaluation of induced ulceration. The alterations detected on the gastric mucosa have been quantified on the basis of their type and largeness, with a value ranging from 0 to 1 (ulcerating index, UI), according to the following empirical scale:

0 = mucose not damaged (control submitted to surgical handling and to placebo)

0.25 = diffused accentuated hyperemia

0.50 = diffused erosion

0.75 = diffused hemorrhagic ulceration

1 = diffused hemorrhagic ulceration with perforation and damaging of the whole gastric mucosa.

The activity of the form of sucralfate and FANS with sequential action according to the invention has been expressed as percentage inhibition of the lesion relatively to that observed in the control group as treated with the ligature of pylorus and administering of FANS only, and compared to that obtained from the contemporary administering of sucralfate and FANS. The ID_{50} (Inhibiting Dosis 50) was

computated by the probit method.

In Table 1 the values of ID_{50} of sucralfate for various FANS are reported, in the case of the contemporary administering of FANS and sucralfate, and in the case of the administering in the form with sequential activity according to the present invention.

TABLE 1

Inhibiting Dosis 50 of sucralfate for the ulcerogenic activity of some FANS (mg)

FANS	Contemporary administering of sucralfate and of FANS	Administering of the sucralfate-FANS form with sequential action
Sodium indoprofen betainate (200 mg/kg as indoprofen)	206	85.6
Diclofenac Na (50 mg/kg)	157	96.6
Indomethacin (100 mg/kg)	204	97

It results from Table 1 in a clear way that the administering of the form of sucralfate-FANS with sequential action is capable of protecting to a significantly greater extent the gastric mucosa against the lesioning power of FANS.

To illustrative, but not limitative, purpose of the present invention, the following Example is reported, relating to a formulation of the pharmaceutic form with sequential action (the numbers indicate parts by weight):

a) Formulation of the core of sodium indoprofen betainate

Sodium indoprofen betainate	290
Ethylcellulose	5
Carboxymethyl starch	12

Magnesium stearate	3

b) Preparation of the core

Indoprofen betainate is made into a paste with an alcoholic solution of ethylcellulose, the paste is granulated and dried. The dried granulate is mixed with the lubricant agent (magnesium stearate) and then with the disintegrating agent (carboxymethyl starch), and is compressed to form tablets of slightly crowned shape, with punches of 9 mm in diameter.

c) Formulation of the coating layer

Sucralfate	100
Crosslinked carboxymethylcellulose	10
Microcrystalline cellulose	40
Magnesium carbonate	10
CL Polyvinylpirrolidone	5
Magnesium stearate	2

The components of the formulation are mixed in a V-mixer.

d) Application of sucralfate coating on the core of sodium indoprofen betainate.

The application of the coating layer on the core is carried out by means of the double-compression technique, by compressing two layers of coating positioned on the core and under it, a coated tablet of suitable diameter being obtained, wherein the outer coating is constituted by sucralfate, and the inner core is constituted by indoprofen betainate (see figure 1).

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Claims

1. Solid pharmaceutical form, for administration by oral way, with sequential release of the contained active principles, characterized in that it is constituted by

(a) a centre core containing an active principle displaying antiinflammatory and analgesic activity, with ulcerogenic side effects;

(b) a coating layer for said core, containing a second active principle displaying a protective action for the gastric and duodenal mucosa, which is immediately released.

2. Pharmaceutical form according to claim 1, characterized in that the active principle contained in said core is constitutend by FANS (Non Steroidic Antiinflammatory drugs, NSAD), such as ASA, Indoprofen, Naproxen, Ketoprofen, Indomethacin, Diflunisal, Diclofenac or derivatives.

3. Pharmaceutical form according to claim 1, characterized in that said core shows a slow disintegration, or constitutes a system with bioeroded matrix and however of the type with properties of controlled release of the contained active principle.

4. Pharmaceutical form according to claim 1, characterized in that said core containes active principles provided with anti-inflammatory and analgesic activity, with ulcerogenic side effects, combined with each other or with other medicaments.

5. Pharmaceutical form according to claim 1, characterized in that said coating layer is constituted by active principles capable of performing a protective action on the gastric and duodenal mucosa such as, e.g., sucralfate, mucin, cellulose derivatives, natural or synthetic polymeric materials capable of forming a protective lining.

6. Pharmaceutical form according to claim 1, characterized in that said coating layer shows a disintegration quick and of the microgranular type in the acidic medium of the stomach, determining an immediate dispersion of the contained protective agent.

7. Pharmaceutical form according to claim 1, characterized in that sucralfate or another mucose-protecting agent and FANS are contained in a weight ratio comprised within the range of from 1 : 4 to 8 : 1.

8. Pharmaceutical form for oral usage according to claims from 1 to 7 and method for the preparation thereof, which is carried out by means of the double-compression technique, i.e., by compressing around said core containing the active principle provided with antiinflammatory and analgesic activity with ulcerogenic side effects, said coating layer containing an active principle provided with protective action for the gastric and duodenal mucosa.

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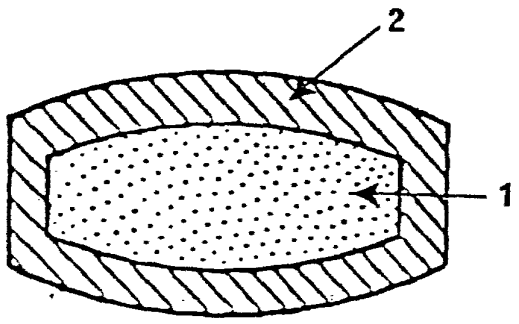

FIGURE 1

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 174 726**
A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **85305458.3**

(22) Date of filing: **31.07.85**

(51) Int. Cl.⁴: **C 07 D 401/12**
A 61 K 31/44

(30) Priority: **16.08.84 JP 171069/84**

(43) Date of publication of application:
19.03.86 Bulletin 86/12

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

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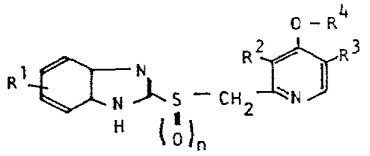
(54) Pyridine derivatives and their production.

(57) The compound of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl and n denotes 0 or 1, or a pharmacologically acceptable salt thereof is novel, and useful for prophylaxis and therapy of digestive ulcers (e.g. gastric ulcer, duodenal ulcer) and gastritis.

Croydon Printing Company Ltd.

Pyridine Derivatives and Their Production

This invention relates to pyridine derivatives useful as e.g. anti-ulcer agents and to a method of preparing them.

As the pyridine derivatives having anti-ulcer activity, those disclosed in USP. 4,255,431 (Japanese Unexamined Patent Laid-open No. 141783/79) and USP. 4,472,409 (Japanese Unexamined Patent Laid-open No. 135881/83) etc. have been known.

However, while these known compounds have an acid-secretion-inhibiting action, their gastric mucous membrane protecting action is insufficient, thus being hardly considered satisfactory as anti-ulcer agents. Besides, these compounds are possessed of such drawbacks in the physico-chemical properties as being unstable and readily decomposed.

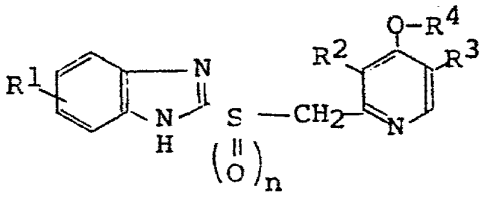
It is considered that gastrointestinal ulcer is induced by unbalance between aggressive factors, e.g. hydrochloric acid, pepsin, and defensive factors, e.g. mucus secretion and mucosal blood flow. Therefore, a medicine having both an action of inhibiting gastric acid secretion and an action of enhancing protection of gastric mucosa has been desired.

The present inventors diligently studied with the purpose of preparing an anti-ulcer agent having excellent actions of inhibiting gastric acid secretion, of

protecting gastric mucosa and of anti-ulceration. They found that a certain type of pyridine derivatives meet the said purpose, and they conducted further study to accomplish the present invention.

The present invention relates to

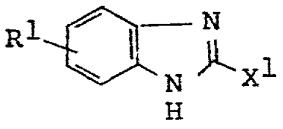
(1) pyridine derivatives of the formula (I)



(I)

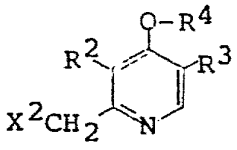
wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl, and n denotes 0 or 1, or their pharmacologically acceptable salts and

(2) a method for preparing a compound (I) or its pharmacologically acceptable salt, which comprises allowing a compound of the formula (II)



(II)

wherein R^1 is of the same meaning as defined above, to react with a compound of the formula (III)



(III)

wherein R^2, R^3 and R^4 are of the same meaning as defined above, one of X^1 and X^2 is SH and the other

is a leaving group and, when necessary, by subjecting the reaction product to oxidation.

In the above formulae, C_{2-5} fluorinated alkyl groups shown by R^4 are exemplified by 2,2,2-trifluoroethyl, 2,2,3,3,3-pentafluoropropyl, 2,2,3,3-tetrafluoropropyl 1-(trifluoromethyl)-2,2,2-trifluoroethyl, 2,2,3,3,4,4,4-heptafluorobutyl and 2,2,3,3,4,4,5,5-octafluoropentyl.

Examples of the leaving groups X^1 and X^2 in the above formulae are halogen, preferably chlorine, bromine or iodine, or a reactive esterified hydroxy group, e.g. an arylsulfonyloxy, for example, phenylsulfonyloxy or tosyloxy, or a C_{1-4} alkylsulfonyloxy, for example, methanesulfonyloxy, or an organic phosphoryloxy, for example, diphenylphosphoryloxy, dibenzylphosphoryloxy or di-C_{1-4} alkylphosphoryloxy (e.g. dimethylphosphoryloxy) and the like.

R^1 may be located at 4- or 5-position, and preferably at 5-position.

A sulfide derivative (I) (n = 0), among the object compounds of this invention, can be prepared by allowing a compound (II) to react with a compound (III). It is convenient to conduct this reaction in the presence of a base. The base is exemplified by alkali metal hydride e.g. sodium hydride and potassium hydride; alkali metal e.g. metallic sodium; sodium alcoholate e.g. sodium methoxide and sodium ethoxide; alkali metal carbonate e.g. potassium carbonate and sodium carbonate; and organic amines e.g. triethylamine. The solvent used for the reaction is exemplified by alcohols e.g. methanol and ethanol, as well as dimethylformamide. The amount of a base used for the reaction is usually in a little excess to the equivalent, but it may be in a large excess. Specifically, it is about 1-10 equivalents, more preferably about 1-4 equivalents. The reaction temperature ranges usually from about 0°C to about the boiling point of the solvent then used, more preferably from about 20°C

to about 80°C. The reaction time ranges from about 0.2 to about 24 hours, more preferably from about 0.5 to about 2 hours.

A sulfinyl derivative (I) (n = 1), which is also among the object compounds of this invention, can be prepared by subjecting a compound (I) (n = 0) to oxidation. The oxidizing agent to be employed here is exemplified by peracid e.g. m-chloroperbenzoic acid, peracetic acid, trifluoroperacetic acid and permaleic acid, or sodium bromite or sodium hypochlorite or hydrogen peroxide. The solvent used for the reaction is exemplified by halogenated hydrocarbon e.g. chloroform and dichloromethane, ethers e.g. tetrahydrofuran and dioxane, amides e.g. dimethylformamide, alcohols, e.g. methanol, ethanol, propanol, and t-butanol or water, and these solvents may used singly or in admixture. The oxidizing agent is used preferably in approximately equivalent or a little excess amount relative to the compound (I) (n = 0). Specifically, it is about 1 to about 3 equivalents, more preferably about 1-1.5 equivalent. The reaction temperature ranges from that under ice-cooling to about the boiling point of the solvent then employed, usually from that under ice-cooling to room temperature, more preferably from about 0°C to about 10°C. The reaction time usually ranges from about 0.1 to about 24 hours, more preferably from about 0.1 to about 4 hours.

The object compound (I) produced by the above reaction can be isolated and purified by conventional means e.g. recrystallization and chromatography.

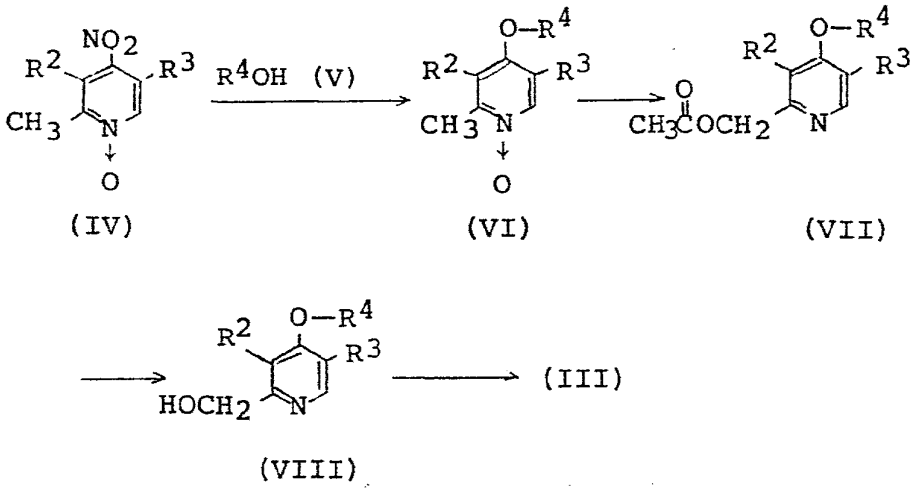
The compound (I) of this invention may be led to pharmacologically acceptable salts thereof by per se conventional means, the salts being exemplified by hydrochloride, hydrobromide, hydroiodide, phosphate, nitrate, sulfate, acetate and citrate.

Among the compounds (I), those of n = 0 give stable

salts, while those of n = 1 may exist as an aqueous solution though unstable.

The process of preparing the starting material (III) is described as follows.

Process 1)



(IV) (VI) (VII) (VIII) (III)

A nitro compound of the formula (IV) [wherein R^2 and R^3 are of the same meaning as defined above] is allowed to react with an alcohol derivative R^4OH (V) [wherein R^4 is of the same meaning as defined above] in the presence of a base to give an alkoxy derivative of the formula (VI) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The base is exemplified by alkali metal e.g. lithium, sodium and potassium; alkali metal hydride e.g. sodium hydride and potassium hydride; alcoholate e.g. potassium t-butoxide and sodium propoxide; alkali metal carbonate or hydrogen carbonate e.g. potassium carbonate, lithium carbonate, sodium carbonate, potassium hydrogen carbonate and sodium hydrogen carbonate; or alkali hydroxide e.g. sodium hydroxide and potassium hydroxide. The solvent used for the reaction is exemplified by, besides R^4OH itself, ethers such as tetrahydrofuran and dioxane as well as ketones such as acetone and methyl ethyl ketone, aceto-

nitrile, dimethylformamide and hexamethylphosphoric acid triamide. The reaction temperature is suitably selected within the range from those under ice-cooling to those near the boiling point of the solvent used. The reaction time ranges usually from about 1 to about 48 hours.

The thus-obtained compound (VI) is subjected to heating (about 80 to about 120°C) in the presence of acetic anhydride singly or together with a mineral acid e.g. sulfuric acid and perchloric acid to give a 2-acetoxymethylpyridine derivative of the formula (VII) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The reaction time ranges usually from about 0.1 to about 10 hours.

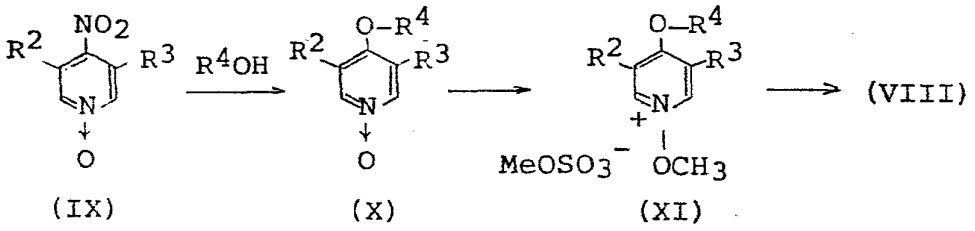
Then, the compound (VII) is subjected to alkali-hydrolysis to give a 2-hydroxymethyl pyridine derivative of the formula (VIII) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The alkali is exemplified by sodium hydroxide, potassium hydroxide, potassium carbonate and sodium carbonate. The solvent used for the reaction is exemplified by methanol, ethanol and water. The reaction temperature ranges usually from about 20°C to about 60°C. The reaction time is within the range of from about 0.1 to about 2 hours.

The compound (VIII) is further subjected to reaction with a chlorinating agent such as thionyl chloride, or an esterifying agent, e.g. an organic sulfonic acid chloride such as methanesulfonyl chloride or p-toluene-sulfonyl chloride, or an organic phosphoric acid chloride such as diphenylphosphoryl chloride to give the compound (III). The amount of the chlorinating agent used for the reaction is usually in equivalent to a large excess relative to the compound (VIII). The solvent used for the reaction is exemplified by chloroform, dichloro-methane and tetrachloroethane. The reaction temperature is usually within the range of from about 20°C to about

80°C, and the reaction time is about 0.1 to about 2 hours.

The amount of the organic sulfonic acid chloride or organic phosphoric acid chloride used for the reaction is usually in equivalent to a little excess, and the reaction is usually conducted in the presence of a base. The base is exemplified by organic base e.g. triethylamine and tributylamine, or inorganic base e.g. sodium carbonate, potassium carbonate and sodium hydrogen carbonate. The amount of a base used for the reaction is usually in equivalent to a little excess. The solvent used for the reaction is exemplified by chloroform, dichloromethane, carbon tetrachloride or acetonitrile. The reaction temperature ranges usually from that under ice-cooling to about the boiling point of the solvent then used. The raction time ranges usually from a few minutes to a few hours. It is usually preferable to use the thus-produced compound (III) immediately for the reaction with a compound (II).

Process 2)



(IX) (X) (XI)

By a reaction similar to the above-described process (1), a compound of the formula (IX) [wherein R^2 and R^3 are of the same meaning as defined above] is led to a compound of the formula (X) [wherein R^2, R^3 and R^4 are of the same meaning as defined above].

Then, the compound (X) is subjected to methylation with dimethyl sulfate to give a compound of the formula

(XI) [wherein R^2, R^3 and R^4 are of the same meaning as defined above]. The reaction can be conducted usually without solvent. The reaction temperature ranges from about 100°C to about 120°C, and the reaction time is within the range of from about 0.1 to about 4 hours.

Further, the compound (XI) is allowed to react with a radical source such as ammonium persulfate or any other persulfate in methanol to give the above-mentioned compound (VIII). The reaction temperature is within the range of from about 20°C to about 80°C, and the reaction time ranges from about 0.5 to about 4 hours.

Pharmacological actions of the compounds of the present invention are described as follows.

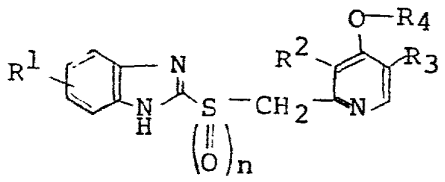
As the models of gastrointestinal ulcers, restraint and water-immersion stress-induced ulcer, indomethacin-induced ulcer and ethanol-induced gastric mucosal lesions have been used. However, as a model mimicking human gastric ulcer, indomethacin-induced gastric antral ulcer was reported in "Gastroenterology" (Satoh et al. 81, p. 719, 1981), which is considered to be of value as an experimental model. Therefore, the following are data of anti-ulcer actions of the object compounds (I) and of some representable known compounds, on the ulcer model in the above-mentioned literature reference.

Experimental Method:

Male Sprague-Dawley rats of 7-weeks old were fasted for 24 hours. These animals were administered test compounds into stomach by using a gastric tube. After 30 minutes, indomethacin, 30 mg/kg subcutaneously, was administered. During 30-90 minutes after the administration of indomethacin, these animals had free access to chow pellets (Japan Clea, CE-2). At 5 hours after the administration of indomethacin, 1 ml of 1% Evans blue was injected to the animals via the tail vein, followed by sacrificing these animals with carbon dioxide gas. The

stomach was removed together with the lower part of esophagus and the duodenum. The esophagus was clipped, 10 ml of 1% formalin solution was instilled into the stomach from the duodenum, and then the duodenum was clipped. The whole stomach was immersed in 1% formalin solution. About 15 minutes later, the stomachs were opened along the greater curvature. Area of the lesions occurred in the gastric antral mucosa was measured under a dissecting microscope with a square-grid eye piece (x10). The sum total of the individual lesions in each animal was measured, and the average value per group was calculated. Based on the difference between the average value of each group and that of the control group, the inhibition rate was determined. The test compound on indomethacin was suspended in a 5% gum arabic solution, and administered in a volume of 2 ml/kg.

Experimental Results:



R^1	R^2	R^3	R^4	n	Anti-ulcer action[a] ID_{50} (mg/kg, p.o.)
H	H	H	CH_2CF_3	1	2.4
H	CH_3	H	CH_2CF_3	1	<1.0
H	H	H	$CH_2CF_2CF_3$	1	1.3
H	CH_3	H	$CH_2CF_2CF_3$	1	<1.0
H	H	H	$CH_2CF_2CF_2H$	1	1.3
H	CH_3	H	$CH_2CF_2CF_2H$	1	<1.0

R^1	R^2	R^3	R^4	n	Anti-ulcer action[a] ID_{50} (mg/kg, p.o.)
H	CH_3	H	$CH_2CF_2CF_3$	0	3.7
5-OCH_3	CH_3	CH_3	CH_3 *1		21.0
5-CF_3	CH_3	H	CH_3 *2		5.5

*1 The compound disclosed in Example 23 of USP. 4,255,431 (Japanese Unexamined Patent Laid-open No. 141783/1979)

*2 The compound disclosed in Example 3 of USP. 4,472,409 (Japanese Unexamined Patent Laid-open No. 135881/1983)

a) Using 6 rats per group, each of the test compounds was administered in a dose of 1, 3, 10 and 30 mg/kg to determine ID_{50}.

As shown by the above data, the compounds of this invention have superior anti-ulcer action as compared with known compounds by about 1.5-20 times or more. Besides, the compound (I) of this invention shows excellent actions of inhibiting gastric acid secretion, protecting gastric mucous membrane and preventing ulceration.

Stating about the toxicity of the compound (I) of this invention, oral administration of the compound employed for the experiment of anti-ulceration (compound of R^1 = H, R^2 = CH_3, R^3 = H, R^4 = $CH_2CF_2CF_3$, n = 1) to mice even in a dose of 2000 mg/kg caused no fatal effect, thus the compound (I) being low in toxicity.

As described in the foregoing, the compound (I) of this invention has an anti-ulcer action, a gastric acid secretion controlling action and a mucous membrane protecting action, furthermore is of low toxicity and is

relatively stable as a chemical substance. The compound (I) of this invention can thus be used for prophylaxis and therapy of digestive ulcers (e.g. gastric ulcer, duodenal ulcer) and gastritis in mammalian animals (e.g. mouse, rat, rabbit, dog, cat and man).

When the compound (I) of this invention is used as an anti-ulcer agent for the therapy of digestive ulcers in mammalian animals, it can be administered orally in a dosage form of capsules, tablets, granules, etc. by formulating with a pharmacologically acceptable carrier, excipient, diluent, etc. The daily dose is about 0.01-30 mg/kg, more preferably about 0.1-3 mg/kg.

Incidentally, the compound of this invention (I) (n = 0) is useful as a starting material for preparing the compound (I) (n = 1).

The processes of producing the starting compounds to be employed in the method of this invention as well as those of producing the compound (I) of this invention are specifically explained by the following Reference Examples and Working Examples.

Reference Example 1

In 2,2,3,3-tetrafluoropropanol (10 ml) was dissolved 2,3-dimethyl-4-nitropyridine-1-oxide (2 g). To the solution was added potassium t-butoxide (1.6 g) little by little at room temperature. The mixture was then heated at 80-90°C for 22 hours. The reaction solution was diluted with water, which was subjected to extraction with chloroform. The extract was dried on magnesium sulfate, and then concentrated. The concentrate was chromatographed on a column of silica gel (70 g). Elution was conducted with methanol-chloroform (1:10), and then subjected to recrystallization from ethyl acetate-hexane to yield 2.6 g of 2,3-dimethyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine-1-oxide as colorless needles, m.p. 138-139°C.

After the manner similar to the above, compounds (VI) were prepared from compounds (IV).

Compound (VI)			
R^2	R^3	R^4	Melting point (°C)
H	H	CH_2CF_3	148-150
CH_3	CH_3	CH_2CF_3	138-139

Reference Example 2

A mixture of 2,3-dimethyl-4-nitropyridine-1-oxide (2.0 g), methyl ethyl ketone (30 ml), 2,2,3,3,3-pentafluoropropanol (3.05 ml), anhydrous potassium carbonate (3.29 g) and hexamethyl phosphoric acid triamide (2.07 g) was heated at 70-80°C for 4.5 days under stirring, then insolubles were filtered off. The filtrate was concentrated, to which was added water. The mixture was subjected to extraction with ethyl acetate. The extract solution was dried on magnesium sulfate, followed by removing the solvent by evaporation. The residue was chromatographed on a column of silica gel (50 g), eluted with chloroform-methanol (10:1), and recrystallized from ethyl acetate-hexane to yield 2.4 g of 2,3-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as colorless needles, m.p. 148-149°C.

After the manner similar to the above, compounds (VI) were prepared from starting compounds (IV).

Compound (VI)			
R^2	R^3	R^4	Melting point (°C)
CH_3	H	CH_2CF_3	131.0-131.5
H	CH_3	CH_2CF_3	153-154
H	H	$CH_2CF_2CF_3$	79-81

Compound (VI)			
R^2	R^3	R^4	Melting point (°C)
H	CH_3	$CH_2CF_2CF_3$	140-142
H	H	$CH_2CF_2CF_2H$	Oily
H	CH_3	$CH_2CF_2CF_2H$	143.5-144.5
CH_3	H	$CH_2CF_2CF_2H$	138-139

Reference Example 3

Concentrated sulfuric acid (two drops) was added to a solution of 2,3-dimethyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine-1-oxide (2.6 g) in acetic anhydride (8 ml). The mixture was stirred at 110°C for 4 hours, which was then concentrated. The residue was dissolved in methanol (20 ml), to which was added sodium hydroxide (1.2 g) dissolved in water (5 ml). The mixture was stirred at room temperature for 30 minutes, which was concentrated. To the residue was added water, and the mixture was subjected to extraction with ethyl acetate. The extract was dried on magnesium sulfate, followed by removal of the solvent by evaporation. The residue was chromatographed on a column of silica gel (50 g), eluted with chloroform-methanol (10:1), and recrystallized from isopropyl ether to yield 1.6 g of 2-hydroxymethyl-3-methyl-4-(2,2,3,3-tetrafluoropropoxy)pyridine as yellow crystals, m.p. 67-68°C.

After the manner similar to the above, compounds (VIII) were prepared from compounds (VI).

Compound (VIII)			
R^2	R^3	R^4	Melting point (°C)
H	H	CH_2CF_3	Oily
CH_3	H	CH_2CF_3	93.5-94.0
H	H	$CH_2CF_2CF_3$	Oily
CH_3	H	$CH_2CF_2CF_3$	Oily
H	CH_3	$CH_2CF_2CF_3$	87-89
H	H	$CH_2CF_2CF_2H$	88-89
H	CH_3	$CH_2CF_2CF_2H$	98-99
CH_3	H	$CH_2CF_2CF_2H$	67-68

Reference Example 4

To a solution of 3,5-dimethyl-4-nitropyridine-1-oxide (2.0 g) in 2,2,3,3,3-pentafluoropropanol (10 g) was added at 0°C little by little potassium t-butoxide (2 g) over 15 minutes. The mixture was stirred at 60°C for 18 hours. To the reaction mixture was added chloroform, which was subjected to filtration with celite. The filtrate was chromatographed on a column of silica gel (80 g), eluted with ethyl acetate-hexane (1:1), then with 20% methanol-ethyl acetate, and recrystallized from ether-hexane to yield 2.6 g of 3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide as crystals, m.p. 89-91°C.

After the manner similar to the above, compounds (X) were prepared from compounds (IX).

Compound (X)			
R^2	R^3	R^4	Melting point (°C)
CH_3	H	CH_2CF_3	82-94
CH_3	CH_3	CH_2CF_3	138-139

Reference Example 5

A mixture of 3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine-1-oxide (2.5 g) and dimethyl sulfate (1 ml) was heated at 120°C for 30 minutes, to which was then added methanol (12.5 ml). To the mixture was added dropwise at 80°C ammonium persulfate (4.3 g) dissolved in water (20 ml)-methanol (10 ml) over 30 minutes, which was stirred for further 30 minutes. The resultant solution was concentrated. To the residue was added ice, which was neutralized with sodium carbonate, followed by extraction with chloroform. The extract was dried on sodium sulfate, followed by removing the solvent by evaporation to give 2.2 g of 3,5-dimethyl-2-hydroxymethyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine as an oily substance.

After the manner similar to the above, compounds (VIII) were prepared from compounds (X).

Compound (VIII)			
R^2	R^3	R^4	Melting point (°C)
H	CH_3	CH_2CF_3	116-119
CH_3	CH_3	CH_2CF_3	62-63

Example 1

To a solution of 2-hydroxymethyl-3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyridine (350 mg) in chloroform (10 ml) was added thionyl chloride (0.2 ml). The mixture was refluxed for 30 minutes, which was then concentrated. The residue was dissolved in methanol (5 ml). The solution was added to a mixture of 2-mercaptobenzimidazole (200 mg), 28% sodium methoxide solution (1 ml) and methanol (6 ml), which was refluxed for 30 minutes. From the resultant was removed methanol by evaporation. To the residue was added water, which was subjected to extraction with ethyl acetate. The extract was washed with a dilute sodium hydroxide solution, followed by drying on magnesium sulfate. From the resultant was removed the solvent by evaporation. The residue was then chromatographed on a column of silica gel (20 g), eluted with ethyl acetate-hexane (2:1), and then recrystallized from ethyl acetate-hexane to yield 370 mg of 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylthiobenzimidazole·$\frac{1}{2}$ hydrate as colorless plates, m.p. 145-146°C.

After the manner similar to the above, compounds (I) (n = 0) were prepared by allowing compounds (II) with compounds (III).

Compound (I) (n=0)				
R^1	R^2	R^3	R^4	Melting point (°C)
H	H	H	CH_2CF_3	138-139
H	CH_3	H	CH_2CF_3	149-150
H	H	CH_3	CH_2CF_3	168-170
H	CH_3	CH_3	CH_2CF_3	151.5-152.0
H	H	H	$CH_2CF_2CF_3$	125-126

Compound (I) (n=0)					
	R^1	R^2	R^3	R^4	Melting point (°C)
	H	H	CH_3	$CH_2CF_2CF_3$	151-152
	H	H	H	$CH_2CF_2CF_2H$	Oily *3
	H	CH_3	H	$CH_2CF_2CF_2H$	134-135
	H	H	CH_3	$CH_2CF_2CF_2H$	148-149
	H	CH_3	CH_3	$CH_2CF_2CF_3$	158-160
*4	5-CF_3	CH_3	H	CH_2CF_3	92-93
	5-OCH_3	CH_3	H	CH_2CF_3	159-160
	5-OCH_3	H	H	CH_2CF_3	152-153

*3 NMR spectrum ($CDCl_3$)δ:4.35(S),4.39(t,t,J=1.5 and 12 Hz), 5.98 (1H,t,t,J=52.5 and 4 Hz), 6.81 (1H,d,d,J=2 and 6 Hz) 6.95 (1H,d,J=2Hz), 7.1-7.3 (2H,m), 7.4-7.7 (2H,m), 8.50 (1H,d,J=6 Hz)

*4: $\frac{1}{4}H_2O$ (crystal water)

Example 2

To a solution of 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyrid-2-yl]methylthiobenzimidazole (2.2 g) in chloroform (20 ml) was added dropwise under ice-cooling over a period of 30 minutes m-chloroperbenzoic acid (1.3 g) dissolved in chloroform (15 ml). The solution was washed with a saturated aqueous solution of sodium hydrogen carbonate, then dried on magnesium sulfate, and concentrated. The residue was chromatographed on a column of silica gel (50 g), eluted with ethyl acetate, and then recrystallized from acetone-isopropyl ether to give 1.78 g of 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)pyrid-2-yl]methylsulfinylbenzimidazole as pale yellow prisms, m.p. 161-163°C (decomp.).

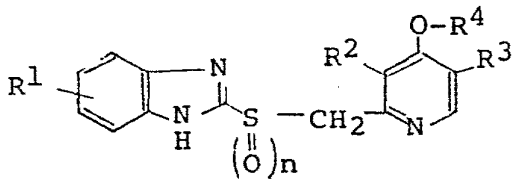
After the manner similar to the above, compounds (I) (n = 1) were prepared from compounds (I) (n = 0).

Compound (I) (n=1)				
R^1	R^2	R^3	R^4	Melting point (°C)
H	H	H	CH_2CF_3	176-177
H	CH_3	H	CH_2CF_3	178-182(d)
H	H	CH_3	CH_2CF_3	175-177(d)
H	CH_3	CH_3	CH_2CF_3	177-178(d)
H	H	H	$CH_2CF_2CF_3$	148-150(d)
H	H	CH_3	$CH_2CF_2CF_3$	145-148(d)
H	H	H	$CH_2CF_2CF_2H$	132-133
H	CH_3	H	$CH_2CF_2CF_2H$	147-148(d)
H	H	CH_3	$CH_2CF_2CF_2H$	136-139(d)
H	CH_3	CH_3	$CH_2CF_2CF_3$	157-159
5-CF_3	CH_3	H	CH_2CF_3	161-162(d)
5-OCH_3	CH_3	H	CH_2CF_3	140.5-142(d)
5-OCH_3	H	H	CH_2CF_3	162-163(d)

(Note) (d): decomposition

What we claim is:

1. A compound of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl and n denotes 0 or 1, and a pharmacologically acceptable salt thereof.

2. A compound according to claim 1, wherein R^1 is hydrogen.

3. A compound according to claim 1 or 2, wherein R^2 is methyl.

4. A compound according to any of claims 1 to 3, wherein R^3 is hydrogen.

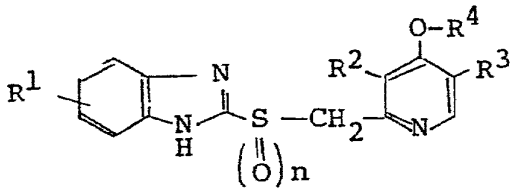
5. A compound according to any of claims 1 to 4, wherein R^4 is a C_{2-3} fluorinated alkyl.

6. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

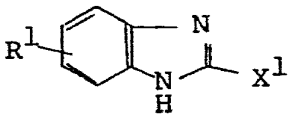
7. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3,3-pentafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

8. A compound according to claim 1, wherein the compound is 2-[3-methyl-4-(2,2,3,3-tetrafluoropropoxy)-pyrid-2-yl]methylsulfinylbenzimidazole.

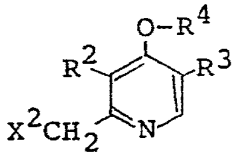
9. A method for producing a pyridine derivative of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl and n denotes 0 or 1, or a pharmacologically acceptable salt thereof, which comprises allowing a compound of the formula



wherein R^1 is of the same meaning as defined above, to react with a compound of the formula

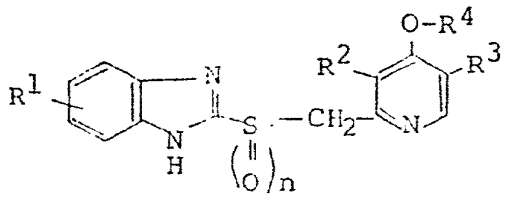


wherein R^2, R^3 and R^4 are of the same meaning as defined above, and one of X^1 and X^2 is SH and the other is a leaving group, and when necessary, by subjecting the reaction product to oxidation.

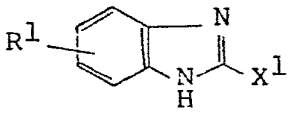
10. A method according to claim 9, wherein X^1 is SH and X^2 is halogen.

Claims for contracting state: AT (Austria)

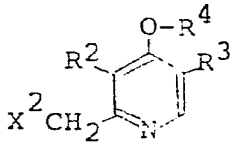
1. A method for producing a pyridine derivative of the formula



wherein R^1 is hydrogen, methoxy or trifluoromethyl, R^2 and R^3 are independently hydrogen or methyl, R^4 is a C_{2-5} fluorinated alkyl and n denotes 0 or 1, or a pharmacologically acceptable salt thereof, which comprises allowing a compound of the formula



wherein R^1 is of the same meaning as defined above, to react with a compound of the formula



wherein R^2, R^3 and R^4 are of the same meaning as defined above, and one of X^1 and X^2 is SH and the other is a leaving group, and when necessary, by subjecting the reaction product to oxidation.

2. A method according to claim 1, wherein X^1 is SH and X^2 is halogen.

European Patent Office

EUROPEAN SEARCH REPORT

0174726
Application number

EP 85 30 5458

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl.4)
A	EP-A-0 005 129 (HÄSSLE)		C 07 D 401/12 A 61 K 31/44
A	EP-A-0 080 602 (BYK GULDEN)		

TECHNICAL FIELDS SEARCHED (Int Cl.4)

C 07 D 401/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	29-11-1985	DE BUYSER I.A.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1503 03 82

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 244 380**
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **87850126.1**

(22) Date of filing: **16.04.87**

(51) Int. Cl.³: **A 61 K 9/32**
A 61 K 9/52, A 61 K 9/54

(30) Priority: **30.04.86 GB 8610573**

(43) Date of publication of application:
04.11.87 Bulletin 87/45

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

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(54) Pharmaceutical formulations of acid labile substances for oral use.

(57) Pharmaceutical preparation containing an acid labile compound together with an alkaline reacting compound or an alkaline salt of an acid labile compound optionally together with an alkaline compound as the core material, one or more subcoating layers comprising inert reacting compounds which are soluble or rapidly disintegrating in water, or polymeric, water soluble filmforming compounds, optionally containing pH-buffering alkaline compounds and an enteric coating as well as a process for the preparation thereof and the use in the treatment of gastrointestinal diseases.

EP 0 244 380 A2

Pharmaceutical formulations of acid labile substances for oral use

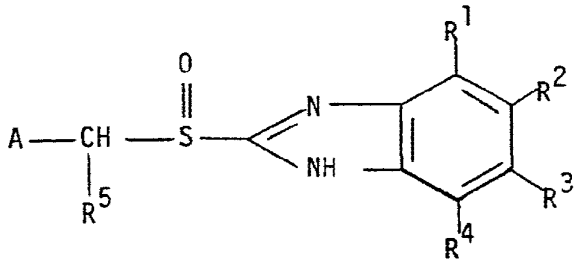
Field of the Invention

The present invention is related to new pharmaceutical preparations containing acid labile substances for oral use, to a method for the manufacture of such preparations and to a method of affecting gastric acid secretion and providing gastrointestinal cytoprotective effect when using them.

Background of the Invention

Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating. The coating is a group of substances/polymers with the common feature of being practically insoluble in acid media, while they are soluble in neutral to alkaline media. For substances that are labile in acid media, but have better stability in neutral to alkaline media, it is often advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and storage.

A group of compounds exerting these stability properties are substituted benzimidazoles with the general formula I



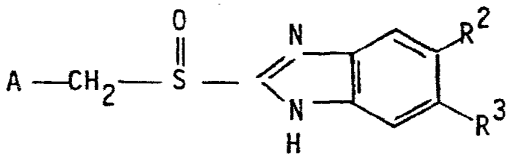
wherein A is an optionally substituted heterocyclic group and R^1, R^2, R^3, and R^4 are the same or different as defined below and R^5 is H or a lower alkyl, or the compound 2-[(2-dimethylamino-benzyl)sulfinyl]-benzimidazole.

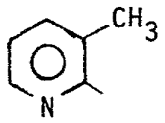
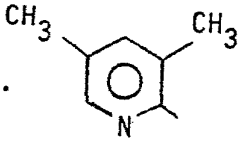
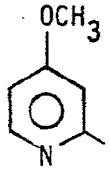
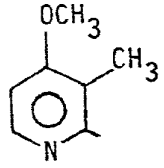
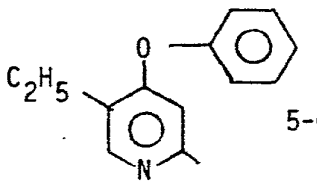
The compounds with the general formula I are virtually biologically inactive as such, but degrade/transform to active inhibitors of certain enzyme systems in acid media.

As examples of compounds with the mentioned properties the compounds described in the patents US-A-4045 563, EP-B1-0 005 129 and BE-898 880 and the patent applications EP-85850258,6, EP-A1-0 080 602, EP-0127 736, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-3415971 GB-2 082 580 and SE-A-8504048-3 may be mentioned. The last application describes 2- (2-disubstituted-aminobenzyl)sulfinyl benzimidazoles, e.g. 2- (2-di--methylaminobenzyl)sulfinyl benzimidazole, also called, NC-1300 and presented by Prof. S. Okabe at the Symposium on Drug Activity held on Oct 17th 1985 in Nagoya, Japan, and which interacts with the H^+K^+-ATPase after acid degradation within the parietal cells. (See for instance B. Wallmark, A. Brändström and H. Larsson "Evidence for acid-induced transformation of omeprazole into an active inhibitor of H^+K^+-ATPase within the parietal cell", Biochemica et Biophysica Acta 778, 549-558, 1984). Other compounds with similar properties are further mentioned in the patent US-4 182 766 and the patent applications GB-2 141 429, EP-0 146 370 and GB-2 082 580. A common feature of these compounds are that they are transformed into the biologically active compounds via rapid degradation/transformation in acid media.

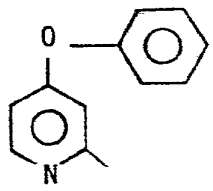
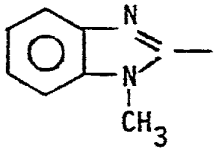
The stability profile of some compounds with the general formula I above is exemplified in the Table 1 below, where the half-life of the degradation/transformation reaction in solution at pH 2 and 7 are given.

Table 1. Rate of degradation/transformation of compounds with the general structure



Compound No	A	R^2 R^3	Half-life (minutes) for the transformation to the active moiety at pH = 2	at pH = 7
1.		5-$COOCH_3$;6-CH_3	11	150
2.		5-CH_3;H	5.4	1700
3.		5-CF_3;H	1.9	122
4.		5-CF_3;H	2.0	8.8
5.		5-OCH_3;H	3.7	1620

Cont.

Compound No	A	R^2 R^3	Half-life (minutes) for the transformation to the active moiety at pH = 2	at pH = 7
6.		5-OCH_3;H	4.0	3900
7.		5-C_2H_5;H	33	not determined

Substituted sulfoxides, such as for instance the substituted benzimidazoles described in EP-B1-0005129 are potent inhibitors of gastric acid secretion. The substituted benzimidazoles are susceptible to degradation/transformation in acid reacting and neutral media.

It is an inherent property of these compounds to be activated to the active moiety in the acid environment within the parietal cells. The activated compound interacts with the enzyme in the parietal cells, which mediates the production of hydrochloric acid in the gastric mucosa. All compounds of the class of substituted benzimidazoles, containing a sulfoxide grouping, which interferes with the H^+K^+--ATPase in the parietal cells hitherto known are all also degraded in acid media.

A pharmaceutical dosage form of acid labile substances, which prevents the substances from contact with acidic gastric juice, must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, the acid labile substance rapidily decomposes by direct or indirect contact with it, with the result that the preparations become badly discoloured and lose in content of the active compound with the passage of time.

In order to enhance the storage stability, the cores which contain the acid labile substance must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water or gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

In DE-A1-3 046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of the compounds with the general formula I above in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing a compound with the general formula I since direct contact between substances such as cellulose acetate phthalate (CAP) and a compound of formula I causes degradation and discolouration of the compounds of the formula I.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivatives. Such a membrane will not give a proper protection of the acid labile compounds of the formula I in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for the compounds of the formula I, where a rapid release of the drug in the small intestine is needed. DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention. GB-A-1 485 676 describes a way to obtain a preparation which effervesces in the small intestine. This is obtained by the enteric coating of a core containing the active drug and an effervescing system such as a

combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing a compound of formula I as the presence of an acid in contact with a compound of formula I in the cores would give as a result that the compound of formula I was degraded.

WO 85/03436 describes a pharmaceutical preparation, wherein cores containing active drugs mixed with for instance buffering components such as sodium dihydrogenphosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for acid labile compounds where a rapid release in the small intestive is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing acid labile compounds.

Outline of the invention

According to the present invention it has been found that the known acid labile compounds with the general formula I above in which R^1, R^2, R^3 and R^4 are the same or different and are

(a) hydrogen

(b) halogen, e.g. F, Cl, Br, I

(c) -CN

(d) -CHO

(e) $-CF_3$

(f) $-\overset{O}{\overset{\|}{C}}-R^{11}$

(g) $-O-\overset{O}{\overset{\|}{C}}-R^{12}$

(h) $-CH(OR^{13})_2$

(i) $-(Z)_n-B-D$

(j) aryl containing up to 10 carbon atoms

(k) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms

(l) -alkylthio containing 1-6 carbon atoms

(m) $-NO_2$

(n) -alkylsulfinyl containing 1-6 carbon atoms

(o) or wherein adjacent groups R^1, R^2, R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring, which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected from -N- and -O-, and which rings may be optionally substituted with 1-4 substituents selected from alkyl groups with 1-3 carbon atoms, alkylene radicals containing 4-5 carbon atoms giving spiro compounds, or two or four of these substituents together form one or two oxo groups $(-\overset{O}{\overset{\|}{C}}-)$, whereby if R^1 and R^2, R^2 and R^3 or R^3 and

R^4 together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R^{11} and R^{12}, which are the same or different, are

(a) aryl containing up to 10 carbon atoms
(b) alkoxy containing 1-4 carbon atoms
(c) alkoxyalkoxy containing 1-3 carbon atoms in each alkoxy part
(d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(e) aryloxy containing up to 10 carbon atoms
(f) dialkylamino containing 1-3 carbon atoms in the alkyl parts, or
(g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms;

R^{13} is (a) alkyl containing 1-4 carbon atoms, or
(b) alkylene containing 2-3 carbon atoms;

Z is -O- or $-\overset{O}{\overset{\|}{C}}-$;

n is 0 or 1;

B is (a) alkylene containing 1-6 carbon atoms
(b) cycloalkylene containing 3-6 carbon atoms

(c) alkenylene containing 2-6 carbon atoms
(d) cycloalkylene containing 3-6 carbon atoms, or
(e) alkynylene containing 2-6 carbon atoms;

D is
(a) H
(b) -CN
(c) $-\overset{O}{\overset{\|}{C}}-R^9$
(d) $-(Y)_m-(\overset{O}{\overset{\|}{C}})_r-R^{10}$

wherein

R^9 is
(a) alkoxy containing 1-5 carbon atoms, or
(b) dialkylamino containing 1-3 carbon atoms in the alkyl parts;

m is 0 or 1;

r is 0 or 1;

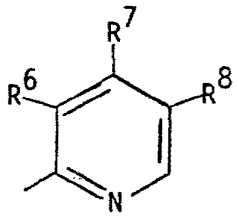
Y is
(a) -O-
(b) -NH-
(c) $-NR^{10}-$;

R^{10} is
(a) H
(b) alkyl containing 1-3 carbon atoms
(c) arylalkyl containing 1-2 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part

(d) aryl containing up to 10 carbon atoms;

R^5 is H, CH_3 or C_2H_5;

A is especially a pyridyl group in which R^6 and R^8 are the same or different, are



(a) H or
(b) alkyl containing 1-6 carbon atoms;

R^7 is
(a) H
(b) alkyl containing 1-8 carbon atoms
(c) alkoxy containing 1-8 carbon atoms
(d) alkenyloxy containing 2-5 carbon atoms
(e) alkynyloxy containing 2-5 carbon atoms
(f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group
(g) aryl containing up to 10 carbon atoms
(h) arylalkyl containing 1-6 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part
(i) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
(j) arylalkoxy containing 1-6 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(k) dialkylaminoalkoxy containing 1-2 carbon atoms in the alkyl substituents on the amino nitrogen and 1-4 carbon atoms in the alkoxy group
(l) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms
(m) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms
(n) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms

(o) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or

(p) R^6 and R^7, or R^7 and R^8 together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R^6 and R^7, or R^7 and R^8, is

$-CH=CH-CH=CH-$

$-O-(CH_2)_p-$

$-S-(CH_2)_v-$

$-CH_2(CH_2)_p-$

$-O-CH=CH-$

$-NH-CH=CH-$

$-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{N}}-CH=CH-$

wherein p is 2, 3 or 4, v is 2 or 3 and the O and N atoms always are attached to position 4 in the pyridine ring; provided that not more than one of R^6, R^7 and R^8 is hydrogen can be formulated into an enteric coated dosage form.

The object of the present invention is thus an enteric coated dosage form of acid labile compounds with the general formula I defined above except the compound omeprazole, 5-methoxy-2- (4-methoxy-3,5 dimethyl--2-pyridinyl methyl sulfinyl -1H-benzimidazole. Another compound, which may be enteric coated according to the invention is 2- (2-dimethyl-aminobenzyl)sulfinyl -benzimidazole. The new preparations are resistant to dissolution in acid media, dissolve rapidly in neutral to alkaline media and have a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing the acid labile compound mixed with alkaline compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline compound are coated with two or more layers, whereby the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good

stability of the dosage form during long-term storage.

As examples of compounds especially suitable for the pharmaceutical dosage form according to the invention the compounds listed in Table 1 can be mentioned.

The half-life of degradation of the compounds 1-6 in Table 1 in water solution at pH-values less than four is in most cases shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH=7 the half-life of degradation is between 10 minutes and 65 hours while at higher pH-values the stability in solution for most compounds is much better. The stability profile is similar in solid phase. The degradation is catalyzed by acid reacting substances. The acid labile compounds are stabilized in mixtures with alkaline reacting substances.

From what is said about the stability properties of the acid labile compounds listed above it is obvious that an oral dosage form of the said compounds must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

Detailed description of the invention

Cores

The acid labile active compound is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of the active compound in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each particle of active compound of not less than pH=7, preferably not less than pH=8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among, but are not restricted to substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as

aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances such as $Al_2O_3.6MgO\ CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3\ 4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than 2 or similar compounds; organic pH-buffering substances such as trishydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting, salt of the active compound such as the sodium, potassium, magnesium, calcium etc. salts of acid labile compounds,either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets or tablets, by conventional pharmaceutical procedures. The pellets, tablets or gelatin capsules are used as cores for further processing.

Separating layer

The alkaline reacting cores containing an acid labile compound must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of the acid labile compound during the coating process or during storage. The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated articles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3.6MgO\ CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3,4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than 2 or similar compounds; or other pharmaceutically acceptable pH-buffering substances such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layers, optionally containing pH-buffering substances.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance sugar, polyethylene glycol, polyvinylpyrollidone, polyvinyl alcohol, hydroxypropyl cellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose or the like. The thickness of the separating layer is not less than 2 µm, for small spherical pellets preferably not less than 4 µm, for tablets preferably not less than 10 µm.

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing the acid labile compound is compressed as described above. Around this tablet another layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers, pigments, titanium dioxide talc and other additives may also be included into the separating layer.

In the case of gelatin capsules the gelatin capsule itself serves as separating layer.

Enteric coating layer

The enteric coating layer is applied on to the sub-coated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the

trade name Eudragit^{R} L 12,5 or Eudragit^{R} L 100,(Röhm Pharma) or similar compounds used to obtain enteric coatings.

The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric (FMC Corporation), Eudragit^{R} L 100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex^{R} (Pfizer) phthalic acid esters, dibutyl succinate or similar plasticizers.

The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20 % of the enteric coating polymer(s). Dispersants such as talc, colourants and pigments may also be included into the enteric coating layer.

Thus the special preparation according to the invention consists of cores containing the acid labile compound mixed with an alkaline reacting compound or cores containing an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin

capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing acid labile compound (enteric coated tablets, capsules or pellets) is kept low, preferably not exceeding 1.5 % by weight.

Process

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is usually administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as for example the individual requirement of the patients, the mode of administration and the disease. In general the dosage will be in the range of 1 to 400 mg per day of active substance. A method for the treatment of such conditions using the vovel oral dosage form represents a further aspect of the invention.

The invention is described in detail in the following examples:

EXAMPLES

Examples 1 - 3 exemplify the invention.

Example 1

Uncoated pellets

I	Lactose powder	253	g
	Lactose anhydrous	167	g
	Hydroxypropyl cellulose	25	g

II	Compound 1, Table I	50	g
	Sodium lauryl sulphate	5	g
	Disodium hydrogen phosphate	1.5	g
	Sodium dihydrogen phosphate	0.1	g
	Distilled water	125	g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing the suspended active compound was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methyl-cellulose	20	g
	Distilled water	400	g

The polymer solution (III) was sprayed onto the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric coated pellets

	Subcoated pellets	500	g
IV	Hydroxypropyl methylcellulose phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 284 mg, corresponding to 25 mg of active compound 1. 30 capsules were packed in tight containers together with a desiccant.

Example 2

Formulation with the sodium salt of compound 2 according to Table I.

Uncoated pellets

I		Compound 2, Table I sodium salt	339	g
		Mannitol powder	2 422	g
		Lactose anhydrous	120	g
		Hydroxypropyl cellulose	90	g
		Microcrystalline cellulose	60	g
II		Sodium lauryl sulphate	7	g
		Distilled water	650	g

The preparation was made as described in Example 1 with the exception that the sodium salt of compound 2 was added together with the other ingredients in mixture I.

Subcoated pellets

		Uncoated pellets	500	g
III		Hydroxypropyl methylcellulose	20	g
		Aluminium hydroxide/magnesium carbonate	4	g
		Distilled water	400	g
		Pellets subcoated with III	500	g
IV		Hydroxypropyl methylcellulose	20	g
		Distilled water	400	g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

Subcoated pellets	500	g
Hydroxypropyl methylcellulose phthalate	57	g
Cetyl alcohol	3	g
Acetone	540	g
Ethanol	231	g

The preparation of enteric coated pellets was performed as described in Example 1.

Example 3

Formulation with compound 6, according to Table 1. This example gives the composition of one unit dose according to the invention.

Tablet core

Compound 6, Table 1	15 mg
Lactose	119 mg
Hydroxypropyl cellulose (low substitution)	5 mg
Hydroxypropyl cellulose	1 mg
Talc	5 mg
$Mg(OH)_2$	15 mg
Total	160 mg

Tablet cores having the composition above and each weighing 160 mg were first made by known techniques.

Separating layer (inner)

Hydroxypropyl cellulose	2 mg
Synthetic hydrotalcite $[Al_2O_3.6MgO.CO_2.12H_2O]$	0.3 mg

Separating layer (outer)

Hydroxypropyl cellulose	2 mg

The two separating layers were applied to the cores by known coating techniques.

Enteric coating layer

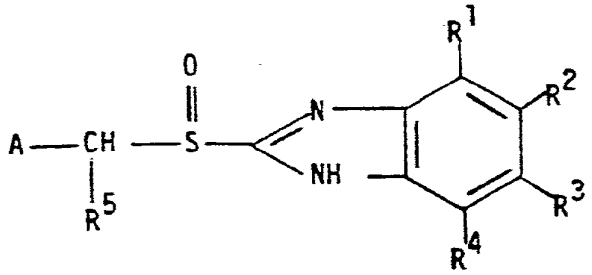
Hydroxypropyl methylcellulose phthalate	7 mg
Cetyl alcohol	0.5 mg

The enteric coating solution was sprayed on the cores coated by the two separating layers by known enteric coating techniques.

CLAIMS

1. An oral, pharmaceutical preparation containing an acid labile compound as the active ingredient characterized in that it is composed of core material containing the active ingredient together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

2. A preparation according to claim 1, wherein the acid labile compound has the general formula I.



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$, $-O-\overset{O}{\overset{\|}{C}}-$lower alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2[[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl] -1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

3. A preparation according to claim 1 wherein the subcoating layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance [$Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$], wherein n not is an integer and less than two.

4. A preparation according to claim 2 or 3 wherein the subcoating comprises two or more sub-layers.

5. A preparation according to claim 4 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinyl--pyrrolidone.

6. A preparation according to claim 1 wherein the alkaline core comprises the acid labile compound and pH-buffering alkaline compound rendering to the micro-environment of the acid labile compound a pH of 7-12.

7. A preparation according to claim 6 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than two.

8. A preparation according to claim 1 wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.

9. A preparation according to claim 7 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an inert, alkaline compound.

10. A preparation according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

11. A preparation according to claim 1 wherein the water content of the final dosage form containing the acid labile compound does not exceed 1.5 % by weight.

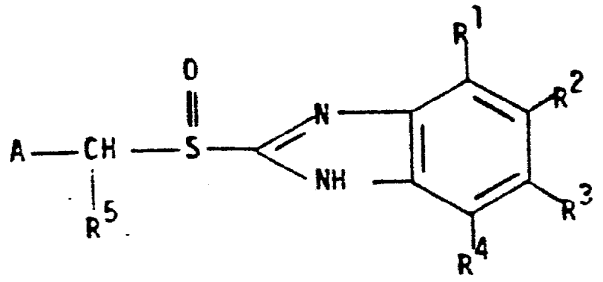
12. Process for the preparation of an oral pharmaceutical formulation containing an acid labile compound in which cores containing the acid labile compound mixed with an alkaline reacting compound or compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound or compounds are coated with one or more inert reacting subcoating layers whereafter the subcoated cores are further coated with an enteric coating layer.

13. Use of the preparation according to claim 1 for the manufacture of a medicament for treatment of gastrointestinal diseases.

CLAIMS FOR THE CONTRACTING STATES AT, ES, GR.

1. A process for the preparation of an oral, pharmaceutical formulation containing an acid labile compound as the active ingredient characterized in that the cores containing the acid labile compound mixed with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, are coated with one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating layer, whereafter the subcoated cores are further coated with said outer enteric coating layer.

2. A process according to claim 1, wherein the acid labile compound has the general formula I.



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$, $-O-\overset{O}{\overset{\|}{C}}$-lower alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2 [[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl] -1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl] -benzimidazole.

3. A process according to claim 1 wherein the subcoating layer comprises one or more of magnesium oxide, magnesium hydroxide or composite

substance [$Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$], wherein n not is an integer and less than two.

4. A process according to claim 2 or 3 wherein the subcoating comprises two or more sub-layers.

5. A process according to claim 4 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinyl--pyrrolidone.

6. A process according to claim 1 wherein the alkaline core comprises the acid labile compound and pH-buffering alkaline compound rendering to the micro-environment of the acid labile compound a pH of 7-12.

7. A process according to claim 6 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than two.

8. A process according to claim 1 wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.

9. A process according to claim 7 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an inert, alkaline compound.

10. A process according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

11. A process according to claim 1 wherein the water content of the final dosage form containing the acid labile compound does not exceed 1.5 % by weight.

12. Use of the formulation prepared according to claim 1 for the manufacture of a medicament for treatment of gastrointestinal diseases.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 244 380 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **07.01.93**

(51) Int. Cl.5: **A61K 9/32**, A61K 9/52, A61K 9/54

(21) Application number: **87850126.1**

(22) Date of filing: **16.04.87**

Divisional application 92107178.3 filed on 16/04/87.

(54) **Pharmaceutical formulations of acid labile substances for oral use.**

(30) Priority: **30.04.86 GB 8610573**

(43) Date of publication of application:
04.11.87 Bulletin 87/45

(45) Publication of the grant of the patent:
07.01.93 Bulletin 93/01

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
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EP-A- 0 080 602
EP-A- 0 124 495
EP-A- 0 173 664
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GB-A- 1 190 387

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BROCHURE ON HPCM TC-5, Shinetsa Chemical Japan, 1975.

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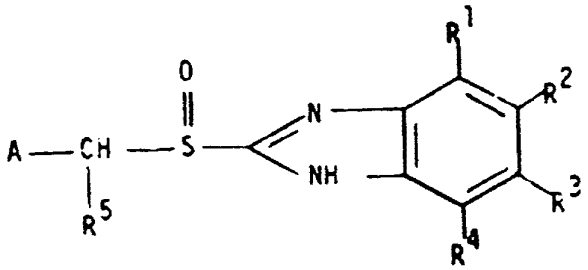
Description

The present invention is related to new pharmaceutical preparations containing acid labile substances for oral use and, to a method for the manufacture of such preparations.

Acid labile substances present a problem to the formulator when formulating a pharmaceutical dosage form for oral use. In order to prevent the substances from contact with the acid reacting gastric juice after oral intake, the conventional way to solve this problem is to coat the dosage form with an enteric coating. The coating is a group of substances/polymers with the common feature of being practically insoluble in acid media, while they are soluble in neutral to alkaline media. For substances that are labile in acid media, but have better stability in neutral to alkaline media, it is often advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and storage.

A group of compounds exerting these stability properties are substituted benzimidazoles with the general formula I



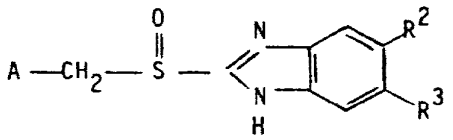
wherein A is an optionally substituted heterocyclic group and R^1, R^2, R^3, and R^4, are the same or different as defined below and R^5 is H or a lower alkyl, or the compound 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole.

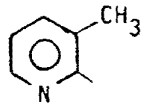
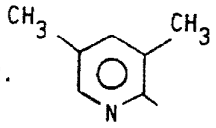
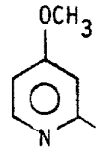
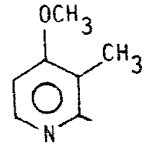
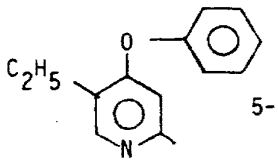
The compounds with the general formula I are virtually biologically inactive as such, but degrade/transform to active inhibitors of certain enzyme systems in acid media.

As examples of compounds with the mentioned properties the compounds described in the patents US-A-4045 563, EP-B1-0 005 129 and BE-898 880 and the patent applications, EP-A-173664, EP-A1-0 080 602, EP-0127 763, EP-0 134 400, EP-0 130 729, EP-0 150 586, DE-3415971 GB-2 082 580 and SE-A-8504048-3 may be mentioned. The last application describes 2- (2-disubstituted-aminobenzyl)sulfinyl benzimidazoles, e.g. 2- (2-di-methylaminobenzyl)sulfinyl benzimidazole, also called, NC-1300 and presented by Prof. S. Okabe at the Symposium on Drug Activity held on Oct 17th 1985 in Nagoya, Japan, and which interacts with the H^+K^+-ATPase after acid degradation within the parietal cells. (See for instance B. Wallmark, A. Brändström and H. Larsson "Evidence for acid-induced transformation of omeprazole into an active inhibitor of H^+K^+-ATPase within the parietal cell", Biochemica et Biophysica Acta 778, 549-558, 1984). Other compounds with similar properties are further mentioned in the patent US-4 182 766 and the patent applications GB-2 141 429, EP-0 146 370 and GB-2 082 580. A common feature of these compounds is that they are transformed into the biologically active compounds via rapid degradation/transformation in acid media.

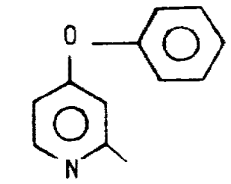
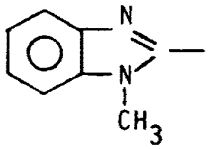
The stability profile of some compounds with the general formula I above is exemplified in the Table 1 below, where the half-life of the degradation/transformation reaction in solution at pH 2 and 7 are given.

Table 1. Rate of degradation/transformation of compounds with the general structure



Compound No	A	R^2 R^3	Half-life (minutes) for the transformation to the active moiety at pH = 2	at pH = 7
1.		5-$COOCH_3$;6-CH_3	11	150
2.		5-CH_3;H	5.4	1700
3.		5-CF_3;H	1.9	122
4.		5-CF_3;H	2.0	8.8
5.		5-OCH_3;H	3.7	1620

Cont.

Compound No	A	R^2 R^3	Half-life (minutes) for the transformation to the active moiety at pH = 2	at pH = 7
6.		5-OCH_3;H	4.0	3900
7.		5-C_2H_5;H	33	not determined

Substituted sulfoxides, such as for instance the substituted benzimidazoles described in EP-B1-0005129 are potent inhibitors of gastric acid secretion. The substituted benzimidazoles are susceptible to degradation/transformation in acid reacting and neutral media.

It is an inherent property of these compounds to be activated to the active moiety in the acid environment within the parietal cells. The activated compound interacts with the enzyme in the parietal cells, which mediates the production of hydrochloric acid in the gastric mucosa. All compounds of the class of substituted benzimidazoles, containing a sulfoxide grouping, which interferes with the H^+K^+-ATPase in the parietal cells hitherto known are all also degraded in acid media.

A pharmaceutical dosage form of acid labile substances, which prevents the substances from contact with acidic gastric juice, must be enteric coated. Ordinary enteric coatings, however, are made of acidic compounds. If covered with such a conventional enteric coating, the acid labile substance rapidily decomposes by direct or indirect contact with it, with the result that the preparations become badly discoloured and lose in content of the active compound with the passage of time.

In order to enhance the storage stability, the cores which contain the acid labile substance must also contain alkaline reacting constituents. When such an alkaline core is enteric coated with an amount of a conventional enteric coating polymer such as, for example, cellulose acetate phthalate, that permits the dissolution of the coating and the active drug contained in the cores in the proximal part of the small intestine, it also will allow some diffusion of water or gastric juice through the enteric coating into the cores, during the time the dosage form resides in the stomach before it is emptied into the small intestine. The diffused water or gastric juice will dissolve parts of the core in the close proximity of the enteric coating layer and there form an alkaline solution inside the coated dosage form. The alkaline solution will interfere with the enteric coating and eventually dissolve it.

In DE-A1-3 046 559 a way to coat a dosage form is described. First the dosage form is coated with a water insoluble layer containing microcrystalline cellulose and then with a second enteric coating with the aim to achieve a dosage form which releases the active drug in the colon. This method of preparation will not give the desired release of the compounds with the general formula I above in the small intestine.

US-A-2 540 979 describes an enteric coated oral dosage form, where the enteric coating is combined with a second and/or first coating of a water insoluble "wax" layer. This method of preparation is not applicable on cores containing a compound with the general formula I since direct contact between substances such as cellulose acetate phthalate (CAP) and a compound of formula I causes degradation and discolouration of the compounds of the formula I.

DE-B2-23 36 218 describes a method to produce a dialysis membrane consisting of a mixture of one or more conventional enteric coating polymers and one or more insoluble cellulose derivatives. Such a

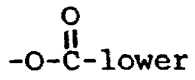
membrane will not give a proper protection of the acid labile compounds of the formula I in gastric juice.

DE-A1-1 204 363 describes a three-layer coating procedure. The first layer is soluble in gastric but is insoluble in intestinal juice. The second is water soluble regardless of pH and the third layer is an enteric coating. This preparation as well as the preparation described in DE-A1-1 617 615 result in a dosage form which is not dissolved in gastric juice and which only dissolves slowly in intestinal juice. Such preparations cannot be used for the compounds of the formula I, where a rapid release of the drug in the small intestine is needed. DE-A1 12 04 363 describes coating with three layers to achieve release of a drug in the ileum, an aim which is outside the scope of the present invention. GB-A-1 485 676 describes a way to obtain a preparation which effervesces in the small intestine. This is obtained by the enteric coating of a core containing the active drug and an effervescing system such as a combination of carbonate and/or bicarbonate salt and a pharmaceutically acceptable acid. This formulation cannot be adopted for a pharmaceutical dosage form containing a compound of formula I as the presence of an acid in contact with a compound of formula I in the cores would give as a result that the compound of formula I was degraded.

WO 85/03436 describes a pharmaceutical preparation, wherein cores containing active drugs mixed with for instance buffering components such as sodium dihydrogen-phosphate with the aim of maintaining a constant pH and a constant rate of diffusion, are coated with a first coating which controls the diffusion. This formulation cannot be adopted for acid labile compounds where a rapid release in the small intestive is wanted. Direct application of an enteric coating onto the cores would also adversely influence the storage stability of such dosage forms containing acid labile compounds.

EP-A-124 495 and EP-A-173 664 describe enteric coated granules without subcoating or a powder that are filled into hard gelatine capsules or a solution that is filled into a soft capsule.

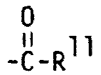
The object of the present invention is to provide an oral, pharmaceutical preparation stable to discolouration containing an acid labile compound of the general formula I above wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4, are the same or different and preferably hydrogen, lower alkyl, lower alkoxy, $-CF_3$,



alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, methoxy-2[[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-bensimidazole as the active ingredient. The core material is in the form of small beads or tablets containing the active ingredient together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

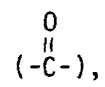
R^1, R^2, R^3 and R^4, which are the same or different and especially

(a) hydrogen
(b) halogen, e.g. F, Cl, Br, I
(c) -CN
(d) -CHO
(e) $-CF_3$
(f)



(g) $-O-C-R^{12}$
(h) $-CH(OR^{13})_2$
(i) $-(Z)_n-B-D$
(j) aryl containing up to 10 carbon atoms
(k) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms
(l) -alkylthio containing 1-6 carbon atoms

(m) $-NO_2$
(n) -alkylsulfinyl containing 1-6 carbon atoms
(o) or wherein adjacent groups R^1 R^2 R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form a 5-, 6- or 7-membered monocyclic ring or a 9-, 10- or 11-membered bicyclic ring, which rings may be saturated or unsaturated and may contain 0-3 hetero atoms selected from -N- and -O-, and which rings may be optionally substituted with 1-4 substituents selected from alkyl groups with 1-3 carbon atoms, alkylene radicals containing 4-5 carbon atoms giving spiro compounds, or two or four of these substituents together form one or two oxo groups



whereby if R^1 and R^2, R^2 and R^3 or R^3 and R^4 together with the adjacent carbon atoms in the benzimidazole ring form two rings they may be condensed with each other, in which formulas R^{11} and R^{12}, which are the same or different, are
(a) aryl containing up to 10 carbon atoms
(b) alkoxy containing 1-4 carbon atoms
(c) alkoxyalkoxy containing 1-3 carbon atoms in each alkoxy part
(d) arylalkoxy containing 1-2 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part
(e) aryloxy containing up to 10 carbon atoms
(f) dialkylamino containing 1-3 carbon atoms in the alkyl parts, or
(g) pyrrolidino or piperidino, optionally substituted with alkyl containing 1-3 carbon atoms;
R^{13} is
(a) alkyl containing 1-4 carbon atoms, or
(b) alkylene containing 2-3 carbon atoms;
Z is -0- or

n is 0 or 1;
B is
(a) alkylene containing 1-6 carbon atoms
(b) cycloalkylene containing 3-6 carbon atoms
(c) alkenylene containing 2-6 carbon atoms
(d) cycloalkylene containing 3-6 carbon atoms, or
(e) alkynylene containing 2-6 carbon atoms;
D is
(a) H
(b) -CN
(c)

(d) $-(Y)_m$

$-R^{10}$

wherein

R^9 is

(a) alkoxy containing 1-5 carbon atoms, or

(b) dialkylamino containing 1-3 carbon atoms in the alkyl parts;

m is 0 or 1;

r is 0 or 1;

Y is

(a) -O-

(b) -NH-

(c) $-NR^{10}-$;

R^{10} is

(a) H

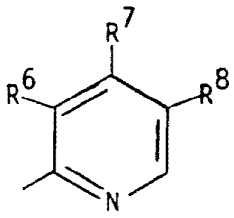
(b) alkyl containing 1-3 carbon atoms

(c) arylalkyl containing 1-2 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part

(d) aryl containing up to 10 carbon atoms;

R^5 is H, CH_3 or C_2H_5;

A is especially a pyridyl group in which R^6 and R^8 are the same or different, are



(a) H or

(b) alkyl containing 1-6 carbon atoms;

R^7 is

(a) H

(b) alkyl containing 1-8 carbon atoms

(c) alkoxy containing 1-8 carbon atoms

(d) alkenyloxy containing 2-5 carbon atoms

(e) alkynyloxy containing 2-5 carbon atoms

(f) alkoxyalkoxy containing 1-2 carbon atoms in each alkoxy group

(g) aryl containing up to 10 carbon atoms

(h) arylalkyl containing 1-6 carbon atoms in the alkyl part and up to 10 carbon atoms in the aryl part

(i) aryloxy containing up to 10 carbon atoms, optionally substituted by alkyl containing 1-6 carbon atoms

(j) arylalkoxy containing 1-6 carbon atoms in the alkoxy part and up to 10 carbon atoms in the aryl part

(k) dialkylaminoalkoxy containing 1-2 carbon atoms in the alkyl substituents on the amino nitrogen and 1-4 carbon atoms in the alkoxy group

(l) oxacycloalkyl containing one oxygen atom and 3-7 carbon atoms

(m) oxacycloalkoxy containing two oxygen atoms and 4-7 carbon atoms

(n) oxacycloalkylalkyl containing one oxygen atom and 4-7 carbon atoms

(o) oxacycloalkylalkoxy containing two oxygen atoms and 4-6 carbon atoms, or

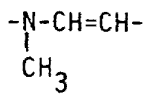
(p) R^6 and R^7, or R^7 and R^8 together with the adjacent carbon atoms in the pyridine ring form a ring wherein the part constituted by R^6 and R^7, or R^7 and R^8, is

$-CH=CH-CH=CH-$

$-O-(CH_2)_p-$

$-S-(CH_2)_v-$

$-CH_2(CH_2)_p-$
-O-CH = CH-
-NH-CH = CH-



wherein p is 2, 3 or 4, v is 2 or 3 and the 0 and N atoms always are attached to position 4 in the pyridine ring; provided that not more than one of R^6, R^7 and R^8 is hydrogen can be formulated into an enteric coated dosage form.

The object of the present invention is thus an enteric coated dosage form of acid labile compounds with the general formula I defined above except the compound omeprazole, 5-methoxy-2-[[(4-methoxy-3,5 dimethyl-2-pyridinyl)methyl]sulfinyl] -1H-benzimidazole. Another compound, which may be enteric coated according to the invention is 2- (2-dimethylaminobenzyl)sulfinyl -benzimidazole. The new preparations are resistant to dissolution in acid media, dissolve rapidly in neutral to alkaline media and have a good stability during long-term storage. The new dosage form is characterized in the following way. Cores containing the acid labile compound mixed with alkaline compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline compound are coated with two or more layers, in which the first layer/layers is/are soluble in water or rapidly disintegrating in water and consist(s) of non-acidic, otherwise inert pharmaceutically acceptable substances. This/these first layer/layers separates/separate the alkaline core material from the outer layer, which is an enteric coating. The final, enteric coated dosage form is treated in a suitable way to reduce the water content to a very low level in order to obtain a good stability with virtually no discolouration of the dosage form during long-term storage.

As examples of compounds especially suitable for the pharmaceutical dosage form according to the invention the compounds listed in Table 1 can be mentioned.

The half-life of degradation of the compounds 1-6 in Table 1 in water solution at pH-values less than four is in most cases shorter than ten minutes. Also at neutral pH-values the degradation reaction proceeds rapidly, e.g. at pH = 7 the half-life of degradation is between 10 minutes and 65 hours while at higher pH-values the stability in solution for most compounds is much better. The stability profile is similar in solid phase. The degradation is catalyzed by acid reacting substances. The acid labile compounds are stabilized in mixtures with alkaline reacting substances.

From what is said about the stability properties of the acid labile compounds listed above it is obvious that an oral dosage form of the said compounds must be protected from contact with the acid reacting gastric juice in order to reach the small intestine without degradation.

Cores

The acid labile active compound is mixed with inert, preferably water soluble, conventional pharmaceutical constituents to obtain the preferred concentration of the active compound in the final mixture and with an alkaline reacting, otherwise inert, pharmaceutically acceptable substance (or substances), which creates a "micro-pH" around each particle of active compound of not less than pH = 7, preferably not less than pH = 8, when water is adsorbed to the particles of the mixture or when water is added in small amounts to the mixture. Such substances can be chosen among substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances such as $Al_2O_3.6MgO\ CO_2.12H_2O$, $(Mg_6Al_2(OH)_{16}CO_3\ 4H_2O)$, $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than 2 or similar compounds; organic pH-buffering substances such as trishydroxymethylaminomethane or other similar, pharmaceutically acceptable pH-buffering substances. The stabilizing, high pH-value in the powder mixture can also be achieved by using an alkaline reacting, salt of the active compound such as the sodium, potassium, magnesium, calcium salts of acid labile compounds, either alone or in combination with a conventional buffering substance as previously described.

The powder mixture is then formulated into small beads i.e. pellets or tablets, by conventional pharmaceutical procedures. The pellets or tablets are used as cores for further processing.

Separating layer

The alkaline reacting cores containing an acid labile compound must be separated from the enteric coating polymer(s) containing free carboxyl groups, which otherwise causes degradation/discolouration of the acid labile compound during the coating process or during storage. The subcoating layer, (the separating layer), also serves as a pH-buffering zone in which hydrogen ions diffusing from the outside in towards the alkaline core can react with hydroxyl ions diffusing from the alkaline core towards the surface of the coated particles. The pH-buffering properties of the separating layer can be further strengthened by introducing in the layer substances chosen from a group of compounds usually used in antacid formulations such as, for instance, magnesium oxide, hydroxide or carbonate, aluminium or calcium hydroxide, carbonate or silicate; composite aluminium/magnesium compounds such as, for instance $Al_2O_3.6MgO\ CO_2.12H_2O$, ($Mg_6Al_2(OH)_{16}CO_3,4H_2O$), $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than 2 or similar compounds; or other pharmaceutically acceptable pH-buffering substances such as, for instance the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric, citric or other suitable, weak, inorganic or organic acids.

The separating layer consists of one or more water soluble inert layers, optionally containing pH-buffering substances.

The separating layer(s) can be applied to the cores - pellets or tablets - by conventional coating procedures in a suitable coating pan or in a fluidized bed apparatus using water and/or conventional organic solvents for the coating solution. The material for the separating layer is chosen among the pharmaceutically acceptable, water soluble, inert compounds or polymers used for film-coating applications such as, for instance sugar, polyethylene glycol, polyvinylpyrollidone, polyvinyl alcohol, hydroxypropyl cellulose, hydroxymethyl cellulose or hydroxypropyl methylcellulose. The thickness of the separating layer is not less than 2 μm, for small spherical pellets preferably not less than 4 μm, for tablets preferably not less than 10 μm.

In the case of tablets another method to apply the coating can be performed by the drycoating technique. First a tablet containing the acid labile compound is compressed as described above. Around this tablet another layer is compressed using a suitable tableting machine. The outer, separating layer, consists of pharmaceutically acceptable, in water soluble or in water rapidly disintegrating tablet excipients. The separating layer has a thickness of not less than 1 mm. Ordinary plasticizers, pigments, titanium dioxide talc and other additives may also be included into the separating layer.

The enteric coating layer is applied on to the sub-coated cores by conventional coating techniques such as, for instance, pan coating or fluidized bed coating using solutions of polymers in water and/or suitable organic solvents or by using latex suspensions of said polymers. As enteric coating polymers can be used, for example, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl esters such as, for instance, compounds known under the trade name Eudragit^R L 12,5 or Eudragit^R L 100, (Röhm Pharma) or similar compounds used to obtain enteric coatings.

The enteric coating can also be applied using water-based polymer dispersions, e.g. Aquateric (FMC Corporation), Eudragit^R L 100-55 (Röhm Pharma), Coating CE 5142 (BASF). The enteric coating layer can optionally contain a pharmaceutically acceptable plasticizer such as, for instance, cetanol, triacetin, citric acid esters such as, for instance, those known under the trade name Citroflex^R (Pfizer) phthalic acid esters, dibutyl succinate or similar plasticizers.

The amount of plasticizer is usually optimized for each enteric coating polymer(s) and is usually in the range of 1-20 % of the enteric coating polymer(s). Dispersants such as talc, colourants and pigments may also be included into the enteric coating layer.

Thus the special preparation according to the invention consists of cores containing the acid labile compound mixed with an alkaline reacting compound or cores containing an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound. The cores suspended in water forms a solution or a suspension which has a pH, which is higher than that of a solution in which the polymer used for enteric coating is just soluble. The cores are coated with a water soluble or in water rapidly disintegrating coating, optionally containing a pH-buffering substance, which separates the alkaline cores from the enteric coating. Without this separating layer the resistance towards gastric juice would be too short and the storage stability of the dosage form would be unacceptably short. The sub-coated dosage form is finally coated with an enteric coating rendering the dosage form insoluble in acid media, but rapidly disintegrating/dissolving in neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, the site where dissolution is wanted.

Final dosage form

The final dosage form is either an enteric coated tablet or in the case of enteric coated pellets, pellets

dispensed in hard gelatin capsules or sachets or pellets formulated into tablets. It is essential for the long term stability during storage that the water content of the final dosage form containing acid labile compound (enteric coated tablets, capsules or pellets) is kept low, preferably not exceeding 1.5 % by weight.

A process for the manufacture of the oral dosage form represents a further aspect of the invention. After the forming of the cores the cores are first coated with the separating layer and then with the enteric coating layer. The coating is carried out as described above.

The preparation according to the invention is especially advantageous in reducing gastric acid secretion and/or providing a gastrointestinal cytoprotective effect. It is usually administered one to several times a day. The typical daily dose of the active substance varies and will depend on various factors such as for example the individual requirement of the patients, the mode of administration and the disease. In general the dosage will be in the range of 1 to 400 mg per day of active substance.

The invention is described in detail in the following examples:

EXAMPLES

Examples 1 - 3 exemplify the invention.

Example 1

Uncoated pellets

I	Lactose powder	253	g
	Lactose anhydrous	167	g
	Hydroxypropyl cellulose	25	g
II	Compound 1, Table I	50	g
	Sodium lauryl sulphate	5	g
	Disodium hydrogen phosphate	1.5	g
	Sodium dihydrogen phosphate	0.1	g
	Distilled water	125	g

The dry ingredients (I) were premixed in a mixer. Addition of a granulation liquid (II) containing the suspended active compound was made and the mass was wet-mixed to a proper consistency. The wet mass was pressed through an extruder and spheronized to pellets. The pellets were dried and classified into suitable particle size ranges.

Subcoated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methyl-cellulose	20	g
	Distilled water	400	g

The polymer solution (III) was sprayed onto the uncoated pellets in a fluidized bed apparatus. The spray guns were placed above the fluidized bed.

Enteric coated pellets

	Subcoated pellets	500	g
IV	Hydroxypropyl methylcellulose phthalate	57	g
	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The polymer solution (IV) was sprayed on the subcoated pellets in a fluidized bed apparatus with spray guns placed above the bed. After drying to a water content of 0.5 % the enteric coated pellets were classified and filled into hard gelatin capsules in an amount of 284 mg, corresponding to 25 mg of active compound 1. 30 capsules were packed in tight containers together with a desiccant.

Example 2

Formulation with the sodium salt of compound 2 according to Table I.

Uncoated pellets

I	Compound 2, Table I sodium salt	339	g
	Mannitol powder	2 422	g
	Lactose anhydrous	120	g
	Hydroxypropyl cellulose	90	g
	Microcrystalline cellulose	60	g
II	Sodium lauryl sulphate	7	g
	Distilled water	650	g

The preparation was made as described in Example 1 with the exception that the sodium salt of compound 2 was added together with the other ingredients in mixture I.

Subcoated pellets

	Uncoated pellets	500	g
III	Hydroxypropyl methylcellulose	20	g
	Aluminium hydroxide/magnesium carbonate	4	g
	Distilled water	400	g
	Pellets subcoated with III	500	g
IV	Hydroxypropyl methylcellulose	20	g
	Distilled water	400	g

The two subcoat layers, III and IV, were applied to the uncoated pellets in a fluidized bed apparatus in consecutive order as previously described.

Enteric coated pellets

	Subcoated pellets	500	g
	Hydroxypropyl methylcellulose phthalate	57	g
V	Cetyl alcohol	3	g
	Acetone	540	g
	Ethanol	231	g

The preparation of enteric coated pellets was performed as described in Example 1.

Example 3

Formulation with compound 6, according to Table 1. This example gives the composition of one unit dose according to the invention.

Tablet core

Compound 6, Table 1	15 mg
Lactose	119 mg
Hydroxypropyl cellulose (low substitution)	5 mg
Hydroxypropyl cellulose	1 mg
Talc	5 mg
$Mg(OH)_2$	15 mg
Total	160 mg

Tablet cores having the composition above and each weighing 160 mg were first made by known techniques.

Separating layer (inner)

Hydroxypropyl cellulose	2 mg
Synthetic hydrotalcite [$Al_2O_3.6MgO.CO_2.12H_2O$]	0.3 mg

Separating layer (outer)

Hydroxypropyl cellulose	2 mg

The two separating layers were applied to the cores by known coating techniques.

Enteric coating layer

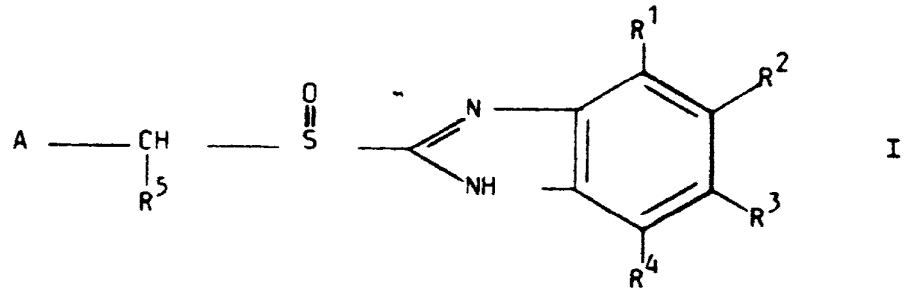
Hydroxypropyl methylcellulose phthalate	7 mg
Cetyl alcohol	0.5 mg

The enteric coating solution was sprayed on the cores coated by the two separating layers by known enteric coating techniques.

Claims

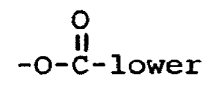
Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. An oral, pharmaceutical preparation stable to discolouration containing an acid labile compound of the general formula I



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen,
lower alkyl, lower alkoxy, $-CF_3$,



alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2[[(4-methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminobenzyl)sulfinyl]-benzimidazole as the active ingredient characterized in that it is composed of core material in the form of small beads or tablets containing the active ingredient together with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally together with an alkaline reacting compound, and on said core material one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally contain-

ing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating.

2. A preparation according to claim 1 wherein the subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinylpyrrolidone.

3. A preparation according to claim 1 wherein the subcoating comprises two or more sub-layers and where the inner layer comprises one or more of magnesium oxide, magnesium hydroxide or composite substance $Al_2O_3.6MgO_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n is not an integer and less than two.

4. A preparation according to claim 1 wherein the alkaline core comprises the acid labile compound and a pH-buffering alkaline compound rendering to the microenvironment of the acid labile compound a pH of 7-12.

5. A preparation according to claim 4 wherein the alkaline compound comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than two.

6. A preparation according to claim 1 wherein the alkaline core comprises an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt.

7. A preparation according to claim 5 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an alkaline otherwise inert compound.

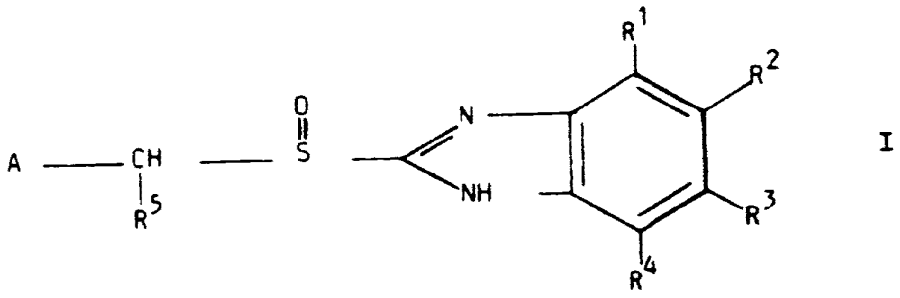
8. A preparation according to claim 1 wherein the enteric coating comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer.

9. A preparation according to claim 1 wherein the water content of the final dosage form containing the acid labile compound does not exceed 1.5 % by weight.

10. Process for the preparation of an oral pharmaceutical formulation stable to discolouration containing an acid labile compound according to claim 1 in which cores containing the acid labile compound mixed with an alkaline reacting compound or compounds or an alkaline salt of the acid labile compound optionally mixed with an alkaline reacting compound or compounds are coated with one or more inert reacting subcoating layers whereafter the subcoated cores are further coated with an enteric coating layer.

Claims for the following Contracting States : AT, ES, GR

1. A process for the preparation of an oral, pharmaceutical formulation stable to discolouration containing an acid labile compound of the general formula I



I

wherein A is an optionally substituted heterocyclic group, R^1, R^2, R^3 and R^4 are the same or different and preferably hydrogen,

lower alkyl, lower alkoxy, $-CF_3$,

alkyl or halogen and R^5 is H or a lower alkyl group wherein "lower" denotes 1-6 carbon atoms except the compound omeprazole, 5-methoxy-2[[(methoxy-3,5 dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole; or the acid labile compound is 2-[(2-dimethylaminozyl)sulfinyl]-benzimidazole as the active ingredient characterized in that the acid labile compound mixed with an alkaline reacting compound, or an alkaline salt of the active ingredient optionally mixed with alkaline reacting compound, are formed to cores and said cores, which are in the form of small beads or tablets, are coated with one or more inert reacting subcoating layers comprising tablet excipients which are soluble or rapidly disintegrating in water, or polymeric, water soluble, filmforming compounds, optionally containing pH-buffering, alkaline compounds between the alkaline reacting core and an outer layer, which is an enteric coating layer, whereafter the subcoated cores are further coated with said outer enteric coating layer.

2. A process according to claim 1, wherein the applied subcoating comprises hydroxypropyl methylcellulose, hydroxypropyl cellulose or polyvinyl-pyrrolidone.

3. A process according to claim 1 wherein the applied subcoating comprises two or more sub-layers and where the inner sub-layer contains one or more of magnesium oxide, magnesium hydroxide or composite substance $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$, wherein n not is an integer and less than two.

4. A process according to claim 1 wherein the acid labile compound is mixed with a pH-buffering alkaline compound rendering to the micro-environment of the acid labile compound a pH of 7-12, to form an alkaline core.

5. A process according to claim 4 wherein the alkaline compound which the acid labile compound is mixed with comprises one or more of magnesium oxide, hydroxide or carbonate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, the composite aluminium/magnesium compounds $Al_2O_3.6MgO.CO_2.12H_2O$ or $MgO.Al_2O_3.2SiO_2.nH_2O$ wherein n not is an integer and less than two.

6. A process according to claim 1 wherein an alkaline salt of the acid labile compound such as the sodium, potassium, magnesium, calcium or ammonium salt is formed and incorporated into the alkaline core.

7. A process according to claim 6 wherein the alkaline core comprises an alkaline salt of the acid labile compound mixed with an alkaline otherwise inert compound.

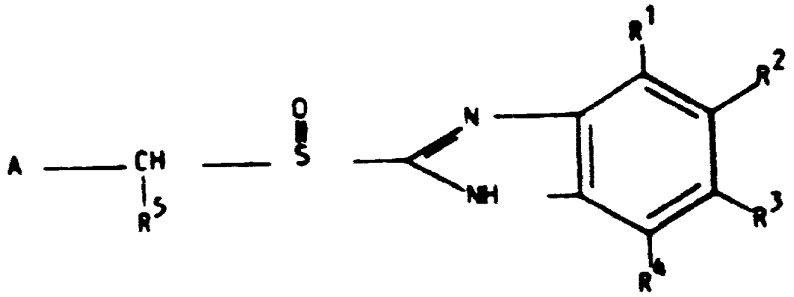
8. A process according to claim 1 wherein the enteric coating which comprises hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, co-polymerized methacrylic acid/methacrylic acid methyl ester or polyvinyl acetate phthalate, optionally containing a plasticizer is applied.

9. A process according to claim 1 wherein a dosage form containing the acid labile compound is prepared in which the water content does not exceed 1.5 % by weight.

Patentansprüche

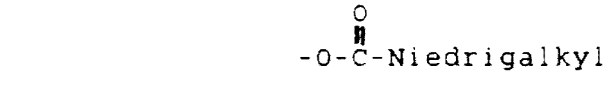
Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT LI, LU, NL, SE

1. Orale pharmazeutische Präparation, die gegen Verfärbung stabil ist, welche Präparation eine säurelabile Verbindung der allgemeinen Formel I



I,

worin A eine gegebenenfalls substituierte heterocyclische Gruppe ist, R^1, R^2, R^3 und R^4 gleich oder verschieden und vorzugsweise Wasserstoff, Niedrigalkyl, Niedrigalkoxy, $-CF_3$,



oder Halogen sind, und R_5 für H oder eine Niedrigalkylgruppe steht, worin "Niedrig" 1 bis 6 Kohlenstoffatome bezeichnet, mit Ausnahme der Verbindung Omeprazol, 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) -methyl]-sulfinyl]-1H-benzimidazol; oder die säurelabile Verbindung 2-[(2-Dimethylaminobenzyl)-sulfinyl]-benzimidazol als aktiven Inhaltsstoff umfaßt, dadurch gekennzeichnet, daß die Präparation aus Kernmaterial in Form von kleinen Kügelchen oder Tabletten, welches den aktiven Inhaltsstoff zusammen mit einer alkalisch reagierenden Verbindung oder ein Alkalisalz des aktiven Inhaltsstoffes, gegebenenfalls zusammen mit einer alkalisch reagierenden Verbindung enthält, und einer oder mehreren inert reagierenden Basisüberzugsschichten auf dem Kernmaterial, umfassend in Wasser lösliche oder rasch zerfallende Tablettenhilfsstoffe oder polymere wasserlösliche filmbildende Verbindungen, die gegebenenfalls pH-puffernde Alkaliverbindungen zwischen dem alkalisch reagierenden Kern und einer äußeren Schicht, welche eine enterische Überzugsschicht ist, enthalten, zusammengesetzt ist.

2. Präparation nach Anspruch 1, worin der Basisüberzug Hydroxypropylmethylcellulose, Hydroxypropylcellulose oder Polyvinylpyrrolidon umfaßt.

3. Präparation nach Anspruch 1, worin der Basisüberzug zwei oder mehrere Unterschichten umfaßt, und wobei die innere Schicht eines oder mehrere von Magnesiumoxid, Magnesiumhydroxid oder der zusammengesetzten Substanz $Al_2O_3.6MgO.CO_2.12H_2O$ oder $MgO.Al_2O_3.2SiO_2.nH_2O$, worin n keine ganze Zahl und weniger als 2 ist, umfaßt.

4. Präparation nach Anspruch 1, worin der alkalische Kern die säurelabile Verbindung und eine pH-puffernde Alkaliverbindung zur Herstellung einer Mikroumgebung der säurelabilen Verbindung von pH 7-12 umfaßt.

5. Präparation nach Anspruch 4, worin die Alkaliverbindung eines oder mehrere von Magnesiumoxid, -hydroxid oder -carbonat, Aluminiumhydroxid, Aluminium-, Calcium-, Natrium- oder Kaliumcarbonat, phosphat oder -citrat, der zusammengesetzten Aluminium/Magnesiumverbindungen $Al_2O_3.6MgO.CO_2.12H_2O$ oder $Mgo.Al_2O_3.2SiO_2 .nH_2O$, worin n keine ganze Zahl und weniger als 2 ist, umfaßt.

6. Präparation nach Anspruch 1, worin der alkalische Kern ein Alkalisalz der säurelabilen Verbindung, wie das Natrium-, Kalium-, Magnesium-, Calcium- oder Ammoniumsalz umfaßt.

7. Präparation nach Anspruch 5, worin der alkalische Kern ein Alkalisalz der säurelabilen Verbindung in Mischung mit einer alkalischen, sonst inerten Verbindung umfaßt.

8. Präparation nach Anspruch 1, worin der enterische Überzug Hydroxypropylmethylcellulosephthalat,

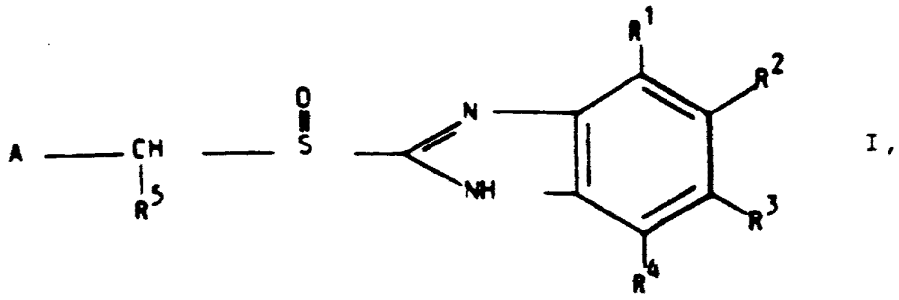
Celluloseacetatphthalat, copolymerisierten Methacrylsäure/Methacrylsäuremethylester oder Polyvinylacetatphthalat umfaßt und gegebenenfalls einen Weichmacher enthält.

9. Präparation nach Anspruch 1, worin der Wassergehalt der die säurelabile Verbindung enthaltenden endgültigen Dosisform 1,5 Gew.-% nicht übersteigt.

10. Verfahren zur Herstellung einer oralen pharmazeutischen Formulierung, die gegen Verfärbung stabil ist und eine säurelabile Verbindung nach Anspruch 1 enthalt, in welcher Formulierung Kerne, enthaltend die säurelabile Verbindung in Mischung mit einer alkalisch reagierenden Verbindung oder Verbindungen oder ein Alkalisalz der säurelabilen Verbindung, gegebenenfalls gemischt mit einer alkalisch reagierenden Verbindung oder Verbindungen, mit einer oder mehreren inerten reagierenden Basisüberzugsschichten überzogen werden, wonach die mit dem Basisüberzug überzogenen Kerne weiters mit einer enterischen Überzugsschicht überzogen werden.

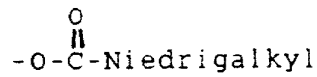
Patentansprüche für folgende Vertragsstaaten : AT, ES, GR

1. Verfahren zur Herstellung einer oralen pharmazeutischen Formulierung, die gegen verfärbung stabil ist, welche Formulierung eine säurelabile Verbindung der allgemeinen Formel I



I,

worin A eine gegebenenfalls substituierte heterocyclische Gruppe ist, R^1, R^2, R^3 und R^4 gleich oder verschieden und vorzugsweise Wasserstoff, Niedrigalkyl, Niedrigalkoxy, $-CF_3$,



oder Halogen sind, und R_5 für H oder eine Niedrigalkylgruppe steht, worin "Niedrig" 1 bis 6 Kohlenstoffatome bezeichnet, mit Ausnahme der Verbindung Omeprazol, 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]-sulfinyl]-1H-benzimidazol; oder die säurelabile Verbindung 2-[(2-Dimethylaminobenzyl)-sulfinyl]-benzimidazol als aktiven Inhaltsstoff enthält, dadurch gekennzeichnet, daß die säurelabile Verbindung in Mischung mit einer alkalisch reagierenden Verbindung oder ein Alkalisalz des aktiven Inhaltsstoffes, gegebenenfalls gemischt mit einer alkalisch reagierenden Verbindung, zu Kernen geformt werden, und die Kerne, welche die Form von kleinen Kügelchen oder Tabletten aufweisen, mit einer oder mehreren inert reagierenden Basisüberzugsschichten, umfassend in Wasser lösliche oder rasch zerfallende Tablettenhilfsstoffe oder polymere wasserlösliche filmbildende Verbindungen, die gegebenenfalls pH-puffernde Alkaliverbindungen zwischen dem alkalisch reagierenden Kern und einer äußeren Schicht, welche eine enterische überzugsschicht ist, enthalten, überzogen werden, worauf die mit dem Basisüberzug uberzogenen Kerne weiters mit der äußeren enterischen überzugsschicht überzogen werden.

2. Verfahren nach Anspruch 1, worin der aufgebrachte Basisüberzug Hydroxypropylmethylcellulose, Hydroxypropylcellulose oder Polyvinylpyrrolidon umfaßt.

3. Verfahren nach Anspruch 1, worin der aufgebrachte Basisüberzug zwei oder mehrere Unterschichten umfaßt, und wobei die innere Unterschicht eines oder mehrere von Magnesiumoxid, Magnesiumhydro-

xid oder der zusammengesetzten Substanz $Al_2O_3.6MgO.CO_2.12H_2O$ oder $MgO.Al_2O_3.2SiO_2.nH_2O$, worin n keine ganze Zahl und weniger als 2 ist, umfaßt.

4. Verfahren nach Anspruch 1, worin die säurelabile Verbindung mit einer pH-puffernden Alkaliverbindung zur Herstellung einer Mikroumgebung der säurelabilen Verbindung von pH 7-12 gemischt ist, wobei ein alkalischer Kern gebildet wird.

5. Verfahren nach Anspruch 4, worin die Alkaliverbindung mit welcher die säurelabile Verbindung in Mischung ist, eines oder mehrere von Magnesiumoxid, -hydroxid oder -carbonat, Aluminiumhydroxid, Aluminium-, Calcium-, Natrium- oder Kaliumcarbonat, -phosphat oder -citrat, der zusammengesetzten Aluminium/Magnesiumverbindungen $Al_2O_3.6MgO.CO_2.12H_2O$ oder $MgO.Al_2O_3.2SiO_2.nH_2O$, worin n keine ganze Zahl und weniger als 2 ist, umfaßt.

6. Verfahren nach Anspruch 1, worin ein Alkalisalz der säurelabilen Verbindung, wie das Natrium-, Kalium- , Magnesium-, Calcium- oder Ammoniumsalz, gebildet wird und in den alkalischen Kern inkorporiert wird.

7. Verfahren nach Anspruch 6, worin der alkalische Kern ein Alkalisalz der säurelabilen Verbindung in Mischung mit einer alkalischen, sonst inerten Verbindung umfaßt.

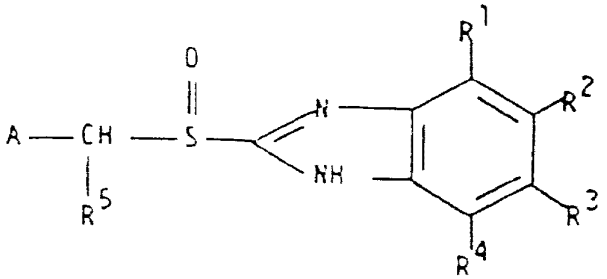
8. Verfahren nach Anspruch 1, worin der enterische Überzug, welcher Hydroxypropylmethylcellulosephthalat, Celluloseacetatphthalat, copolymerisierten Methacrylsäure/Methacrylsäuremethylester oder Polyvinylacetatphthalat umfaßt und gegebenenfalls einen Weichmacher enthält, angewandt wird.

9. Verfahren nach Anspruch 1, worin eine die säurelabile Verbindung enthaltende Dosisform hergestellt wird, wobei ihr Wassergehalt 1,5 Gew.-% nicht übersteigt.

Revendications

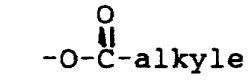
Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE,

1. Préparation pharmaceutique orale résistant à la décoloration contenant un composé sensible aux acides de formule générale I :



I

dans laquelle A est un groupe hétérocyclique éventuellement substitué , R^1, R^2, R^3 et R^4 sont identiques ou différents et sont de préférence des atomes d'hydrogène , des groupes alkyle inférieurs , alcoxy inférieurs $-CF_3$,



inférieur ou halogène et R^5 est un atome d'hydrogène ou un groupe alkyle inférieur , où "inférieur" signifie de 1 à 6 atomes de carbone, exception faite du composé oméprazole, 5-méthoxy-2-[[(4-méthoxy-3,5-diméthyl-2-pyridinyl)méthyl]sulfinyl]-1H-benzimidazole ; ou bien le composé sensible aux acides est le 2-[(2-diméthylaminobenzyl)sulfinyl]benzimidazole, comme ingrédient actif , caractérisée

en ce que' elle est composée d'une substance de noyau sous la forme de petites perles ou de comprimés contenant l'ingrédient actif ainsi qu'un composé à réaction alcaline , ou un sel alcalin de l'ingrédient actif ainsi éventuellement qu'un composé à réaction alcaline, et , sur ladite substance de noyau, d'une ou plusieurs couches de sous-enrobage inertes comprenant des excipients pour comprimés qui sont solubles ou qui se désintègrent rapidement dans l'eau, ou des composés filmogènes polymères hydrosolubles, contenant éventuellement des composés alcalins servant de tampon de pH entre le noyau à réaction alcaline et une couche externe , qui est un enrobage à délitement entérique .

2. Préparation selon la revendication 1, dans laquelle le sous-enrobage comprend de l'hydroxypropylméthylcellulose , de l'hydroxypropylcellulose ou de la polyvinylpyrrolidone .

3. Préparation selon la revendication 1, dans laquelle le sous-enrobage comprend deux ou plusieurs souscouches et dans laquelle la couche intérieure comprend une ou plusieurs substances parmi l'oxyde de magnésium, l'hydroxyde de magnésium ou une substance composite Al_2O_3,6MgO, CO_2, $12H_2O$ ou MgO, Al_2O_3, $2SiO_2$, nH_2O, où n n'est pas un nombre entier et est inférieur à 2.

4. Préparation selon la revendication 1, dans laquelle le noyau alcalin comprend le composé sensible aux acides et un composé alcalin servant de tampon de pH conférant au micro-environnement du composé sensible aux acides un pH de 7-12.

5. Préparation selon la revendication 4, dans laquelle le composé alcalin comprend une ou plusieurs substances parmi l'oxyde, l'hydroxyde ou le carbonate de magnésium, l'hydroxyde d'aluminium, le carbonate , le phosphate ou le citrate d'aluminium, de calcium, de sodium ou de potassium, les composés composites aluminium/magnésium Al_2O_3, 6MgO, CO_2, $12H_2O$ ou MgO, Al_2O_3, $2SiO_2$, nH_2O, où n n'est pas un nombre entier et est inférieur à 2.

6. Préparation selon la revendication 1, dans laquelle le noyau alcalin comprend un sel alcalin du composé sensible aux acides comme le sel de sodium, de potassium, de magnésium, de calcium ou d'ammonium.

7. Préparation selon la revendication 5, dans laquelle le noyau alcalin comprend un sel alcalin du composé sensible aux acides mélangé avec un composé alcalin inerte par ailleurs.

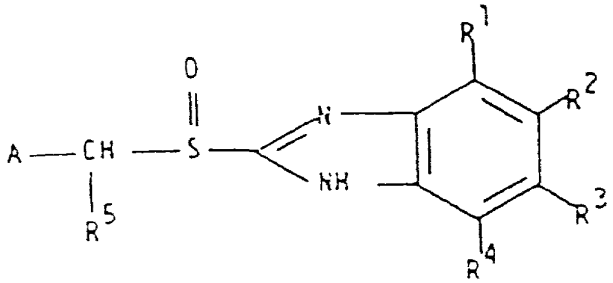
8. Préparation selon la revendication 1, dans laquelle l'enrobage à délitement entérique comprend du phtalate d'hydroxypropylméthylcellulose, de l'acétate-phtalate de cellulose, un copolymère d'acide méthacrylique et d'ester méthylique d'acide méthacrylique ou du poly(acétate-phtalate de vinyle), contenant éventuellement un plastifiant.

9. Préparation selon la revendication 1, dans laquelle la teneur en eau de la forme posologique finale contenant le composé sensible aux acides ne dépasse pas 1,5% en poids .

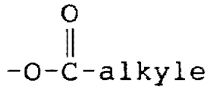
10. Procédé de préparation d'une formulation pharmaceutique orale résistante à la décoloration contenant un composé sensible aux acides selon la revendication 1 dans lequel les noyaux contenant le composé sensible aux acides mélangé avec un composé ou des composés à réaction alcaline ou un sel alcalin du composé sensible aux acides éventuellement mélangé avec un composé ou des composés à réaction alcaline sont enrobés avec une ou plusieurs couches de sous-enrobage inertes, puis les noyaux sous-enrobés sont ensuite enrobés d'un enrobage à délitement entérique.

Revendications pour les Etats contractants suivants : AT, ES, GR

1. Procédé de préparation d'une formulation pharmaceutique orale résistant à la décoloration contenant un composé sensible aux acides de formule générale I :



dans laquelle A est un groupe hétérocyclique éventuellement substitué, R^1, R^2, R^3 et R^4 sont identiques ou différents et sont de préférence des atomes d'hydrogène, des groupes alkyle inférieurs, alcoxy inférieurs, $-CF_3-$,



inférieur ou halogène et R^5 est un atome d'hydrogène ou un groupe alkyle inférieur, où "inférieur" signifie de 1 à 6 atomes de carbone, exception faite du composé oméprazole, 5-méthoxy-2-[[(méthoxy-3,5-diméthyl-2-pyridinyl)méthylsulfinyl]-1H-benzimidazole ; ou bien le composé sensible aux acides est le 2-[(2-diméthylaminobenzyl)sulfinyl]benzimidazole, comme ingrédient actif, caractérisé en ce que l'on met sous forme de noyaux le composé sensible aux acides mélangé avec un composé à réaction alcaline, ou un sel alcalin de l'ingrédient actif éventuellement mélangé avec les composés à réaction alcaline, ces noyaux, qui se présentent sous la forme de petites perles ou de comprimés, sont enrobés d'une ou plusieurs couches de sous-enrobage inertes comprenant des excipients pour comprimés qui sont solubles ou qui se désintègrent rapidement dans l'eau, ou des composés filmogènes polymères hydrosolubles, contenant éventuellement des composés alcalins servant de tampon de pH entre le noyau à réaction alcaline et une couche externe, qui est un enrobage à délitement entérique, puis les noyaux sous-enrobés sont ensuite enrobés de ladite couche d'enrobage externe à délitement entérique.

2. Procédé selon la revendication 1, dans lequel le sousenrobage appliqué comprend de l'hydroxypropyl-méthylcellulose, de l'hydroxypropylcellulose ou de la polyvinyl-pyrrolidone.

3. Procédé selon la revendication 1, dans lequel le sousenrobage appliqué comprend deux ou plusieurs sous-couches et dans lequel la sous-couche intérieure contient une ou plusieurs substances parmi l'oxyde de magnésium, l'hydroxyde de magnésium ou une substance composite Al_2O_3,6MgO, CO_2, $12H_2O$ ou MgO, Al_2O_3, $2SiO_2$, nH_2O, où n n'est pas un nombre entier et est inférieur à deux.

4. Procédé selon la revendication 1, dans lequel le composé sensible aux acides est mélangé avec un composé alcalin servant de tampon de pH conférant au micro-environnement du composé sensible aux acides un pH de 7-12, pour former un noyau alcalin.

5. Procédé selon la revendication 4, dans lequel le composé alcalin avec lequel est mélangé le composé sensible aux acides comprend une ou plusieurs substances parmi l'oxyde, l'hydroxyde ou le carbonate de magnésium, l'hydroxyde d'aluminium, le carbonate, le phosphate ou le citrate d'aluminium, les composés composites d'aluminium et de magnésium Al_2O_3, 6MgO, CO_2, $12H_2O$ ou MgO, Al_2O_3, $2SiO_2$, nH_2O, où n n'est pas un nombre entier et est inférieur à deux.

6. Procédé selon la revendication 1, dans lequel le sel alcalin du composé sensible aux acides, tel que le sel de sodium, de potassium, de magnésium, de calcium ou d'ammonium, est formé et incorporé dans le noyau alcalin.

7. Procédé selon la revendication 6, dans lequel le noyau alcalin comprend un sel alcalin du composé sensible aux acides mélangé avec un autre composé alcalin inerte par ailleurs.

8. Procédé selon la revendication 1, dans lequel on applique l'enrobage à délitement entérique qui comprend du phtalate d'hydroxypropylméthylcellulose, de l'acétate-phtalate de cellulose, un copolymère d'acide méthacrylique et d'ester méthylique d'acide méthacrylique ou du poly(acétatephtalate de vinyle), contenant éventuellement un plastifiant.

9. Procédé selon la revendication 1, dans lequel on prépare une forme posologique contenant le composé sensible aux acides dans lequel la teneur en eau ne dépasse pas 1,5% en poids.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 426 479 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **90311995.6**

(22) Date of filing: **01.11.90**

(51) Int. Cl.5: **A61K 31/415**, A61K 31/34, A61K 31/165, A61K 31/19, A61K 31/44, //(A61K31/415, 31:19,31:165),(A61K31/34, 31:165),(A61K31/165,31:135), (A61K31/19,31:135), (A61K31/44,31:19,31:165)

(30) Priority: **02.11.89 US 430837**

(43) Date of publication of application: **08.05.91 Bulletin 91/19**

(84) Designated Contracting States: **AT BE CH DE ES FR GB IT LI**

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London WC1A 2RA(GB)

(54) Pharmaceutical composition and methods for treating the symptoms of overindulgence.

(57) This invention relates to a pharmaceutical composition for treating the symptoms of overindulgence comprising an analgesic effective amount of acetaminophen or a non-steroidal anti-inflammatory drug and a gastric acid inhibiting effective amount of an H_1 or H_2 blocker, proton pump inhibitor or a combination thereof and methods of treating the symptoms of overindulgence comprising administering such pharmaceutical compositions.

EP 0 426 479 A1

PHARMCEUTICAL COMPOSITIONS AND METHODS FOR TREATING THE SYMPTOMS OF OVERINDULGENCE

Field of the Invention

This invention relates to pharmaceutical compositions for treating the symptoms of overindulgence. More particularly, the invention comprises treating the symptoms of overindulgence with a combination of non-steroidal anti-inflammatory drug or acetaminophen and a histamine receptor blocker and/or a proton pump inhibitor composition

Background of the Invention

Non-steroidal anti-inflammatory drugs (hereinafter referred to as "NSAID(S)") and acetaminophen (hereinafter referred to as "APAP") are known to be effective analgesics for the treatment of mild to moderate pain Histamine receptor blockers (referred to generically herein as H_1 or H_2 blockers) are effective inhibitors of gastric acid production. Proton pump inhibitors have been recently introduced as effective gastric acid inhibitors

The symptoms of overindulgence due to excessive or inappropriate intake of food and/or alcoholic beverage are well known and include headache as well as indigestion, upper abdominal discomfort, bloating, heartburn or pyrosis These latter symptoms collectively are sometimes referred to as acid indigestion or sour stomach. Indigestion has been variously described and will be defined herein as encompassing one or more of the following symptoms: abdominal pain and/or pressure, heartburn, a sense of abdominal fullness or bloating, excessive belching or flatulence and a vague feeling that digestion has not proceeded naturally (See Friedman, L.S., and K. J. Isselbacher, "Indigestion", Harison's Principles of Internal Medicine , 11th Edition, McGraw Hill Book Company, N.Y., p 171-175, 1986).

The pathophysiology of indigestion is generally believed to be related to increased intraluminal acidity. The effects of alcohol and/or food on the gastrointestinal tract are influenced by a number of factors, including the mental state of the patient, the amount and type of food concurrently ingested, the individual subject's tolerance for alcohol and the presence or absence of disease. Gastric secretions stimulated by alcohol are rich in acid and normal in pepsin content. Stimulation of the antral mucosa by alcohol also leads to increased gastric secretion. Histamine has also been shown to be released in response to the alcohol-gastrin interrelationship. (See Glass, G. B. J., B. L. Slomiany and A. Slomiany, "Biochemical and Pathological Derangements of the Gastrointestinal Tract following Acute and Chronic Ingestion of Ethanol", Biochemistry and Pharmacology of Ethanol , Vol 1, Plenum Press, N.Y., p 551-586, 1979.)

Alcohol in concentrations of about 10% in the stomach results in an acid rich secretion. Alcoholic drinks of 40% concentration and over are quite irritating to the gastric mucosa and cause congestive hyperemia and inflammation of the gastric mucosa and can produce erosive gastritis (See Ritchie, J. M., "The Aliphatic Alcohols", The Pharmaclogical Basis of Therapeutics , 7th Edition, MacMillan Publishing Co, N.Y., p 372-386, 1985). The irritation produced by alcohol stimulates sensitized visceral afferent nerves which accompany the abdominal sympathetic pathway and is responsible for the symptom of abdominal discomfort which accompanies overindulgence. Inflammation also generally lowers the threshold for pain from visceral distention or exaggerated muscular contraction (See Lorber, S. H., and V. P. Dimoso, Jr., "Diseases of the Gastrointestinal Tract", The Biology of Alcoholism , Vol 3, Clinical Pathology, Plenum Press, N.Y., p 339-357, 1974).

Heartburn or pyrosis is frequently associated with overindulgence and is the result of reflux of acidic gastric content into the lower esophagus after a large meal or excessive alcohol intake. Heartburn is described as a sensation of warmth or burning located substernally or high in the epigastrum with occasional radiation into the neck and occasionally to the arms.

Treatment of the gastric mucosal irritation and heartburn associated with overindulgence due to alcohol has traditionally been directed toward reducing gastric acidity with various oral antacids. Recent introduction of H_2 receptor blocking agents has added another dimension to the treatment regimen and has only lately been considered as a routine therapy for gastric mucosal irritation due to a variety of causes. Histamine is known to stimulate the release of gastric acid. Evidence is available that blocking the histamine gastric response is possible with agents which selectively block the H_1 receptor. Similarly, combinations of H_1 and H_2 receptor blocking agents have been shown to have a synergistic effect on protecting the gastric mucosa. An appropriate treatment of heartburn or pyrosis could encompass a composition containing an H_1 receptor blocking agent, an H_2 receptor blocking agent or a combination of the two depending upon the desired result or severity of the condition.

Headache due to excessive food or alcohol ingestion is a much more obscure subject. While

the etiology of the common headache due to overindulgence may be related to the essential oils, metabolic by-products of ethyl alcohol metabolism or osmotic changes induced by the anhydrous nature of the alcohol itself, specific details of the mechanism are difficult to determine. Should etiologies and mechanisms of headache production be more precisely known, therapy can be more specifically oriented. Meanwhile, treatnient has been directed at avoidance and symptomatic therapy with analgesic compositions, e.g. aspirin or APAP (See Adams, A. D. and J. B. Martin, "Headache", Harrison's Principles of Internal Medicine , 11th Edition, McGraw Hill Book Company, N.Y., p 26-33, 1986).

The treatment of the symptoms of overindulgence often requires the co-administration of an analgesic to relieve the headache along with an agent to reduce gastric acidity which is generally believed to cause the indigestion and heartburn. For example, effervescent products comprising aspirin or APAP combined with an antacid such as sodium or calcium carbonates have been commercially available as treatments for the symptoms of overindulgence.

The concept of combining an agent to reduce or inhibit the production of gastric acid with an analgesic in a single composition has, however, heretofore been overlooked as a method of treating overindulgence. Such a combination would be a significant advance and meet a long felt need for treating the symptoms of overindulgence, permitting a single composition to more effectively treat all the symptoms concurrently.

Summary of the Invention

The foregoing object of fulfilling a long felt need for pharmaceutical compositions which can relieve the symptoms of overindulgence defined herein as headache and acid indigestion has now been accomplished in accordance with the compositions and methods of the present invention.

In accordance with the purposes of the invention, as embodied and fully described herein, the invention comprises pharmaceutical compositions for treating the symptoms of overindulgence comprising an analgesic effective amount of an NSAID or APAP and a gastric acid inhibiting effective amount of an H_1 or H_2 blocker, a proton pump inhibitor or a combination thereof.

In preferred embodiments the NSAID is selected from the group consisting of propionic acid derivatives including ibuprofen, fenoprofen, naproxen and ketoprofen; fenamic acid derivatives, including meclofenamate and mefenamic acid; oxicams,. including piroxicam; indole acetic acids, including indomethacin, sulindac, tolmetin; and pharmaceutically acceptable salts thereof. The preferred H_1 or H_2 or proton pump inhibitors are selected from the group consisting of the H_2 receptor blocking drugs cimetidine, ranitidine and famotidine; the proton pump inhibitor drug omeprazole; and the H_1 receptor blocking drugs, from the group ethanolamines including diphenhydramine, dimenhydrimate, carbinoxamine, from the group ethylenediamines, including tripelennamine, pyrilamine, from the group alkylamines, including cholphenirdmine, from the group piperazines, including hydroxyzine, cyclizine, meclizine, from the group phenothiarinec, including promethazine. In more preferred embodiments the APAP or ibuprofen are used in combination with cimetidine.

As embodied and broadly described herein, the invention further comprises a method for treating the symptoms of overindulgence comprising administering a combination pharmaceutical composition to a patient comprising an analgesic effective amount of APAP or an NSAID and a gastric acid inhibiting effective amount of an H_1 or H_2 blocker, a proton pump inhibitor or a combination thereof as is described above.

Detailed Description of Preferred Embodiments of the Invention

Reference will now be made in detail to preferred embodiments of the invention, examples of which are illustrated in the following examples section.

To achieve the object of the invention of providing a pharmaceutical composition for treating the symptoms of overindulgence an analgesic effective amount of APAP or an NSAID is combined with a gastric acid inhibiting effective amount of an H_1 or H_2 blocker or a proton pump inhibitor or a combination thereof.

The treatment of overindulgence is directed to the symptomatic relief of the complaints of acid indigestion and headache. This requires the use of an agent which would treat the headache, abdominal discomfort and reduce the intraluminal gastric acidity. Since no single agent has been found to be capable of treating the multiple symptons of overindulgence, a composition such as is described in this invention is recommended.

APAP, a well-known clinically proven analgesic and antipyretic, produces analgesia by elevating the pain threshold. APAP is indicated as an analgesic for both acute and chronic pain conditions, including arthritic and rheumatic conditions involving musculoskeletal pain, headache, dysmenorrhea, myalgias and neuralgias. APAP is an extremely

safe analgesic, rarely producing side-effects and is especially well tolerated by aspirin-sensitive patients. (Seegers, A. J. M., L. P. Jager, and J. Van Noordwijk, "Effects of Phenacetin Parcetamol and Caffeine on the Erosive Activity of Acetylsalicylic Acid in the Rat Stomach: Dose-Response Relationships, Time Course of Erosion Development and Effects of Acid Secretion", J. Pharmacol , 31:840-848, 1979), have shown that APAP decreases the gastric erosive activity of a strongly ulcerogenic NSAID. (Stern, A. I., D. L. Hogan, L. H. Kahn, and J. 1. Isenberg, "Protective Effect of Acetaminophen Against Aspirin - and Ethanol-Induced Damage to the Human Gastric Mucosa", Gastroenterology , 86:728-733, 1984), have additionally shown that a single dose of APAP prevents a significant amount of gastric mucosal damage caused by both aspirin and alcohol. Further, APAP is particularly well suited as an analgesic in patients with hemostatic disturbances as well as in patients with upper gastrointestinal disorders including ulcers, gastritis and hiatus hernia.

Aspirin and other NSAIDs are commonly used for the treatment of pain and inf lammation of a variety of etiologies. The mechanism of action of this class of drugs is by inhibition of the enzyme of prostaglandin synthetase, both contrally and peripherally. The peripheral prostaglandin synthetase inhibiting activity of aspirin and other NSAIDs is responsible for the anti-inflammatory and analgesic activity as well as for many of the varied side-effects of these drugs. Aspirin is specifically excluded from this invention since aspirin, by itself, causes severe inflammation of the gastric mucosa. In the presence of alcohol, this effect of aspirin is enhanced. Similarly, prolongation of bleeding time induced by aspirin, is enhanced in the presence of alcohol (See Deykin, D., P. Janson and L. McMahon, "Ethanol Potentiation of Aspirin-Induced Prolongation of the Bleeding Time", New England Journal of Medicine , 306:852-854, 1982). For these reasons aspirin is not a rational choice either alone or in combination with other compositions for treating acid indigestion in general and as it relates to overindulgence. While other NSAIDs can by themselves lead to increased stomach upset, this effect is not as severe as with aspirin, and they are thus useful in treating the symptoms of overindulgence in accordance with the combination composition of the invention.

The presence of gastrin, acetylcholine and histamine in the stomach interacting with the histamine receptor on the parietal cell results in the increased secretion of hydrochloric acid. The activity of gastrin and acetylcholine are believed to be influenced by histamine. Inhibition of the histamine receptor prevents the attachment of histamine to the parietal cell and subsequently inhibits acid secretion. Omeprazole, a proton pump inhibitor, irreversibly inhibits the enzyme responsible for acid production.

The histzmine receptors are differentiated by the class of inhibitor so that while the acid secreting histamine receptor is called an H_2 receptor with the inhibitors of this site being called the H_2 receptor blocker, the histamine H_1 receptor site blockers comprise another class of antihistamine drugs. The combination of H_1 and H_2 blockers can synergistically protect the gastrointestinal mucosa from the effects of chemically induced damage such as occurs in alcohol and food related overindulgence.

The composition of the present invention shall preferably contain a combination of the following compositions or their pharmaceutically acceptable salts either acetaminophen from 500 to 1000 mg per dose or one of several NSAIDs from the group of: propionic acid derivatives including ibuprofen (the term ibuprofen is meant to include administration of both the racemic mixture of R- and S-enantiomers and the substantially pure S-enantiomer which is the analgesic active form of ibuprofen) from 200 to 400 mg per dose; naproxen from 200 to 500 mg per dose; fenoprofen from 200 to 600 mg per dose; ketoprofen from 50 to 300 mg per dose, meclofenamate from 50 to 400 mg per dose, mefenamic acid from 250 to 500 mg per dose; piroxicam from 10 to 20 mg per dose; indomethacin from 25 to 200 mg per dose, sulindac from 150 to 400 mg per dose, tolmetin from 200 to 1200 mg per dose; in combination with the H_2 receptor blocking drugs including cimetidine from 150 to 800 mg per dose; ranitidine from 50 to 300 mg per dose; famotidine from 5 to 40 mg per dose; or in combination with the proton pump inhibitor drugs including omeprazole from 100 to 500 mg per dose; and/or an H_1 receptor blocking drug from the group ethanolamines including diphenhydramine 25 to 200 mg per dose; dimenhydrimate from 50 to 400 mg per dose, carbinoxamine from 4 to 8 mg per dose; from the group ethylenediamines including tripelennamine frog 25 to 300 mg per dose; pyrilamine from 25 to 300 mg per dose; from the group alkylamines including chorpheniramine from 2 to 24 mg per dose, from the group piperazines including hydroxyzine from 25 to 100 mg per dose, cyclizine from 50 to 300 mg per dose, meclizine from 8 to 400 mg per dose; and from the group phenothiazines including promethazine from 12.5 to 50 mg per dose.

The dosage ranges described above are preferred adult doses and may vary depending upon the age and weight of the patient as would be known by those skilled in the pharmaceutical arts. Further, if a combination of, for example an H_1 and H_2 blocker is used, the dosage for each may be reduced.

To establish the efficacy of the composition of this invention in humans, patients suffering from the symptoms of overindulgence which will include any of the constellation of signs of indigestion, upper abdominal discomfort, bloating, heartburn or pyrosis and headache can be administered acetaminophen or a non-steroidal anti-inflammatory drug with and without histamine receptor blockers (H_1 and/or H_2 blocking agents). To determine efficacy, patients are asked to subjectively estimate onset of relief, duration of relief and time to maximum relief. Appropriate statistical methods are used to show that on the average, acetaminophen or non-steroidal anti-inflammatory agents with H_1 histamine and/or H_2 histamine receptor blocking drugs are more efficacious.

Since appropriate animal models for the evaluation of overindulgence are not available, studies will not be conducted involving laboratory animals.

Other ingredients both active and inactive can be added to the combination pharmaceutical compositions of the invention. For example, flavoring compositions are desirably added to chewable and liquid dosage forms. Further, antidiarrheal, antiflatulent, antispasmodic and/or anticholinergic compositions may be added to the compositions of the invention to reduce and relieve gastrointestinal distress, which may be associated with acid indigestion. Exzmples of antidiarrheals include loperamidc, attapulgite, bismuth subsalicylate, diphenoxylate HCl, polycarbophil, calcium polycarbophil and mixtures thereof. An example of an antiflatulent is simethicone. Examples of antispasmodics include phenobarbital dicyclomine HCl, belladonna alkaloids, and atropine.

Examples

The invention will now be illustrated by examples. The examples are not intended to be limiting of the scope of the present invention but read in conjunction with the detailed and general description above, provide further understanding of the present invention and an outline of a process for preparing the compositions of the invention. Example 1-14 disclose various formulations for preparing tablets or caplets in accordance with the invention. Various conventional techniques for preparing medicament tablets or caplets can be employed as would be known to those skilled in the art as is disclosed for example by Remington's Pharmaceutle Sciences , flack Publishing Co., Chapter 90, "Oral Solid Dosage Forms", pp. 1603-1632 (1985).

Example 1:

A tablet consisting of:
500 mg of acetaminophen;
150 mg of cimetidine; and
other auxiliary agents and coloring agents.

Example 2:

A tablet consisting of:
500 mg of acetaminophen;
mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 3:

A tablet consisting of:
200 mg of ibuprofen;
150 mg of cimetidine; and
other auxiliary agents and coloring agents.

Example 4:

A tablet consisting of:
200 mg of ibuprofen;
mg of ranitidine; and
other auxiliary agents and coloring agents.

Example 5:

A tablet consisting of:
200 mg of ibuprofen;
mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 6:

A tablet consisting of:
500 mg of acetaminophen;
50 mg of ranitidine; and
other auxiliary agents and coloring agents.

Example 7:

A tablet consisting of:
500 mg of acetaminophen;
150 mg of cimetidine;
25 mg of diphenhydramine; and

other auxiliary agents and coloring agents.

Example 8:

A tablet consisting of:
200 mg of ibuprofen;
350 mg of cimetidine;
mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 9:

A tablet consisting of:
500 mg of acetaminophen;
50 mg of ranitidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 10:

A tablet consisting of:
200 mg of ibuprofen;
50 mg of ranitidine;
25 mg of diphenhydramine; and
other auxiliary agents and coloring agents.

Example 11:

A tablet consisting of:
500 mg of acetaminphen;
60 mg of omeprazole; and
other auxiliary agents and coloring agents.

Example 12:

A tablet consisting of:
200 mg ibuprofen;
mg omeprazole; and
other auxiliary agents and coloring agents.

Example 13:

A tablet consisting of:
500 mg acetaminophen;
60 mg omeprazole;
25 mg diphenhydramine; and
other auxiliary agents and coloring agents.

Example 14:

A tablet consisting of:
200 mg ibuprofen;
60 mg omeprazole;
25 mg diphenhydramine; and
other auxiliary agents and coloring agents.

Various other dosage forms can be applied herein such as a filled gelatin capsule, liquid emulsion/suspension or chewable tablet form employing the dosage actives provided above or other dosage amounts in accordance with the present invention. A liquid suspension of ibuprofen to which cimetidine, diphenhydramine, ranitidine or combinations thereof in the amounts provided above can be added to the ibuprofen suspension disclosed in EP-A-90307001.9.

Method of Treating Patients for the Symptoms of Overindulgence

A patient exhibiting the symptoms or suffering from the symptoms of overindulgence is treated by the oral administration of one tablet of the pharmaceutical composition in accordance with any of Examples 1-14.

The scope of the present invention is not limited by the description, examples and suggested uses herein and modifications can be made without departing from the spirit of the invention. For example, the pharmaceutical compositions of the invention may be provided in a sustained release formulation for prolonged and/or nightime treatment of the symptoms of overindulgence. Application of the compositions and methods of the present invention for medical and pharmaceutical uses can be accomplished by any clinical, medical and pharmaceutical methods and techniques as are presently or prospectively known to those skilled in the art. Thus it is intended that the presently claimed invention cover the modifications and variations of this invention provided that they come within the scope of the appended claims and their equivalents.

Claims

1. A pharmaceutical composition comprising:
an analgesic effective amount of acetaminophen or a non-steroidal anti-inflammatory drug; and
a gastric acid inhibiting effective amount of an H_1 or H_2 receptor blocker, a proton pump inhibitor or a

combination thereof.

2. The composition of claim 1 wherein the non-steroidal anti-inflammatory drug is a propionic acid derivative, a fenamic acid derivative, an oxicam, an indole acetic acid or a pharmaceutically acceptable salt thereof.

3. The composition of claim 1 or claim 2 wherein the acetaminophen or non-steroidal anti-inflammatory drug, selected from ibuprofen, fenoprofen, naproxen, ketoprofen, meclofenamate, mefenamic acid, piroxicam, indomethacin, sulindac, tolmetin, or a pharmaceutically acceptable salt thereof, is combined with:

one of the H_2 receptor blocking drugs cimetidine, ranitidine and famotidine;

the proton pump inhibitor drug omeprazole; or one of the H_1 receptor blocking drugs diphenhydramine, dimenhydrimate, carbinoxamine, tripelennamine, pyrilamine, chorpheniramine, hydroxyzine, cyclizine, meclizine, promethazine;

or a pharmaceutically acceptable salt thereof.

4. The composition of any one of claims 1 to 3 which contains:

acetaminophen from 500 to 1000mg per dose, ibuprofen from 200 to 400 mg per dose, naproxen from 200 to 500 mg per dose, fenoprofen from 200 to 600 mg per dose, ketoprofen from 50 to 300 mg per dose, meclofenamate from 50 to 400 mg per dose, mefenamic acid from 250 to 500 mg per dose, piroxicam from 10 to 20 mg per dose, indomethacin from 25 to 200 mg per dose, sulindac from 150 to 400 mg per dose, tolmetin from 200 to 1200 mg per dose or a pharmaceutically acceptable salt thereof;

in combination with:

cimetidine from 150 to 800 mg per dose, ranitidine from 50 to 300 mg per dose, famotidine from 5 to 40 mg per dose, omeprazole from 100 to 500 mg per dose, diphenhydramine from 25 to 200 mg per dose, dimenhydrimate from 50 to 400 mg per dose, carbinoxamine from 4 to 8 mg per dose, tripelennamine from 25 to 300 mg per dose, pyrilamine from 25 to 100 mg per dose, chlorpheniramine from 2 to 24 mg per dose, hydroxyzine from 25 to 100 mg per dose, cyclizine from 50 to 300 mg per dose, meclizine from 8 to 400 mg per dose, promethazine from 12.5 to 50 mg per dose, a pharmaceutically acceptable salt thereof or a combination thereof.

5. The composition of any one of claims 1 to 4 comprising fenoprofen, ketoprofen, meclofenamate, mefenamic acid, piroxicam, indomethacin, sulindac, tolmetin or a pharmaceutically acceptable salt thereof, and

(a) cimetidine, ranitidine or famotidine; or

(b) diphenhydramine, dimenhydrimate, carbinoxamine, tripelennamine, pyrilamine, chlorpheniramine, hydroxyzine, cyclizine, meclizine or promethazine; or

(c) a combination of a drug from group (a) and a drug from group (b).

6. The composition of any one of claims 1 to 5 comprising:

a combination of acetaminophen and cimetidine;

a combination of ibuprofen and cimetidine; or

a combination of naproxen anddiphenhydramine.

7. The composition of any one of claims 1 to 6, in oral tablet, caplet, chewable or liquid dosage form.

8. The composition of any one of claims 1 to 7, for use in treating the symptoms of over indulgence.

9. A method for producing the composition of any one of claims 1 to 8 which comprises forming a pharmaceutical composition containing:

an analgesic effective amount of acetaminophen or a non-steroidal anti-inflammatory drug; and

a gastric acid inhibiting amount of an H_1 or H_2 receptor blocker, a proton pump inhibitor or a combination thereof.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 31 1995

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	UNLISTED DRUGS, vol. 20, no. 11, November 1968, Chatnam, New Jersey, US * Page 167, paragraph e: "Infacete" *	1-9	A 61 K 31/415 A 61 K 31/34 A 61 K 31/165
X	WO-A-8 503 443 (RICHARDSON-VICKS, INC.) * Pages 25-28, claims 1-27 *	1-9	A 61 K 31/19 A 61 K 31/44 // (A 61 K 31/415
X	GB-A-2 105 193 (GLAXO GROUP LTD) * Page 3, lines 19-35, claims 1-7 *	1-9	A 61 K 31:19 A 61 K 31:165) (A 61 K 31/34 A 61 K 31:165) (A 61 K 31/165 A 61 K 31:135) (A 61 K 31/19 A 61 K 31:135) (A 61 K 31/44 A 61 K 31:19 A 61 K 31:165)

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	28 January 91	BRINKMANN C.

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same catagory
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention

E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 550 083 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number: **92203674.4**

(51) Int. Cl.5: **A61K 31/34**

(22) Date of filing: **27.11.92**

(30) Priority: **06.12.91 GB 9126027**
20.03.92 GB 9206083

(43) Date of publication of application:
07.07.93 Bulletin 93/27

(84) Designated Contracting States:
DE DK ES GR NL PT SE

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(54) Medicaments for treating imflammatory conditions or for analgesia containing a NSAID and canitidine bismuth citrate.

(57) The use is described of both (i) ranitidine bismuth citrate and (ii) a non-steroidal anti-inflammatory drug in treating or preventing inflammatory conditions and for analgesia. Pharmaceutical compositions containing both (i) and (ii) and methods for the preparation of pharmaceutical compositions containing (i) and (ii) are also described.

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The present invention relates to improvements in the treatment of inflammatory conditions and for analgesia. More particularly it relates to the co-administration of a non-steroidal anti-inflammatory drug with a salt formed between ranitidine and a complex of bismuth with a carboxylic acid.

Systemic non-steroidal anti-inflammatory drugs, such as aspirin, indomethacin, ibuprofen and piroxicam, are known to give rise to undesirable side effects. In particular, they are known to be ulcerogenic and can thus, for example, give rise to gastric and/or duodenal ulceration when administered orally. This side effect may be further enhanced in combination with other factors such as stress and smoking. Since in some treatments these compounds may have to be used for an extended period, such side effects can prove a serious disadvantage.

In our UK Patent Specification No. 2220937B we describe and claim salts formed between ranitidine and a complex of bismuth with a carboxylic acid, particularly tartaric acid and, more especially, citric acid. One such salt is N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine 2-hydroxy-1,2,3-propanetricarboxylate bismuth (3^+) complex, also known as ranitidine bismuth Citrate.

The salts disclosed in UK Patent Specification No. 2220937B possess the H_2-antagonist antisecretory properties associated with ranitidine, together with antibacterial activity against Helicobacter pylori (formerly Campylobacter pylori). In addition, such salts possess cytoprotective properties and display activity against the human gastric pepsins with preferential inhibition of pepsin 1, a pepsin isozyme associated with peptic ulcer. The salts disclosed in UK Patent Specification No. 2220937B thus possess a particularly advantageous combination of properties for the treatment of gastrointestinal disorders, especially peptic ulcer disease (e.g. gastric and duodenal ulceration) and other gastroduodenal conditions, for example gastritis and non-ulcer dyspepsia.

Tests in animals and humans have now shown that mucosal lesions of the gastrointestinal tract caused by non-steroidal anti-inflammatory drugs are significantly reduced by administering ranitidine bismuth citrate. In particular, we have demonstrated in rats the ability of ranitidine bismuth citrate to prevent indomethacin induced gastric antral ulceration using a modification of the method of Satoh et al., Gastroenterology (1981), 81, 719-725. In this test ranitidine bismuth citrate was markedly more potent than both ranitidine hydrochloride and tripotassium dicitrato bismuthate as DeNol™. A recently published human clinical study (N. Hudson et al., Gut 1992, 33 supplement, s47) also demonstrates that ranitidine bismuth citrate confers substantial protection from aspirin-induced injury to the gastric mucosa.

The present invention thus provides, in one aspect, the use of (i) ranitidine bismuth citrate and (ii) a non-steroidal anti-inflammatory drug in the manufacture of medicaments for simultaneous, separate or sequential use in treating or preventing inflammatory conditions or for analgesia.

In a further, or alternative, aspect the present invention provides the use of ranitidine bismuth citrate in the manufacture of medicaments to prevent gastrointestinal damage caused by non-steroidal anti-inflammatory drugs.

Combination therapy according to the present invention may be used in the treatment of inflammatory conditions, particularly acute and chronic musculo-skeletal inflammatory conditions such as rheumatoid and osteo-arthritis and ankylosing spondylitis and for analgesia in conditions such as dysmenorrhoea, especially where the use of the anti-inflammatory drug is limited by gastrointestinal side effects. As stated above, co-administration of ranitidine bismuth citrate with a systematic non-steroidal anti-inflammatory drug may also be used to prevent gastrointestinal damage caused by non-steroidal anti-inflammatory drugs. Such gastrointestinal damage includes duodenal and/or gastric ulceration, non-steroidal anti-inflammatory drug associated gastritis and gastric erosions, and non-steroidal anti-inflammatory drug associated mucosal damage to the small intestine.

Suitable systemic non-steroidal anti-inflammatory drugs which may be employed in the invention generally also show analgesic activity and include, for example, aspirin, indomethacin, ibuprofen, piroxicam, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, sulindac and tolmetin.

The ranitidine bismuth citrate and the anti-inflammatory drug are preferably co-administered in the form of separate pharmaceutical compositions for simultaneous and/or sequential use. Alternatively the ranitidine bismuth citrate and the anti-inflammatory drug may be administered as a single pharmaceutical composition for oral use comprising effective amounts of the active ingredients.

Thus, according to a further aspect, the invention provides a product containing (i) ranitidine bismuth citrate and (ii) a non-steroidal antiinflammatory drug as a combined preparation for simultaneous, separate or sequential use in treating or preventing inflammatory conditions or for analgesia.

When the ranitidine bismuth citrate and the non-steroidal anti-inflammatory are administered as separate preparations, the anti-inflammatory may be provided in any convenient formulation, such as in the manner known in the art and/or commercially for the compound concerned. Administration of both the ranitidine bismuth citrate and the non-steroidal anti-inflammatory by the oral route is preferred, although the anti-inflammatory, where appropriate, may also be given by another route, for example parenterally (e.g. intravenously) or rectally (e.g. by suppository).

The ranitidine bismuth citrate may conveniently be formulated as tablets (including chewable tablets), capsules (of either the hard or soft type), or as a liquid preparation, as described for example in UK Patent Specification Nos. 2220937B and 2248185A. Tablets are generally preferred.

As stated hereinabove, ranitidine bismuth citrate and the non-steroidal anti-inflammatory drug may be administered as a single pharmaceutical composition for oral use. Thus, according to a further aspect the invention provides a pharmaceutical composition, for oral use in human or veterinary medicine, comprising ranitidine bismuth citrate and a non-steroidal anti-inflammatory drug, together, where appropriate, with a pharmaceutically acceptable carrier or excipient.

Suitable additional carriers or excipients include binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). An alkaline salt of the type described in UK Patent Specification No. 2248185A may be added to improve the rate of disintegration and/or dissolution of the composition.

The compositions may be prepared according to conventional techniques well known in the pharmaceutical industry. Thus, for example, the ranitidine bismuth citrate and the non-steroidal anti-inflammatory drug may be admixed together, if desired, with suitable carriers or excipients. Tablets may be prepared, for example, by direct compression or wet granulation of such a mixture. Capsules may be prepared by filling the blend along with suitable carriers or excipients into gelatin capsules, using a suitable filling machine. Tablets may be coated by methods well known in the art. The preparations may also contain flavouring, colouring and/or sweetening agents as appropriate.

When ranitidine bismuth citrate and the non-steroidal anti-inflammatory drug are administered as a single pharmaceutical composition for oral use the composition is preferably in the form of a capsule or, more particularly, a tablet.

The compositions for use according to the invention may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredients. The pack may for example comprise metal or plastic foil, such as a blister pack. Where the ranitidine bismuth citrate and the non-steroidal anti-inflammatory drug are intended for administration as separate compositions these may be presented in the form of, for example, a twin pack.

Thus, according to a further aspect the present invention provides a twin-container pack for use in treating or preventing inflammatory conditions or for analgesia, one of the containers containing ranitidine bismuth citrate and the other containing a non-steroidal anti-inflammatory drug.

The doses at which the ranitidine bismuth citrate and the non-steroidal anti-inflammatory may be administered to man (of approximately 70kg body weight) will depend on the route of administration of the anti-inflammatory and on the nature and severity of the condition being treated. It will also be appreciated that it may be necessary to make routine variations to the dosage depending on the age and weight of the patient.

A proposed dosage of ranitidine bismuth citrate for use according to the invention is 150mg to 1.5g, preferably 200 - 800mg per unit dose. The unit dose may be administered, for example, 1 to 4 times per day, preferably once or twice per day.

The non-steroidal anti-inflammatory may conveniently be administered at doses within the normal dosage range at which the compound is therapeutically effective, -for example 50mg-1g of aspirin, 10 - 100 mg of indomethacin, 5 - 50 mg of piroxicam, 100-500mg of ibuprofen and 200-800mg of mefenamic acid per dosage unit taken one or more times daily in accordance with the normal dosage regime for the drug in question.

In a further aspect, the present invention provides a method of treating inflammatory conditions or for analgesia in a human or animal subject, which comprises administering to said subject effective amounts of ranitidine bismuth citrate and a non-steroidal anti-inflammatory drug.

In another, or alternative, aspect the present invention provides a method of treating gastrointestinal damage caused by non-steroidal anti-inflammatory drugs in a human or animal subject, which comprises administering to said subject an effective amount of ranitidine bismuth citrate.

References herein to treatment include prophylactic treatment as well as the alleviation of acute symptoms.

The methods of the present invention comprise administering the non-steroidal anti-inflammatory drug and ranitidine bismuth citrate either concurrently or non-concurrently. As used herein, concurrent administration means that the agents are given within 24 hours of each other, whereas non-concurrent administration means that the agents are given more than 24 hours apart. When the agents are administered concurrently, it may be preferable to administer the agents within about 1 hour of each other or, more preferably, within about 5 minutes of each other.

For the methods of the present invention, the duration of administration of the agents during either concurrent or non-concurrent dosing will vary according to the specific condition being treated.

The following examples illustrate pharmaceutical compositions for oral use containing both ranitidine bismuth citrate and a suitable non-steroidal anti-inflammatory drug.

Example 1

TABLETS

		mg/tablet
(a)	Ranitidine bismuth citrate	400.00
	Ibuprofen	400.00
	Lactose	200.00
	Hydroxypropyl methylcellulose	5.00
	Sodium starch glycollate	30.00
	Magnesium stearate	10.00
	Compression weight	1045.00

The ranitidine bismuth citrate and ibuprofen are sieved through a 250μm sieve and blended with the lactose. This mix is granulated with a solution of the hydroxypropyl methylcellulose. The granules are dried, screened and blended with the sodium starch glycollate and the magnesium stearate. The lubricated granules are compressed into tablets using 15.0mm punches.

		mg/tablet
(b)	Ranitidine bismuth citrate	400.00
	Indomethacin	50.00
	Microcrystalline cellulose	114.00
	Anhydrous sodium carbonate	30.00
	Magnesium stearate	6.00
	Compression weight	600.00

The ranitidine bismuth citrate and indomethacin are blended with the microcrystalline cellulose, sodium carbonate and magnesium stearate and compressed using 12.5mm punches.

Example 2

CAPSULES

		Capsule
(a)	Ranitidine bismuth citrate	200.00
	Ibuprofen	400.00
	Starch 1500**	196.00
	Magnesium stearate	4.00
	Fill weight	800.00

** A form of directly compressible starch supplied by Colorcon Ltd, Orpington, Kent.

The ranitidine bismuth citrate and ibuprofen are sieved through a 250μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 0 hard gelatin capsules using a suitable filling machine.

		mg/capsule
(b)	Ranitidine bismuth citrate	200.00
	Indomethacin	50.00
	Starch 1500	48.50
	Magnesium stearate	1.50
	Fill weight	300.00

The ranitidine bismuth citrate and indomethacin are sieved through a 250μm sieve and blended with the Starch 1500 and magnesium stearate. The resultant mix is filled into size 2 hard gelatin capsules using a suitable filling machine.

Example 3

INHIBITION OF INDOMETHACIN-INDUCED GASTRIC LESIONS IN THE RAT

The ability of ranitidine bismuth citrate to prevent indomethacin-induced gastric antral ulceration was compared with that of ranitidine hydrochloride and De-Nol™.

Female rats, which had been fasted for 24 hours and then re-fed, received ranitidine bismuth citrate (1 to 100mg/kg), ranitidine hydrochloride (10 to 100mg/kg) or De-Nol™ (3 to 100mg/kg) by oral gavage. Ranitidine bismuth citrate was administered as a suspension and the other test compounds as solutions. Thirty minutes after dosing with the test compound, animals received indomethacin (60mg/kg sc) as an ulcerogenic stimulus and after a further 6 hours the animals were killed and the antral region assessed macroscopically for damage.

Results are presented in the table below. Ranitidine bismuth citrate produced a dose-related inhibition of indomethacin-induced lesions and was relatively potent, an ED_{50} value of 4.5mg/kg po being calculated. Ranitidine hydrochloride and De-Nol™ were markedly less potent.

ED_{50} Values for Inhibition of Indomethacin - Induced Antral Ulceration			
Compound	Ranitidine Bismuth Citrate	Ranitidine Hydrochloride	De-Nol™
ED_{50} mg/kg p.o.	4.5	23.4	43.2
95% confidence limits	0.5 - 10.7	16.0 - 33.0	23.6 - 93.0

Claims

1. The use of (i) ranitidine bismuth citrate and (ii) a non-steroidal anti-inflammatory drug in the manufacture of medicaments for simultaneous, separate or sequential use in treating or preventing inflammatory conditions or for analgesia.

2. The use of ranitidine bismuth citrate in the manufacture of medicaments to prevent gastrointestinal damage caused by non-steroidal anti-inflammatory drugs.

3. The use according to Claim 1 in which the compounds (i) and (ii) are presented as separate compositions for said use.

4. A product containing compounds (i) and (ii) as defined in Claim 1 as a combined preparation for simultaneous, separate or sequential use in treating or preventing inflammatory conditions or for analgesia.

5. A pharmaceutical composition, for oral use, which comprises both a compound (i) and a compound (ii) as defined in Claim 1, together with a pharmaceutical carrier or excipient.

6. A use, product or composition according to any preceding claim in which the non-steroidal anti-inflammatory drug is selected from aspirin, indomethacin, ibuprofen, piroxicam, fenoprofen, ketoprofen, naproxen, mefenamic acid, diflunisal, benorylate, azapropazone, diclofenac, fenbufen, feprazone, fenclofenac, flufenamic acid, flurbiprofen, oxyphenbutazone, phenylbutazone, sulindac and tolmetin.

7. A use or product according to any preceding claim in which compounds (i) and (ii) are in forms suitable for oral administration.

8. A use or product according to any preceding claim in which compound (i) is formulated as a tablet.

9. A use or product according to Claim 8 in which compound (i) is administered at a dosage of 200-800mg per unit dose.

10. A twin-container pack for use in treating or preventing inflammatory conditions or for analgesia, one of the containers containing (i) and the other containing (ii) as defined in the preceding claims.

11. A composition according to Claim 5 or Claim 6 or a pack according to Claim 10, in association with instructions for the use of both (i) and (ii) in treating or preventing inflammatory conditions or for analgesia.

12. A method for the preparation of a composition according to Claim 5 or Claim 6 which comprises admixing (i) and (ii) together, if desired, with suitable carriers or excipients.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 20 3674

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y	GB-A-2 105 193 (GLAXO GROUP LIMITED) * abstract * ---	1-12	A61K31/34 A61K31/54 A61K31/415
Y	EP-A-0 426 479 (MCNEIL-PPC, INC.) * abstract; claims 1-3 * ---	1-12	A61K31/40 A61K31/405 A61K31/62
Y,D	GB-A-2 220 937 (GLAXO GROUP LIMITED) * abstract * -----	1-12	A61K31/645 //(A61K31/645,31:34)(A61K31/54,31:34)(A61K31/415,31/34)(A61K31/405,31:34)(A61K31/40,31:34)(A61K31/34,31:24)(A61K31/34,31:195)(A61K31/34,31:19)

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	11 MARCH 1993	LEHERTE C.F.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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EPO FORM 1503 03.82 (P0401)

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 020 461 A2

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
19.07.2000 Bulletin 2000/29

(51) Int. Cl.[7]: **C07D 401/12**, A61K 31/44

(21) Application number: **00108480.5**

(22) Date of filing: **27.05.1994**

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
SI

(30) Priority: **28.05.1993 SE 9301830**

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
94917244.9 / 0 652 872

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Remarks:
This application was filed on 18 - 04 - 2000 as a divisional application to the application mentioned under INID code 62.

(54) Use of alkaline salts of the (-)-enantiomer of omeprazole

(57) The use of an alkaline salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical preparation having improved pharmacokinetic and metabolic properties, such as improved therapeutic profile when treating gastric acid related diseases.

EP 1 020 461 A2

Description

Field of the invention

[0001] The present invention is directed to new compounds with high optical purity, their use in medicine, a process for their preparation and their use in the manufacture of pharmaceutical preparation. The invention also relates to novel intermediates in the preparation of the compounds of the invention.

Background of the invention

[0002] The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable alkaline salts thereof are described in EP 5129 and EP 124 495, respectively. Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation. The present invention provides such compounds, which are novel salts of single enantiomers of omeprazole.

[0003] The separation of the enantiomers of omeprazole in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19 and in a preparative scale in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group, omeprazole is quite sensitive and the acid has to be quickly neutralized with a base to avoid degradation of the acid-sensitive compound. In the above mentioned application this is done by adding the reaction mixture containing concentrated sulfuric acid to a concentrated solution of NaOH. This is disadvantageous because there is a great risk of locally reaching pH values between 1-6, which would be devastating for the substance. Moreover, instantaneous neutralisation will create heat which will be difficult to handle in large scale production.

[0004] The present invention in a further aspect provides a novel method for preparing the novel compounds of the invention in large scale. This novel method can also be used in large scale to obtain single enantiomers of omeprazole in neutral form.

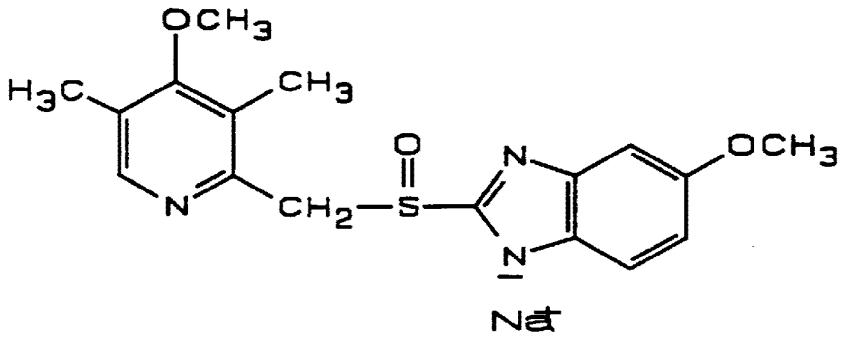
[0005] There is no example known in the prior art of any isolated or characterized salt of optically pure omeprazole, i.e. single enantiomers of omeprazole neither of any isolated or characterized salt of any optically pure omeprazole analogue.

Detailed description of the invention

[0006] The present invention refers to the new Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of the single enantiomers of omeprazole, where R is an alkyl with 1-4 carbon atoms, i.e. Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole, where R is an alkyl with 1-4 carbon atoms.

[0007] Particularly preferred salts according to the invention are the Na^+, Ca^{2+} and Mg^{2+} salts, i.e (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole magnesium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole calcium salt.

[0008] Most preferred salts according to the invention are the optically pure Na^+ salts of omeprazole according to compounds Ia and Ib

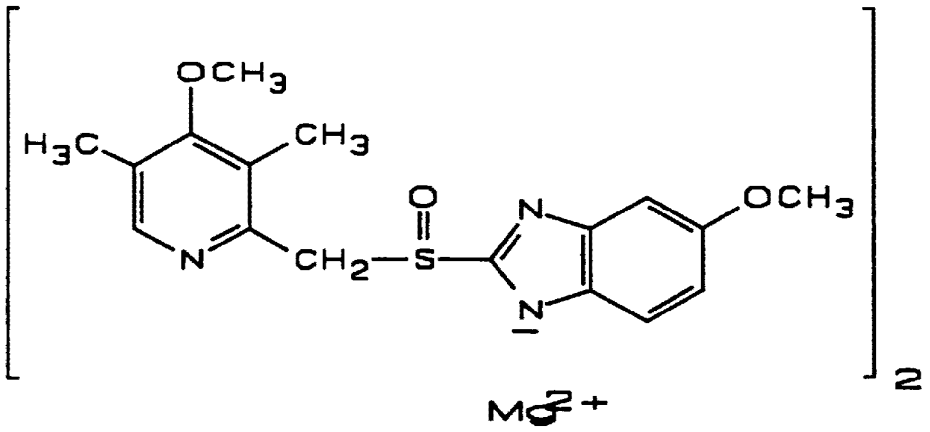


(Ia, Ib)

Ia (+)-enantiomer

Ib (-)-enantiomer

and the optically pure magnesium salts of omeprazole according to compounds IIa and IIb



(IIa, IIb)

IIa (+)-enantiomer

IIb (-)-enantiomer

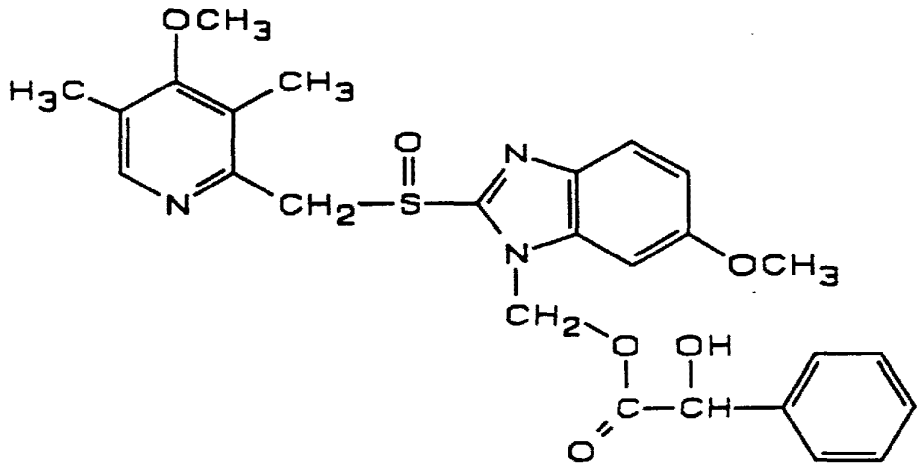
[0009] With the expression "optically pure Na^+ salts of omeprazole" is meant the (+)-enantiomer of omeprazole Na-salt essentially free of the (-)-enantiomer of omeprazole Na-salt and the (-)-enantiomer essentially free of the (+)-enantiomer, respectively. Single enantiomers of omeprazole have hitherto only been obtained as syrups and not as crystalline products. By means of the novel specific method according to one aspect of the invention of preparing the single enantiomers of omeprazole, the salts defined by the present invention are easy to obtain. In addition, the salts, however not the neutral forms, are obtained as crystalline products. Because it is possible to purify optically impure salts of the enantiomers of omeprazole by crystallisation, they can be obtained in very high optical purity, namely ≥99.8% enantiomeric excess (e.e.) even from an optically contaminated preparation. Moreover, the optically pure salts are stable towards racemization both in neutral pH and basic pH, which was surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulphur atom was expected to cause racemization under alkaline conditions. This high stability towards racemization makes it possible to use a single enantiomeric salt of the invention

in therapy.

[0010] The specific method of preparation of the single enantiomers of omeprazole is a further aspect of the invention as mentioned above and it can be used to obtain the single enantiomers of omeprazole in neutral from as well as the salts thereof.

[0011] The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with accute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.

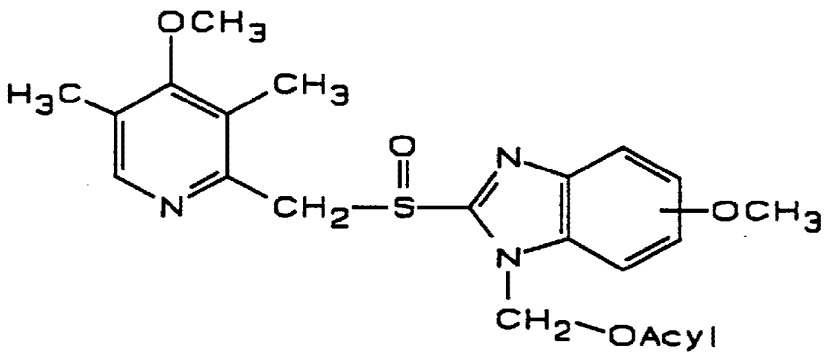
[0012] Yet a further aspect of the invention is the compound III, which is an intermediate used in the specific method of preparation.



(III)

Preparation

[0013] The optically pure compounds of the invention, i.e. the single enantiomers, are prepared by separating the two stereoisomers of a diastereomeric mixture of the following type, 5- or 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1-[acyloxymethyl]-1H-benzimidazole, formula IV



(IV)

wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6, and wherein the Acyl radical is as defined below, followed by a solvolysis of each separated diastereomer in an alkaline solution. The formed single enantiomers of omeprazole are then isolated by neutralizing aqueous solutions of the salts of the single enantiomers of omeprazole with a neutralizing agent which can be an acid or an ester such as methyl formate.

[0014] The Acyl moiety in the diastereomeric ester may be a chiral acyl group such as mandeloyl, and the asymmetric center in the chiral acyl group can have either R or S configuration.

[0015] The diastereomeric esters can be separated either by chromatography or fractional crystallization.

[0016] The solvolysis usually takes place together with a base in a protic solvent such as alcohols or water, but the acyl group may also be hydrolysed off by a base in an aprotic solvent such as dimethylsulfoxide or dimethylformamide. The reacting base may be OH^- or R^1O^- where R^1 can be any alkyl or aryl group.

[0017] To obtain the optically pure Na^+ salts of the invention, i.e. the single enantiomers of omeprazole Na^+ salts, the resulting compound is treated with a base, such as NaOH, in an aqueous or nonaqueous medium, or with $NaOR^2$ wherein R^2 is an alkyl group containing 1-4 carbon atoms, or with $NaNH_2$. Also alkaline salts wherein the cation is Li^+ or K^+ may be prepared using Lithium or potassium salts of the above mentioned bases. In order to obtain the crystalline form of the Na^+ salt, addition of NaOH in a non-aqueous medium such as a mixture of 2-butanone and toluene, is preferred.

[0018] To obtain the optically pure Mg^{2+} salts of the invention, optically pure Na^+ salts are treated with an aqueous solution of an inorganic magnesium salt such as $MgCl_2$, whereupon the Mg^{2+} salts are precipitated. The optically pure Mg^{2+} salts may also be prepared by treating single enantiomers of omeprazole with a base, such as $Mg(OR^3)_2$, wherein R^3 is an alkyl group containing 1-4 carbon atoms, in a non-aqueous solvent such as alcohol (only for alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran. In an analogous way, also alkaline salts wherein the cation is Ca^{2+} can be prepared, using an aqueous solution of an inorganic calcium salt such as $CaCl_2$.

[0019] Alkaline salts of the single enantiomers of the invention are, as mentioned above, beside the sodium salts (compounds Ia and Ib) and the magnesium salts (compound IIa and IIb), exemplified by their salts with Li^+, K^+, Ca^{2+} and $N^+R)_4$, where R is an alkyl with 1-4 C-atoms.

[0020] For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1-50% by weight in preparations for oral administration.

[0021] In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalysed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different amounts of the active

compound present.

[0022] Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above.

[0023] Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivates or gelatin. The capsules may be enteric-coated as described above.

[0024] Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

[0025] Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of dry powder to be reconstituted with a suitable solvent prior to use.

[0026] Solutions for parenteral administrations may be prepared as solutions of the optically pure compounds of the invention in pharmaceutically acceptable solvents, preferably in a concentration from 0.1 to 10% by weight These soultions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as dry preparations to be reconstituted with a suitable solvent extemporaneously before use.

[0027] The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

[0028] The invention is illustrated by the following examples.

Example 1. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

[0029] 100 mg (0.3 mmol) of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (+)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 µl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The tesultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 51 mg (46%) of the title compound as white crystals m.p. (decomposition) 246-248°C. The optical purity (e.e.) which was analyzed by chiral column chromatography was ≥99.8%. $[\alpha]_D^{20}$ = +42,80° (c=0.5%, water).

[0030] NMR data are given below.

Example 2. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

[0031] 100 mg (0.3 mmol) of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (-)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 µl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night The formed precipitate was filtered off and washed with ether. There was obtained 56 mg (51%) of the title compound as white crystals m.p. (decomposition) 247-249°C.

[0032] The optical purity (e.e.) which was analyzed by chiral column chromatography was ≥99.8%. $[a]_D^{20}$ = -44.1° (c=0.5%, water).

[0033] NMR data are given below.

Example 3. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

[0034] 2.9 ml of a 0.1 M solution of NaOH was added to 0.10 g (0.29 mmol) (+)-5-methoxy-2-[[(4-methoxy-3,5-

dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole. To this mixture 2 ml methylene chloride was added, and after mixing in a separatory funnel the aqueous solution was separated off A solution of 14 mg (0.145 mmol) $MgCl_2$ in water was added dropwise. The formed precipitate was isolated by centrifugation, and 52 mg (50%) of the product was isolated as an amorphous powder. The optical purity (e.e.) was 98%, and thus the same as the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$ = +101.2° (c=1%, methanol). The Mg content of the sample was found to be 3.0%, shown by atomic absorption spectroscopy.

Example 4. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

[0035] (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole sodium salt (0.500 g, 1.36 mmol) was dissolved in water (10 ml). To this mixture 10 ml of an aqueous solution of $MgCl_2xH_2O$ (138 mg, 0.68 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 418 mg (86%) of the product as a white powder. The optical purity (ee) of the product was 99.8% which was the same as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$ = +129.9° (c=1%, methanol).

Example 5. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

[0036] (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt (0.165 g, 0.45 mmol) was dissolved in water (3 ml). To this mixture 2 ml of an aqueous solution of $MgCl_2xH_2O$ (46 mg, 0.23 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 85 mg (51%) of the product as a white powder. The optical purity (ee) of the product was 99.9% which was the same or better as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$ = -128.2° (c=1%, methanol).

Table I

Ex.	Solvent	NMR data δ ppm
1.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.37 (d, 1H), 4.75 (d. 1H), 6.54 (dd. 1H), 6.96 (d, 1H) 7.30 (d, 1H), 8.21 (s, 1H).
2.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.38 (d, 1H), 4.73 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H), 7.31 (d, 1H), 8.21 (s, 1H).

[0037] Preparation of the synthetic intermediates according to the invention will be described in the following examples.

Example 6. Preparation of 6-methoxy-2-[[4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

[0038] A solution of 3.4 g sodium hydroxide in 40 ml water was added to a mixture of 14.4 g (42 mmol) tetrabutylammonium hydrogen sulphate and 6.4 g (42 mmol) (R)-(-)-mandelic acid. The mixture was extracted with 400 ml chloroform. After separation, the organic extract was heated to reflux with 16.6 g (42 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimerhyl-2-pyridinyl)methyl]-sulfinyl]-l-[chloromethyl]-1H-benzimidazole. Evaporation of the solvent was followed by dilution with 100 ml dichloromethane and 700 ml ethyl acetate. The mixture was washed with 3 x 200 ml water and the organic solution was dried over $MgSO_4$ and then evaporated. The crude material was purified by recrystallization from 100 ml acetonitrile, giving 8.1 g of the tide compound (38%) as a diastereomeric mixture.

[0039] NMR data are given below.

Example 7. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3.5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

[0040] The diastereomers of the tide compound in Example 6 were separated using reversed phase chromatography (HPLC). Approximately 300 mg of the diastereomeric mixture was dissolved in 10 ml hot acetonitrile which was diluted with 10 ml of a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The solution was injected

to the column and the compounds were eluted with a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The more hydrophilic isomer was easier to obtain pure than the less hydrophilic one. The work up procedure for the fraction which contained pure isomer was as follows; extraction with dichloromethane, washing the organic solution with aqueous 5 % sodium hydrogen carbonate solution, drying over Na_2SO_4 and evaporation of the solvent on a rotavapor (at the end of the evaporation the removal of acetonitrile was facilitated by adding more dichloromethane). Using 1.2 g of the diastereomeric mixture with the above mentioned technique, the more hydrophilic isomer, 410 mg, was obtained in a pure state as a colourless syrup.

[0041] NMR data are given below.

Example 8. Preparation of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

[0042] The product was obtained from 8.1 g (202 mmol) sodium hydroxide in 100 ml water, 34.4 g (101 mmol) tetrabutylammonium hydrogen sulfate, 15.4 g (101 mmol) (S)-(+)-mandelic acid and 39.9 g (101 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole using the same procedure as in Example 6. Recrystallization from 100 ml acetonitrile yielded 21.3 g, i.e. 41% of the title compound as a diastereomeric mixture.

[0043] NMR data are given below.

Example 9. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

[0044] The diastereomers of the title compound in Example 8 were separated using reversed phase chromatography (HPLC) in the same way as in Example 7, but using the diasteromeric mixture of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloloxymethyl]-1H-benzimidazole instead of the (R)-mandelic ester used in Example 7. Using 2.1 g of the diastereomeric mixture, the more hydrophilic isomer, 760 mg, was obtained in a pure state as a colourless syrup.

[0045] NMR data are given below.

Example 10. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

[0046] 0.23 g (0.45 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 15 ml methanol. A solution of 36 mg (0.9 mmol) sodium hydroxid in 0.45 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 15 ml water and 15 ml dichloromethane. The organic solution was extracted with 15 ml water and to the combined aqueous solutions was added 85 µl (1.4 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x10 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.12 g (77%) of the tide compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 94%. $[\alpha]_D^{20}$ = -155° (c=0.5%, chloroform).

[0047] NMR data are given below

Example 11. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

[0048] 0.76 g (1.5 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 50 ml methanol. A solution of 0.12 mg (3.0 mmol) sodium hydroxid in 1.5 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 25 ml water and 25 ml dichloromethane. The organic solution was extracted with 25 ml water and to the combined aqueous solutions was added 200 µl (3.2 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x25 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.42 g (81%) of the title compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 98%. $[\alpha]_D^{20}$ = +157° (c=0.5%, chloroform).

[0049] NMR data are given below

Table 2

Ex.	Solvent	NMR data δ ppm
6.	$CDCl_3$ 500 MHz	2.18 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.95-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
7.	$CHCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
8.	$CDCl_3$ 500 MHz	2.19 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.96-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
9.	$CDCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
10.	$CDCl_3$ 300 MHz	2.18, (s, 3H), 2.22 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 4.77 (m, 2H), 6.93 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b, 1H), 8.19 (s, 1H).
11.	$CDCl_3$	2.21 (s, 3H), 2.23 (s, 3H), 3.69 (s, 3H), 3.84 (s, 3H), 4.76 (m, 2H), 6.94 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b. 1H), 8.20 (s, 1H).

[0050] The best mode of carrying out the invention known at present is to use the sodium salts of the optically pure compounds of the invention, thus the compounds described in Example 1 and Example 2.

[0051] Pharmaceutical preparations containing the compounds of the invention as active ingredient are illustrated in the following formulations.

Syrup

[0052] A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

Compound according to Example 2	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	5.0 g
Flavouring agent	0.05 g
Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

[0053] Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Enteric-coated tablets

[0054] An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

I	Compound according to Example 3 as Mg salt	500 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Sodium carbonate	6 g
	Distilled water	q.s.
II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

I Compound according to Example 3, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcolhol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota^{R}, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Solution for intravenous administration

[0055] A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

Compound according to Example 2	4 g
Sterile water to a final volume of	1000 ml

[0056] The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a 0.22 µm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

Capsules

[0057] Capsules containing 30 mg of active compound were prepared from the following ingredients:

Compound according to Example 1	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g

(continued)

Disodium hydrogen phosphate	2 g
Purified water	q.s.

[0058] The active compound was mixed with the dry ingredients and granulated wit a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

[0059] 500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. After drying, the pellets were coated wit a second coating as given below:

[0060] Coating solution:

Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	4 g
Acetone	200 g
Ethanol	600 g

[0061] The final coated pellets were filled into capsules.

Suppositories

[0062] Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

Compound according to Example 2	4 g
Witepsol H-15	180 g

[0063] The active compound was homogenously mixed with Witepsol H- 15 at a temperature of 41° C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

Stability towards racemization at different pH:es

[0064] The stability of the optically pure compounds of the invention towards racemization has been measured at low concentrations in refrigerator in aqueous buffer solutions at pH 8, 9.3, 10 and 11.2. The stereochemical stability was measured by comparing the optical purity for the (-)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in buffer solution immediately after dissolving and after several days. The measurement was performed by chromatography on an analytical chiral column. The surprising high stereochemical stability in alkaline conditions for the compounds of invention is exemplified by the fact that no racemization for the test compound was obtained at pH 11.2 even after 21 days. At pH 8, 9.3 and 10, the chemical degradation of the compound is more apparent which makes the racemization measurement more difficult to perform, however at none of these pH values a detectable racemization was obtained after 16 days.

[0065] In another racemization experiment with the optically pure compounds of the invention, an aqueous phosphate buffer solution (pH=11) of the (+)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole ($c=10^{-5}$M) was warmed for 26 hours at 37°C without any racemization at all being observed.

[0066] The following pages 22 - 26 of the description relate to preferred embodiments of the invention, wherein "embt. / embts." means embodiment / embodiments.

1. Optically pure compounds **characterized** in that the compounds are Na^+, Mg^{2+}, Li^+, K^+ Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, wherein R is an alkyl with 1-4 carbon atoms.

2. Compounds according to embt. 1 **characterized** in that the compounds are (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole magnesium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole calcium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium Salt.

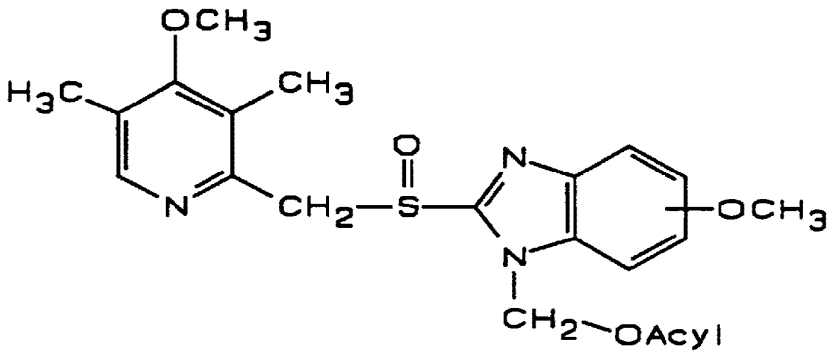
3. Compounds according to embts. 1 and 2 **characterized** in that the compounds are (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt.

4. Compounds according to embts. 1 and 2 **characterized** in that the compounds are (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole sodium salt in their crystalline forms.

5. Compounds according to embts. 1 and 2 **characterized** in that the compound is (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt in its crystalline form.

6. Compounds according to embts. 1 and 2 **characterized** in that the compound is (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimidazole sodium salt in its crystalline form.

7. Process for the preparation of a compound according to embt. 1 **characterized** in that a diastereomeric ester of formula IV



(IV)

wherein Acyl designates a chiral acyl group such as mandeloyl, having either R or S configuration, is separated, and each of the separated diastereomers is dissolved in an alkaline solution where the acyloxymethyl group is hydrolyzed to give the optically pure compound.

8. Process according to embt.7 **characterized** in that the diastereomers are separated by chromatography or fractional crystallization.

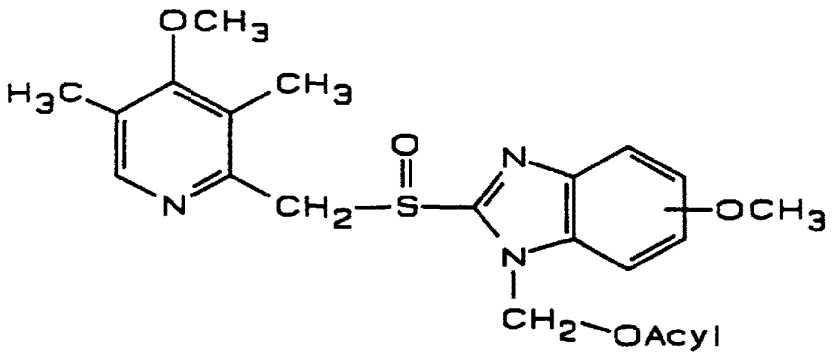
9. Process according to embt. 7 **characterized** in that the solvolysis is performed in alkaline solution consisting of a base in a protic solvent, such as alcohols or water; or a base in an aprotic solvent, such as dimethylsulfoxide or dimethylformamide.

10. Process for the preparation of a compound according to embt. 1 in crystalline form **characterized** in that a product from the process in embt. 7 is neutralized with a neutralizing agent which can be an acid or an ester such as methyl formate, followed by treatment with a base in non-aqueous solution.

11. Process for preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl-1H-benzimi-

dazole sodium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl-1H-benzimidazole sodium salt in their crystalline forms **characterized** in that (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl-1H-benzimidazole sodium salt crude product respectively is neutralized followed by treatment with NaOH in a non-aqueous medium.

12. Process for the preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole **characterized** in that a diastereomeric ester of formula IV



(IV)

wherein Acyl designates a chiral acyl group such as mandeloyl, having either R or S configuration, is separated, and each of the separated diastereomers is dissolved in an alkaline solution where the acyloxymethyl group is hydrolyzed off to give the optically pure compound after neutralization with a neutralizing agent which can be an acid or an ester.

13. Process according to embt. 12 **characterized** in that the diastereomers are separated by chromatography or fractional crystallization.

14. Process according to embt. 12 **characterized** in that the solvolysis is performed in alkaline solution consisting of a base in a protic solvent, such as alcohols or water; or a base in an aprotic solvent, such as dimethylsulfoxide or dimethylformamide.

15. The compound (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole obtained by the process defined in embt. 12.

16. The compound (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole obtained by the process defined in embt. 12.

17. Pharmaceutical preparation containing an optically pure compound according to any of embts. 1-6 as active ingredient.

18. Optically pure compounds according to any of embts. 1-6 for use in therapy.

19. Use of an optically pure compound according to any of embts. 1-6 in the preparation of a pharmaceutical formulation for inhibiting gastric acid secretion.

20. Use of an optically pure compound according to any of embts. 1-6 for the preparation of a pharmaceutical formulation for the treatment of gastrointestinal inflammatory diseases.

21. A method for inhibiting gastric acid secretion comprising administration to a mammal including man in need of such treatment an effective amount of an optically pure compound according to any of embts. 1-6.

22. A method for the treatment of gastrointestinal inflammatory diseases comprising administration to a mammal including man in need of such treatment an effective amount of an optically pure compound according to any of embts. 1-6.

23. The compound 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]-1 -[mandeloyloxymethyl]-1H-benzimidazole.

Claims

1. The use of an alkaline salt of the (-)-enantiomer of omeprazole for the manufacture of a pharmaceutical preparation having improved pharmacokinetic and metabolic properties.

2. The use of claim 1, wherein said improved pharmacokinetic and metabolic properties comprise an improved therapeutic profile when treating gastric acid related diseases.

3. The use of claim 1 or 2, wherein said improvement comprises a lower degree of interindividual variation in plasma levels.

4. The use of any of claims 1 to 3, wherein said alkaline salt is selected from the Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+}, and $N^+(R)_4$ salts, wherein R is an alkyl with 1-4 carbon atoms.

5. The use of claim 4, wherein said salt is selected from the Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 068 867 A2

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
17.01.2001 Bulletin 2001/03

(21) Application number: **00305965.6**

(22) Date of filing: **13.07.2000**

(51) Int Cl.[7]: **A61K 9/24**, A61K 31/5575, A61P 29/00 // (A61K31/5575, 31:196), (A61K31/5575, 31:5415)

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **14.07.1999 CA 2277407**

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(54) Pharmaceutical tablet comprising an NSAID and misoprostol

(57) A pharmaceutical tablet comprising a core and a film coating wherein the core comprises an NSAID and the film coating comprises a polymer and misoprostol.

EP 1 068 867 A2

Description

BACKGROUND OF THE INVENTION

[0001] The invention herein is directed to a pharmaceutical tablet which comprises both an NSAID and misoprostol.

[0002] Nonsteroidal anti-inflammatory drugs (NSAIDs) comprise a class of drugs which have therapeutic value especially for the treatment of inflammatory conditions such as exhibited in inflammatory diseases like osteoarthritis and rheumatoid arthritis. While the NSAIDs present a beneficial therapeutic value, they also exhibit an undesirable ulcerogenic effect generally associated with chronic use. NSAID induced ulcers in the stomach can be dangerous. Such ulcers generally exhibit few or no symptoms and may cause bleeding when undetected. In some instances, bleeding ulcers can prove fatal.

[0003] Certain prostaglandins have been shown to prevent NSAID induced ulcers. Misoprostol is a prostaglandin which has been accepted for use in the treatment of NSAID induced ulcers in many countries, including the United States.

[0004] It is desirable to provide a pharmaceutical composition which exhibits the beneficial properties of an NSAID and which also exhibits the beneficial properties of misoprostol for countering the ulcerogenic side effects attendant to NSAID administration.

[0005] This can be achieved by combining an NSAID and misoprostol in a single pharmaceutical tablet. However, this is not easy to do, because misoprostol is highly unstable, and it is thus desirable not to have the misoprostol and NSAID mixed together, so as to prevent any deleterious effect of the NSAID on the stability of the misoprostol.

[0006] One solution to this problem, which is disclosed in U.S. Patent 5601843, is to produce a composition in the form of a tablet comprising within it a smaller tablet. Such a composition is known in the art as a "compression coated" tablet or "mantle" tablet. The portion of the larger tablet (i.e. the whole composition) that surrounds the smaller inner or "core" tablet is known as the "mantle". In the compositions of U.S. patent 5601843, the misoprostol and NSAID are separated from each other by having the core tablet comprise the NSAID and the mantle comprise the misoprostol.

[0007] It is also disclosed that, in order to prevent contact between the misoprostol and the NSAID at the surface of the inner core, the inner core may be coated with an inert film coating. Such coating may be an enteric film coating, which also serves to reduce the likelihood of the NSAID dissolving in the stomach and thereby prevent exposing the stomach to the NSAID.

[0008] While the invention of U.S. Patent 5601843 accomplishes its objective of separating the NSAID from the misoprostol, it has certain disadvantages.

[0009] One disadvantage is that the process of making the mantle tablet is complicated, and the machinery needed is specialized and relatively expensive. In the process of manufacture of the mantle tablet, it is necessary to first make the smaller core tablet, which is done on a conventional tablet press, and then to use a compression coating press to make the final tablet. Such a press makes the final tablet much the same as a conventional tablet is made, but must have the added feature of being able to insert the core tablet along with the mantle powder mix into each die for compression into the final tablet.

[0010] Another disadvantage is that the final tablet must be substantially larger than the inner core tablet to have an adequate quantity of compressible mantle material completely surrounding the inner core. In the compositions of U.S. patent 5601843, the substantial mass of the mantle is in any event necessary to comprise the misoprostol. This is because misoprostol is unstable in pure form, and the only way known in the art to stabilize misoprostol is to process it into a dispersion comprising 1 part misoprostol in from about 50 to about 500 parts of a polymer, as disclosed in U.S. patent 4301146. The examples of U.S. patent 5601843 all use a dispersion of 1 part misoprostol in 100 parts hydroxypropyl methylcellulose ("HPMC"). Also this dispersion must be mixed with a binder, lubricant and other ingredients to make a mixture which can be compressed into the mantle. Thus it follows that the mass of the mantle must be large relative to the core.

[0011] In all nine examples of U.S. patent 5601843, the core tablet has a mass of 90 mg and the mantle has a mass of 265 mg. The nine examples differ from each other only in details of film coatings applied to the core tablet before it is inserted into the final tablet. Hence, in all nine examples, the total mass of the final tablet is at least 355 mg, despite the fact that the mass of the core tablet is only 90 mg.

[0012] The object of the present invention is to enable a pharmaceutical tablet that incorporates both an NSAID and misoprostol, but overcomes these disadvantages.

BRIEF SUMMARY OF THE INVENTION

[0013] The present invention is a pharmaceutical composition in the form of a tablet comprising a core and a film coating applied over the core, wherein the core comprises an NSAID and the film coating comprises misoprostol.

[0014] As aforesaid, the misoprostol must be stabilized by processing it into a dispersion in a polymer. However, a film coating also must comprise a polymer. The essence of the invention is to film-coat the core tablet with a coating comprised of both the misoprostol and a polymer, so that the polymer simultaneously serves the two purposes of stabilizing the misoprostol and forming a polymeric film coating around the core.

[0015] The procedure of applying the film coating

comprising misoprostol is to dissolve the misoprostol and polymer in solvent, optionally along with other ingredients such as plasticizers and surfactants, and to spray the solution onto the tablets in conventional tablet coating equipment. As the solvent is evaporated, the film coating comprising the misoprostol and polymer is formed around the tablet.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The NSAID contained within the core tablet will preferably be piroxicam, or diclofenac, or a salt of diclofenac, such as diclofenac sodium or diclofenac potassium. Most preferably, the NSAID will be diclofenac sodium.

[0017] Where diclofenac or a salt thereof is used, the amount per tablet will preferably be from about 25 to about 75 mg. The core tablet containing diclofenac or salt thereof will contain, along with the diclofenac or salt thereof, usual tablet excipients such as binders, lubricants, fillers and the like. Preferably, the tablet containing the diclofenac or salt thereof will be coated with an enteric film coating to prevent the diclofenac or salt thereof from dissolving until after it has passed through the stomach and entered the small intestine. The enteric coating can be formulated with any suitable enteric coating polymer, many of which are known to those skilled in the art.

[0018] Where piroxicam is used as the NSAID, the amount per tablet will preferably be from about 10 to about 20 mg. Again, the tablet containing piroxicam will also comprise usual tablet excipients.

[0019] It will be understood that the film coating comprising misoprostol may be sprayed directly on the core tablet containing the NSAID. Optionally, the core tablet may first be coated with an enteric film coating, and the film coating comprising the misoprostol applied as an overcoat.

[0020] Also optionally, the core tablet may first be coated with an enteric film coating and then overcoated with another inert film coating, and then overcoated again with the film coating comprising misoprostol.

[0021] Also optionally, another inert film coating may be applied on top of the film coating which comprises the misoprostol, in order to protect the misoprostol from the effects of light and air.

[0022] The polymer used in the film coating which comprises the misoprostol may be any water-soluble polymer which will form a film coating when sprayed onto a tablet and which will also stabilize misoprostol. The polymer will preferably be selected from povidone and water-soluble cellulose derivatives, and most preferably will be hydroxypropyl methylcellulose. The ratio of polymer to misoprostol by weight will preferably be from about 10 to about 100 parts polymer to 1 part misoprostol, and more preferably from about 15 to about 50 parts polymer to 1 part misoprostol.

[0023] The solvent system used to dissolve the misoprostol and polymer may be comprised of water or organic solvents and will preferably be a mixture of a chlorinated hydrocarbon and an alcohol, and most preferably be a mixture of methylene chloride and an alcohol. The solution will optionally also comprise other ingredients, such as a plasticizer or surfactant.

[0024] The invention will be further understood from the following example, which is intended to be illustrative and not limiting of the invention.

EXAMPLE 1

[0025] Core tablets are made with ingredients per tablet as follows:

	mg per tablet
diclofenac sodium	50.0
lactose (monohydrate)	13.0
microcrystalline cellulose	12.9
corn starch	8.4
povidone	4.8
magnesium stearate	0.9
	90.0

[0026] The process of production of these core tablets is to mix all of the ingredients except the magnesium stearate, granulate by adding water and mixing, dry the granules, add the magnesium stearate, mix again, and compress this final mixture into tablets on a tablet press.

[0027] These core tablets are then enteric coated by applying a coating with ingredients per tablet as follows:

	mg per tablet
cellulose acetate phthalate	5.4
diethyl phthalate	1.5
	6.9

[0028] The process of application of this film coating is to dissolve the cellulose acetate phthalate and the diethyl phthalate in acetone, and to spray the solution onto the tablets in a coating pan and evaporate the acetone.

[0029] These enteric film coated tablets are then overcoated with a film coating comprising hydroxypropyl methylcellulose, polyethylene glycol as plasticizer, and misoprostol, with the following ingredients per tablet:

	mg per tablet
hydroxypropyl methylcellulose	4.0
polyethylene glycol	0.2
misoprostol	0.2
	4.4

[0030] The process of application of this film coating is to dissolve the hydroxypropyl methylcellulose, poly-

ethylene glycol, and misoprostol in a mixture of methylene chloride and methanol, and to spray the solution onto the enteric coated tablets in a coating pan and evaporate the methylene chloride and methanol.

Claims

1. A pharmaceutical composition in the form of a tablet comprising a core and a film coating applied over the core, wherein the core comprises an NSAID and the film coating comprises a polymer and misoprostol.

2. A pharmaceutical composition as in claim 1 further comprising an enteric coating applied between the core and the film coating comprising a polymer and misoprostol.

3. A composition as in claim 1 or 2 wherein the NSAID is piroxicam or diclofenac or a salt thereof.

4. A composition as in claim 1 or 2 wherein the NSAID is diclofenac sodium.

5. A composition as in any of claims 1 to 4, wherein the polymer is povidone or a water-soluble cellulose derivative.

6. A composition as in any of claims 1 to 4, wherein the polymer is hydroxypropyl methylcellulose.

7. A composition as in any of claims 1 to 6 wherein the ratio of polymer to misoprostol by weight is from about 10 to about 100.

8. A composition as in any of claims 1 to 6 wherein the ratio of polymer to misoprostol by weight is from about 15 to about 50.

9. The process of making a composition according to any of claims 1 and 3 to 8 which comprises the steps of making the core tablet comprising the NSAID, and applying around the core a film coating comprising the polymer and misoprostol by dissolving the polymer and misoprostol in solvent, spraying the solution, and evaporating the solvent.

10. The process of making a composition according to any of claims 2 to 8 which comprises the steps of making the core tablet comprising the NSAID, applying an enteric coating around the core, and applying an overcoating around the enteric coating comprising the polymer and misoprostol by dissolving the polymer and misoprostol in solvent, spraying the solution, and evaporating the solvent.

11. A process of claim 9 or 10 wherein the solvent comprises a chlorinated hydrocarbon and an alcohol.

12. A process of claim 9 or 10 wherein the chlorinated hydrocarbon is methylene chloride.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 December 2002 (12.12.2002)

PCT

(10) International Publication Number
WO 02/098352 A2

(51) International Patent Classification[7]: A61K

(21) International Application Number: PCT/US02/17105

(22) International Filing Date: 31 May 2002 (31.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/294,588 1 June 2001 (01.06.2001) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/098352 A2

(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDs

(57) Abstract: The present invention is directed to drug dosage forms that release an agent that raises the pH of a patient's gastrointestinal tract, followed by a non-steroidal anti-inflammatory drug. The dosage form is designed so that the NSAID is not released until the intragastric pH has been raised to a safe level. The invention also encompasses methods of trating patients by administering this coordinated release, gastroprotective, antiarthitic/analgesic combination unit dosage form to achieve pain and symptom relief with a reduced risk of developing gastrointestinal damage such as ulcers, erosions and hemorrhages.

Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs

Field of the Invention

The present invention is directed to pharmaceutical compositions that provide for the coordinated release of an acid inhibitor and a non-steroidal anti-inflammatory drug (NSAID). These compositions have a reduced likelihood of causing unwanted side effects, especially gastrointestinal side effects, when administered as a treatment for pain, arthritis and other conditions amenable to treatment with NSAIDs.

Background of the Invention

Although non-steroidal anti-inflammatory drugs are widely accepted as effective agents for controlling pain, their administration can lead to the development of gastroduodenal lesions, *e.g.*, ulcers and erosions, in susceptible individuals. It appears that a major factor contributing to the development of these lesions is the presence of acid in the stomach and upper small intestine of patients. This view is supported by clinical studies demonstrating an improvement in NSAID tolerability when patients are also taking independent doses of acid inhibitors (*Dig. Dis. 12*:210-222 (1994); *Drug Safety 21*:503-512 (1999); *Aliment. Pharmacol. Ther. 12*:135-140 (1998); *Am. J. Med. 104(3A)*:67S-74S (1998); *Clin. Ther. 17*:1159-1173 (1995)). Other major factors contributing to NSAID-associated gastropathy include a local toxic effect of NSAIDs and inhibition of protective prostaglandins (*Can. J. Gastroenterol. 13*: 135-142 (1999) and *Pract. Drug Safety 21*:503-512, (1999)), which may also make some patients more susceptible to the ulcerogenic effects of other noxious stimuli.

In general, more potent and longer lasting acid inhibitors, such as proton pump inhibitors, are thought to be more protective during chronic administration of NSAIDs than shorter acting agents, *e.g.*, histamine H_2 receptor antagonists (H-2 blockers) (*N. Eng. J. Med. 338*:719-726 (1998); *Am. J. Med. 104(3A)*:56S-61S (1998)). The most likely explanation for this is that gastric pH fluctuates widely throughout the dosing interval with short acting acid inhibitors leaving the mucosa vulnerable for significant periods of time. In particular, the pH is at its lowest point, and hence the mucosa is most vulnerable, at the end of the dosing interval (least amount of acid inhibition) and for some time after the subsequent dose of acid

inhibitor. In general, it appears that when a short acting acid inhibitor and an NSAID are administered simultaneously, NSAID-related mucosal damage occurs before the pH of the gastrointestinal tract can be raised and after the acid inhibiting effect of the short acting acid inhibitor dissipates.

Although longer lasting agents, such as proton pump inhibitors (PPIs), usually maintain a consistently higher gastroduodenal pH throughout the day, after several days dosing, their antisecretory effect may be delayed for several hours and may not take full effect for several days (*Clin. Pharmacokinet. 20*:38-49 (1991)). Their effect may be diminished toward the end of the usual dosing interval. Intragastric pH rises particularly slowly with the first dose in a course of treatment since this class of drugs is enteric coated to avoid destruction by stomach acid. As a result, absorption is delayed for several hours. Even then, some patients fail to respond consistently to drugs of this type and suffer from "acid breakthrough" which again leaves them vulnerable to NSAID-associated gastroduodenaldamage (*Aliment. Pharmacol. Ther. 14*:709-714 (2000)). Despite a significant reduction in gastroduodenal lesions with the concomitant administration of a proton pump inhibitor during six months of NSAID therapy, up to 16% of patients still develop ulcers, indicating that there remains substantial room for improvement (*N. Eng. J. Med. 338*:727-734 (1998)). Thus, the addition of a pH sensitive enteric coating to an NSAID could provide additional protection against gastroduodenal damage not provided by the H2 blocker or PPI alone. In addition, although long acting acid inhibitors may reduce the risk of GI lesions in chronic NSAID users, there are questions about the safety of maintaining an abnormally elevated pH in a patient's GI tract for a prolonged period of time (*Scand. J. Gastroenterol. Suppl. 178*:85-92 (1990)).

Recognizing the potential benefits of PPIs for the prevention of NSAID-induced gastroduodenal damage, others have disclosed strategies for combining the two active agents for therapeutic purposes. However, these suggestions do not provide for coordinated drug release or for reducing intragastric acid levels to a non-toxic level prior to the release of NSAID (U.S. 5,204,118; U.S. 5,417,980; U.S. 5,466,436; and U.S. 5,037,815). In certain cases, suggested means of delivery would expose the gastrointestinal tract to NSAIDs prior to onset of PPI activity (U.S. 6,365,184).

Attempts to develop NSAIDs that are inherently less toxic to the gastrointestinal tract have met with only limited success. For example, the recently developed cyclooxygenase-2 (COX-2) inhibitors show a reduced tendency to produce gastrointestinal ulcers and erosions, but a significant risk is still present, especially if the patient is exposed to other ulcerogens (*JAMA 284*:1247-1255 (2000); *N. Eng. J. Med. 343*:1520-1528 (2000)). In this regard, it appears that even low doses of aspirin will negate most of the benefit relating to lower gastrointestinal lesions. In addition, the COX-2 inhibitors may not be as effective as other NSAIDs at relieving some types of pain and have been associated with significant cardiovascular problems (*JADA 131*:1729-1737 (2000); *SCRIP 2617*, pg. 19, Feb. 14, 2001); NY Times, May 22, 2001, pg. C1)).

Other attempts to produce an NSAID therapy with less gastrointestinal toxicity have involved the concomitant administration of a cytoprotective agent. In 1998, Searle began marketing Arthrotec™ for the treatment of arthritis in patients at risk for developing GI ulcers. This product contains misopristol (a cytoprotective prostaglandin) and the NSAID diclofenac. Although patients administered Arthrotec™ do have a lower risk of developing ulcers, they may experience a number of other serious side effects such as diarrhea, severe cramping and, in the case of pregnant women, potential damage to the fetus.

Another approach has been to produce enteric coated NSAID products. However, even though these have shown modest reductions in gastroduodenal damage in short term studies (*Scand. J. Gastroenterol. 20*: 239–242 (1985) and *Scand. J. Gastroenterol. 25*:231–234 (1990)), there is no consistent evidence of a long term benefit during chronic treatment.

Overall, it may be concluded that the risk of inducing GI ulcers is a recognized problem associated with the administration of NSAIDs and that, despite considerable effort, an ideal solution has not yet been found.

Summary of the Invention

The present invention is based upon the discovery of a new method for reducing the risk of gastrointestinal side effects in people taking NSAIDs for pain relief and for other conditions, particularly during chronic treatment. The method involves the administration of a single, coordinated, unit-dose product that combines: a) an agent that actively raises

intragastric pH to levels associated with less risk of NSAID-induced ulcers; and b) an NSAID that is specially formulated to be released in a coordinated way that minimizes the adverse effects of the NSAID on the gastroduodenal mucosa. Either short or long acting acid inhibitors can be effectively used in the dosage forms. This method has the added benefit of being able to protect patients from other gastrointestinal ulcerogens whose effect may otherwise be enhanced by the disruption of gastroprotective prostaglandins due to NSAID therapy.

In its first aspect, the invention is directed to a pharmaceutical composition in unit dosage form suitable for oral administration to a patient. The composition contains an acid inhibitor present in an amount effective to raise the gastric pH of a patient to at least 3.5, preferably to at least 4, and more preferably to at least 5, when one or more unit dosage forms are administered. The gastric pH should not exceed 7.5 and preferably should not exceed 7.0. The term "acid inhibitor" refers to agents that inhibit gastric acid secretion and increase gastric pH. In contrast to art teaching against the use of H2 blockers for the prevention of NSAID-associated ulcers (*N. Eng. J. Med. 340*: 1888–1899 (1999)), these agents are preferred compounds in the current invention. Specific, H2 blockers that may be used include cimetidine, ranitidine, ebrotidine, pabutidine, lafutidine, loxtidine or famotidine. The most preferred acid inhibitor is famotidine present in dosage forms in an amount of between 5 mg and 100 mg. Other agents that may be effectively used include proton pump inhibitors such as omeprazole, esomeprazole, pantoprazole, lansoprazole or rabeprazole.

The pharmaceutical composition also contains a non-steroidal anti-inflammatory drug in an amount effective to reduce or eliminate pain or inflammation. The NSAID may be a COX-2 inhibitor such as celecoxib, rofecoxib, meloxicam, piroxicam, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337 or NS398. Alternatively, the NSAID may be aspirin, acetaminophen, ibuprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin, etodolac, indomethacin, ketorolac, lornoxicam, nabumetone, or diclofenac. The most preferred NSAID is naproxen in an amount of between 50 mg and 1500 mg, and more preferably, in an amount of between 200 mg and 600 mg. It will be understood that, for the purposes of the present invention, reference to an acid inhibitor, NSAID, or analgesic agent will include all of the common forms of these compounds and, in particular, their pharmaceutically acceptable salts. The amounts of NSAIDs which are therapeutically effective may be lower in the current

invention than otherwise found in practice due to potential positive kinetic interaction and NSAID absorption in the presence of an acid inhibitor.

The term "unit dosage form" as used herein refers to a single entity for drug administration. For example, a single tablet or capsule combining both an acid inhibitor and an NSAID would be a unit dosage form. A unit dosage form of the present invention preferably provides for coordinated drug release, in a way that elevates gastric pH and reduces the deleterious effects of the NSAID on the gastroduodenal mucosa, *i.e.*, the acid inhibitor is released first and the release of NSAID is delayed until after the pH in the GI tract has risen. In a preferred embodiment, the unit dosage form is a multilayer tablet, having an outer layer comprising the acid inhibitor and an inner core which comprises the NSAID. In the most preferred form, coordinated delivery is accomplished by having the inner core surrounded by a polymeric barrier coating that does not dissolve unless the surrounding medium is at a pH of at least 3.5, preferably at least 4 and more preferably, at least 5. Alternatively, a barrier coating may be employed which controls the release of NSAID by time, as opposed to pH, with the rate adjusted so that NSAID is not released until after the pH of the gastrointestinal tract has risen to at least 3.5, preferably at least 4, and more preferably at least 5. Thus, a time-release formulation may be used to prevent the gastric presence of NSAID until mucosal tissue is no longer exposed to the damage enhancing effect of very low pH.

The invention includes methods of treating a patient for pain, inflammation and/or other conditions by administering the pharmaceutical compositions described above. Although the method may be used for any condition in which an NSAID is effective, it is expected that it will be particularly useful in patients with osteoarthritis or rheumatoid arthritis. Other conditions that may be treated include, but are not limited to: all form of headache, including migraine headache; acute musculoskeletal pain; ankylosing spondylitis; dysmenorrhoea; myalgias; and neuralgias.

In a more general sense, the invention includes methods of treating pain, inflammation and/or other conditions by orally administering an acid inhibitor at a dose effective to raise a patient's gastric pH to at least 3.5, preferably to at least 4 or and more preferably to at least 5. The patient is also administered an NSAID, for example in a

coordinated dosage form, that has been coated in a polymer that only dissolves at a pH of least 3.5, preferably at least 4 and, more preferably, 5 or greater or which dissolves at a rate that is slow enough to prevent NSAID release until after the pH has been raised. When acid inhibitor and NSAID are administered in separate doses, *e.g.*, in two separate tablets, they should be given concomitantly (*i.e.*, so that their biological effects overlap) and may be given concurrently, *i.e.*, NSAID is given within one hour after the acid inhibitor. Preferably, the acid inhibitor is an H2 blocker and, in the most preferred embodiment, it is famotidine at a dosage of between 5 mg and 100 mg. Any of the NSAIDs described above may be used in the method but naproxen at a dosage of between 200 and 600 mg is most preferred. It is expected that the inhibitor and analgesic will be typically delivered as part of a single unit dosage form which provides for the coordinated release of therapeutic agents. The most preferred dosage form is a multilayer tablet having an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

The invention also provides a method for increasing compliance in a patient requiring frequent daily dosing of NSAIDs by providing both an acid inhibitor and NSAID in a single convenient, preferably coordinated, unit dosage form, thereby reducing the number of individual doses to be administered during any given period.

Brief Description of the Drawings

Figure 1 is a schematic diagram of a four layer tablet dosage form. There is a naproxen core layer surrounded by a barrier layer. A third, enteric coating, layer delays the release of naproxen sodium until the pH is at a specific level, *e.g.*, above 4. Finally, there is an outer layer that releases an acid inhibitor such as famotidine.

Figure 2 illustrates a three layer dosage form. An acid inhibitor, *e.g.*, famotidine, is released immediately after ingestion by a patient in order to raise the pH of the gastrointestinal tract to above a specific pH, *e.g.*, above 4. The innermost layer contains naproxen. Thus, the dosage form has a naproxen core, an enteric film coat and an acid inhibitor film coat.

Figure 3 illustrates a naproxen sodium pellet which contains a subcoat or barrier coat prior to the enteric film coat.

Detailed Description of the Invention

The present invention is based upon the discovery of improved pharmaceutical compositions for administering NSAIDs to patients. In addition to containing one or more NSAIDs, the compositions include acid inhibitors that are capable of raising the pH of the GI tract of patients. All of the dosage forms are designed for oral delivery and provide for the coordinated release of therapeutic agents, *i.e.*, for the sequential release of acid inhibitor followed by analgesic.

The NSAIDs used in preparations may be either short or long acting. As used herein, the term "long acting" refers to an NSAID having a pharmacokinetic half-life of at least 2 hours, preferably at least 4 hours and more preferably, at least 8-14 hours. In general, its duration of action will equal or exceed about 6-8 hours. Examples of long-acting NSAIDs are: flurbiprofen with a half-life of about 6 hours; ketoprofen with a half-life of about 2 to 4 hours; naproxen or naproxen sodium with half-lives of about 12 to 15 hours and about 12 to 13 hours respectively; oxaprozin with a half life of about 42 to 50 hours; etodolac with a half-life of about 7 hours; indomethacin with a half life of about 4 to 6 hours; ketorolac with a half-life of up to about 8-9 hours, nabumetone with a half-life of about 22 to 30 hours; mefenamic acid with a half-life of up to about 4 hours; and piroxicam with a half-life of about 4 to 6 hours. If an NSAID does not naturally have a half-life sufficient to be long acting, it can, if desired, be made long acting by the way in which it is formulated. For example, NSAIDs such as acetaminophen and aspirin may be formulated in a manner to increase their half-life or duration of action. Methods for making appropriate formulations are well known in the art (see *e.g.* Remington's Pharmaceutical Sciences, 16th ed., A. Oslo editor, Easton, PA (1980)).

It is expected that a skilled pharmacologist may adjust the amount of drug in a pharmaceutical composition or administered to a patient based upon standard techniques well known in the art. Nevertheless, the following general guidelines are provided:

Indomethacin is particularly useful when contained in tablets or capsules in an amount from about 25 to 75 mg. A typical daily oral dosage of indomethacin is three 25 mg doses taken at intervals during the day. However, daily dosages of up to about 150 mg are useful in some patients.

Aspirin will typically be present in tablets or capsules in an amount of between about 250 mg and 1000 mg. Typical daily dosages will be in an amount ranging from 500 mg to about 10 g.

Ibuprofen may be provided in tablets or capsules of 50, 100, 200, 300, 400, 600, or 800 mg. Daily doses should not exceed 3200 mg. 200 mg - 800 mg may be particularly useful when given 3 or 4 times daily.

Flurbiprofen is useful when in tablets at about from 50 to 100 mg. Daily doses of about 100 to 500 mg, and particularly from about 200 to 300 mg, are usually effective.

Ketoprofen is useful when contained in tablets or capsules in an amount of about 25 to 75 mg. Daily doses of from 100 to 500 mg and particularly of about 100 to 300 mg are typical as is about 25 to 50 mg every six to eight hours.

Naproxen is particularly useful when contained in tablets or capsules in an amount of from 250 to 500 mg. For naproxen sodium, tablets of about 275 or about 550 mg are typically used. Initial doses of from 100 to 1250 mg, and particularly 350 to 800 mg are also used, with doses of about 550 mg being generally preferred.

Oxaprozin may be used in tablets or capsules in the range of roughly 200 mg to 1200 mg, with about 600 mg being preferred. Daily doses of 1200 mg have been found to be particularly useful and daily doses should not exceed 1800 mg or 26 mg/kg.

Etodolac is useful when provided in capsules of 200 mg to 300 mg or in tablets of about 400 mg. Useful doses for acute pain are 200-400 mg every six-eight hours, not to exceed 1200 mg/day. Patients weighing less than 60 kg are advised not to exceed doses of 20 mg/kg. Doses for other uses are also limited to 1200 mg/day in divided doses, particularly 2, 3 or 4 times daily.

Ketorolac is usefully provided in tablets of 1-50 mg, with about 10 mg being typical. Oral doses of up to 40 mg, and particularly 10-30 mg/day have been useful in the alleviation of pain.

Nabumetone may be provided in tablets or capsules of between 500 mg and 750 mg. Daily doses of 1500-2000 mg, after an initial dose of 100 mg, are of particular use.

Mefenamic acid is particularly useful when contained in tablets or capsules of 50 mg to 500 mg, with 250 mg being typical. For acute pain, an initial dosage of 1-1000 mg, and particularly about 500 mg, is useful, although other doses may be required for certain patients.

Lornoxicam is provided in tablets of 4 mg or 8 mg. Useful doses for acute pain are 8 mg or 16 mg daily, and for arthritis are 12 mg daily.

One particular group of long acting NSAIDs that may be used are the cyclooxygenase-2 inhibitors. These include: celecoxib, rofecoxib, meloxicam, piroxicam, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337, or NS398. JTE-522, L-745,337 and NS398 as described, *inter alia*, in Wakatani, *et al.* (*Jpn. J. Pharmacol. 78*:365-371 (1998)) and Panara, *et al.* (*Br. J. Pharmacol. 116*:2429-2434 (1995)). The amount present in a tablet or administered to a patient will depend upon the particular COX-2 inhibitor being used. For example:

Celecoxib may be administered in a tablet or capsule containing from about 100 mg to about 500 mg or, preferably, from about 100 mg to about 200 mg.

Piroxicam may be used in tablets or capsules containing from about 10 to 20 mg.

Rofecoxib will typically be provided in tablets or capsules in an amount of 12.5, 25 or 50 mg. The recommended initial daily dosage for the management of acute pain is 50 mg.

Meloxicam is provided in tablets of 7.5 mg, with a recommended daily dose of 7.5 or 15 mg for the management of osteoarthritis.

Valdecoxib is provided in tablets of 10 or 20 mg, with a recommended daily dose of 10 mg for arthritis or 40 mg for dysmenorrhea.

With respect to acid inhibitors, tablets or capsules may contain anywhere from 1 mg to as much as 1g. Typical amounts for H2 blockers are: cimetidine, 100 to 800 mg/unit dose; ranitidine, 50-300 mg/unit dose; famotidine, 5-100 mg/unit dose; ebrotidine 400 – 800 mg/unit dose; pabutidine 40 mg/unit dose; lafutidine 5–20 mg/unit dose; and nizatidine, 50-600 mg/unit dose. Proton pump inhibitors will typically be present at about 5 mg to 600 mg per unit dose. For example, the proton pump inhibitor omeprazole should be present in tablets or capsules in an amount from 5 to 50 mg, with about 20 mg per unit dosage form being preferred. Other typical amounts are: esomeprazole, 5–100 mg, with about 40 mg per unit dosage form being preferred; lansoprazole, 15-150 mg, with about 30 mg per unit dosage form being preferred; pantoprazole, 10-200 mg, with about 40 mg per unit dosage form being preferred; and rabeprazole, 5-100 mg, with about 20 mg per unit dosage form being preferred.

Making of Pharmaceutical Preparations

The pharmaceutical compositions of the invention include tablets, dragees, liquids and capsules and can be made in accordance with methods that are standard in the art (see, *e.g.*, Remington's Pharmaceutical Sciences, 16th ed., A Oslo editor, Easton, Pa. (1980)). Drugs and drug combinations will typically be prepared in admixture with conventional excipients. Suitable carriers include, but are not limited to: water; salt solutions; alcohols; gum arabic; vegetable oils; benzyl alcohols; polyethylene glycols; gelatin; carbohydrates such as lactose, amylose or starch; magnesium stearate; talc; silicic acid; paraffin; perfume oil; fatty acid esters; hydroxymethylcellulose; polyvinyl pyrrolidone; etc. The pharmaceutical preparations can be sterilized and, if desired, mixed with auxiliary agents such as: lubricants, preservatives, disintegrants; stabilizers; wetting agents; emulsifiers; salts; buffers; coloring agents; flavoring agents; or aromatic substances.

Enteric coating layer(s) may be applied onto the core or onto the barrier layer of the core using standard coating techniques. The enteric coating materials may be dissolved or dispersed in organic or aqueous solvents and may include one or more of the following materials: methacrylic acid copolymers, shellac, hydroxypropylmethcellulose phthalate, polyvinyl acetate phthalate, hydroxypropylmethylcellulose trimellitate, carboxymethylethyl-cellulose, cellulose acetate phthalate or other suitable enteric coating polymer(s). The pH at which the enteric coat will dissolve can be controlled by the polymer or combination of polymers selected and/or ratio of pendant groups. For example, dissolution characteristics of the polymer film can be altered by the ratio of free carboxyl groups to ester groups. Enteric coating layers also contain pharmaceutically acceptable plasticizers such as triethyl citrate, dibutyl phthalate, triacetin, polyethylene glycols, polysorbates or other plasticizers. Additives such as dispersants, colorants, anti-adhering and anti-foaming agents may also be included.

The Making of Tablet Dosage Forms

Preferably, the combination of an acid inhibitor and an NSAID will be in the form of a bi- or multi-layer tablet. In a bilayer configuration, one portion of the tablet contains the acid inhibitor in the required dose along with appropriate excipients, agents to aid dissolution, lubricants, fillers, etc. The second portion of the tablet will contain the NSAID, preferably naproxen, in the required dose along with other excipients, dissolution agents, lubricants, fillers, etc. In the most preferred embodiment, the NSAID layer is surrounded by a polymeric coating which does not dissolve at a pH of less than 4. The naproxen may be granulated by methods such as slugging, low- or high- shear granulation, wet granulation, or fluidized-bed granulation. Of these processes, slugging generally produces tablets of less hardness and greater friability. Low-shear granulation, high-shear granulation, wet granulation and fluidized-bed granulation generally produce harder, less friable tablets.

Examples

Example 1: Enteric Coated Naproxen Sodium Core and Famotidine Immediate Release

A schematic diagram of a four layer tablet dosage form is shown in Figure 1. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, PA). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above about 4 or 5. The enteric coating does not dissolve in areas of the GI tract where the pH may be below about 4 or 5 such as in an unprotected stomach. Methacrylic acid copolymers are used as the enteric coating ingredient, triethyl citrate and dibutyl phthalate are plasticisers, and ammonium hydroxide is used to adjust the pH of the dispersion. The coating dissolves only when the local pH is above, for example, 5.5 and, as a result, naproxen sodium is released.

The outermost layer contains an "acid inhibitor" in an effective amount which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably the H2 blocker famotidine, which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of famotidine in the dosage form will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Clear® YS-1-7006 which helps in the formation of the film and in uniformly distributing famotidine within the fourth layer without tablets sticking to the coating pan or to each other during application of the film coat. Other ingredients may include: plasticisers such as triethyl citrate, dibutyl phthalate, and polyethylene glycol; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	% W/W	mg/Tablet
Naproxen sodium, USP	74.074	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.166	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Barrier Film Coating Ingredients	% W/W
Opadry Clear® YS-1-7006	5.00
Purified water USP	95.00
Total	100.00

Enteric Coating Dispersion

Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L-100-55)	7.30
Methacrylic Acid Copolymer, NF (Eudragit L-100)	7.30
Triethyl Citrate, NF	2.95
Dibutyl Phthalate, NF	1.17
Ammonium Hydroxide (30%), NF	0.87
Purified water, USP	80.41
Total	100.00

Famotidine Coating Dispersion

Ingredients	% W/W
Famotidine, USP	3.0
Opadry Clear® (YS-1-7006)	5.0
Talc, USP	3.0

Purified Water, USP	89.0
Total	100.0

Example 2: Enteric Coated Naproxen Core and Famotidine Immediate Release

Figure 2 illustrates a three layered dosage form which releases famotidine immediately after ingestion by the patient in order to raise the pH of the gastrointestinal tract to above about 4. The innermost layer contains naproxen uniformly distributed throughout a matrix of pharmaceutically acceptable excipients. These excipients perform specific functions and may serve as binders, disintegrants, or lubricants. A pharmaceutically acceptable enteric coating surrounds the naproxen core. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the harshly acidic pH of the unprotected stomach. It contains methacrylic acid copolymers which prevent the release of naproxen in the unprotected stomach. Also included are: triethyl citrate, a plasticiser; simethicone emulsion, an anti-foaming agent; and sodium hydroxide which is used to adjust the pH of the dispersion.

The outermost layer contains an "acid inhibitor" in an effective amount which is released from the dosage form immediately after administration to the patient. The acid inhibitor in this example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which raises the pH of the stomach to above 4. A typical film coating formulation contains Opadry Clear® YS-1-7006 which helps in the formation of the film and in uniformly distributing famotidine in the fourth layer without tablets sticking to the coating pan or sticking to each other during application of the film coat. Other ingredients are: plasticisers such as polyethylene glycol 8000; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate;, and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	**% W/W**	**mg /Tablet**
Naproxen, USP	90.91	500.00
Povidone K-90, USP	2.00	11.00
Starch, USP	2.59	14.25

Croscarmellose Sodium, USP	4.00	22.00
Magnesium Stearate, NF	0.50	2.75
Total	100.00	550.00
Purified Water, USP qs		

Enteric Coating Dispersion Ingredients	**% W/W**
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5
Talc, USP	3.8
Sodium Hydroxide, NF	0.2
Triethyl Citrate, NF	1.7
Simethicone Emulsion, USP	0.02
Purified Water, USP	79.78
Total	100.00

Famotidine Coating Dispersion Ingredients	**% W/W**
Famotidine, USP	3.0
Opadry Clear® (YS-1-7006)	5.0
Talc, USP	3.0
Purified Water, USP	89.0
Total	100.0

Example 3: Naproxen Controlled Release Core and Famotidine Immediate Release

A trilayer tablet which separates famotidine contained in the film coat from controlled-release naproxen may be used in the present invention. The core tablet of naproxen is formulated using excipients which control the drug release for therapeutic relief from pain and inflammation for 24 hours. Figure 2 shows an example of an appropriate trilayer tablet. In this particular example, naproxen is mixed with a polymeric material, hydroxypropyl-methylcellulose and granulated with water. The granules are dried, milled, and blended with a lubricant, such as magnesium stearate. They are then compacted into tablets.

The controlled-release core tablet of naproxen is film coated with a pharmaceutically acceptable enteric coating. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the extremely acidic pH of the unprotected stomach. The function of methacrylic acid copolymers is to prevent the release of naproxen until the pH of the stomach rises. Triethyl citrate is a plasticiser, simethicone emulsion is a anti-foaming agent, and sodium hydroxide is used to adjust the pH of the dispersion.

The outermost layer contains an "acid inhibitor" which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which consistently raises the pH of the stomach to above 4. The typical effective amount of famotidine in the dosage will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Blue® YS-1-4215 which is essential for film formation and for the uniform application of famotidine to the core tablet. Polymer film coating ingredients, hydroxypropylmethylcellulose or Opaspray® K-1-4210A (Colorcon, West Point, PA) may also be used. Other ingredients which help in the formation of the film and in the uniform application of famotidine to the core tablet are: plasticisers such as triethyl citrate and dibutyl phthalate; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	**% W/W**	**mg/Tablet**
Naproxen, USP	94.00	750
Hydroxypropyl methylcellulose 2208, USP (viscosity 15000 cps)	5.00	39.9
Magnesium Stearate, NF	1.00	7.95
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Total	100.00	797.85

Enteric Coating Dispersion Ingredients	% W/W
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5
Talc, USP	3.8
Sodium Hydroxide, NF	0.2
Triethyl Citrate, NF	1.7
Simethicone Emulsion, USP	0.02
Purified Water, USP	79.78
Total	100.00

Famotidine Coating Dispersion Ingredients	% W/W
Famotidine, USP	2.0
Opadry Blue® (YS-1-4215)	10.0
Talc, USP	9.0
Purified Water, USP	79.0
Total	100.0

Example 4: Naproxen and Famotidine Controlled Release Core and Famotidine Immediate Release

A trilayer tablet which separates famotidine contained in the film coat from controlled-release naproxen and famotidine may be used in the present invention. The core tablet of naproxen and famotidine is formulated using excipients which control the drug release for therapeutic relief from pain and inflammation for 24 hours. Figure 2 is an example of an appropriate trilayer tablet. In this particular example, naproxen and famotidine are mixed with a polymeric material, hydroxypropylmethylcellulose and granulated with water. The granules are dried, milled, and blended with a lubricant, such as magnesium stearate. They are then compacted into tablets.

The controlled-release core tablet of naproxen and famotidine is film coated with a pharmaceutically acceptable enteric coating. The function of the enteric coat is to delay the release of naproxen until the dosage form reaches an environment where the pH is above about 4. The coating does not dissolve in the extrememly acidic pH of the unprotected stomach. The function of methacrylic acid copolymers is to prevent the release of naproxen

in the pH of the stomach rises. Triethyl citrate is a plasticiser, simethicone emulsion is a anti-foaming agent, and sodium hydroxide is used to adjust the pH of the dispersion.

The outermost later contains an "acid inhibitor" which is released from the dosage form immediately after administration to the patient. The acid inhibitor in the present example is a proton pump inhibitor or, preferably, the H2 blocker famotidine which consistently raises the pH of the stomach to above 4. The typical effective amount of famotidine in the dosage will vary from 5 mg to 100 mg. A typical film coating formulation contains Opadry Blue® YS-1-4215 which is essential for film formation and for the uniform application of famotidine to the core tablet. Polymer film coating ingredients, hydroxypropylmethylcellulose or Opaspray® K-1-4210A (Colorcon, West Point, PA) may also be used. Other ingredients which help in the formation of the film and in the uniform application of famotidine to the core tablet are: plasticisers such as triethyl citrate and dibutyl phthalate; anti-adhering agents such as talc; lubricating ingredients such as magnesium stearate; and opacifiers such as titanium dioxide. In addition, the pH of the film coating solution can be adjusted to aid in dissolution of the famotidine. The film coating is thin and rapidly releases famotidine for absorption.

Core Tablet Ingredients	**% W/W**	**mg/Tablet**
Naproxen, USP	88.05	500
Famotidine, USP	3.52	20.0
Hydroxypropyl methylcellulose 2208, USP (viscosity 15000 cps)	7.03	39.9
Magnesium Stearate, NF	1.40	7.95
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Total	100.00	567.85

Enteric Coating Dispersion Ingredients	**% W/W**
Methacrylic Acid Copolymer Type C, NF (Eudragit L-100-55)	14.5
Talc, USP	3.8
Sodium Hydroxide, NF	0.2
Triethyl Citrate, NF	1.7
Simethicone Emulsion, USP	0.02

Purified Water, USP	79.78
Total	100.00

Famotidine Coating Dispersion Ingredients	**% W/W**
Famotidine, USP	2.0
Opadry Blue® (YS-1-4215)	10.0
Talc, USP	9.0
Purified Water, USP	79.0
Total	100.0

Example 5: Enteric Coated Naproxen Sodium Core and Pantoprazole Immediate Release in Film Coat

A schematic diagram of a four layer tablet dosage form is shown in Figure 1. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, PA). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The third layer is an enteric film coat. It does not dissolve in areas of the GI tract where the pH may be below 4 such as in an unprotected stomach but it dissolves only when the local pH is above about 4. Therefore, the function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above 4. In this example, hydroxypropylmethylcellulose phthalate is the enteric coating ingredient, cetyl alcohol is a plasticiser and acetone and alcohol are solvents.

The fourth layer contains an "acid inhibitor" in an effective amount which is released from the dosage form as soon as the film coat dissolves. The acid inhibitor in this example is

a proton pump inhibitor, pantoprazole which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of pantoprazole in the dosage form may vary from 10 mg to 200 mg. The film coat is applied by conventional pan coating technology and the weight of film coat may vary from 4% to 8% of the core tablet weight. Other ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide, and ammonium hydroxide to adjust the pH of the dispersion. The film coating is thin and rapidly releases pantoprazole for absorption. Therefore, pantoprazole releases first and then the core erodes and releases naproxen sodium.

Core Tablet Ingredients	**% W/W**	**mg/tablet**
Naproxen sodium, USP	74.075	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.165	115.87
Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Naproxen sodium, 50% microcrystalline cellulose and povidone are dry mixed and wet granulated in an appropriate granulator with sufficient purified water. The wet granules are dried, milled, and blended with the remaining 50% microcrystalline cellulose, talc and magnesium stearate. The final granule blend is compressed into tablets.

Barrier Film Coating Ingredients	**%W/W**
Opadry® Clear YS-1-7006	5.00
Purified Water, USP	95.00
Total	100.00

Opadry clear is added slowly to purified water and mixing is continued until Opadry is fully dispersed. The solution is sprayed on to the tablet cores in a conventional coating pan until proper amount of Opadry clear is deposited on the tablets.

Enteric Coating Ingredients	**%W/W**
Hydroxypropyl methylcellulose phthalate, NF	5.5
Cetyl alcohol, NF	0.3
Acetone, NF	66.3
Alcohol, USP	27.9
Total	100.00

Hydroxypropylmethylcellulose phthalate and cetyl alcohol are dissolved in a mixture of alcohol and acetone. The solution is then sprayed on to the tablet bed in proper coating equipment. A sample of the tablets is tested for gastric resistance and the coating stopped if the tablets pass the test.

Pantoprazole Film Coating Ingredients	**%W/W**
Pantoprazole sodium, USP	5.00
Opadry® Clear YS-1-7006	5.00
Sodium carbonate, NF	1.20
Purified Water, USP	88.80
Total	100.00

Pantoprazole sodium is dissolved in purified water containing sodium carbonate in solution. After thorough mixing, Opadry clear is added slowly and mixing is continued until Opadry is fully dispersed. The suspension is sprayed on to the tablet cores in a conventional coating pan until the proper amount of pantoprazole sodium is deposited.

Example 6: Enteric Coated Naproxen Sodium Core and Omeprazole Immediate Release in Film Coat

A schematic diagram of a four layer tablet dosage form is shown in Figure 1. The first layer contains naproxen sodium distributed throughout a matrix of pharmaceutically acceptable fillers, excipients, binding agents, disintegrants, and lubricants.

The second layer is a barrier layer which protects the first layer containing naproxen sodium. The barrier film coat is applied by conventional pan coating technology and the weight of the barrier coat may vary from 1% to 3% of the core tablet weight. In particular embodiments, the core naproxen sodium tablet is coated with coating ingredients such as Opaspray® K-1-4210A or Opadry® YS-1-7006 (Colorcon, West Point, PA). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a coating suspension may also be used.

The third layer is an enteric film coat. It does not dissolve in areas of the GI tract where the pH is below 4 such as in an unprotected stomach but it dissolves only when the local pH is above 4. Therefore, the function of the third layer is to prevent the release of naproxen sodium until the dosage form reaches an environment where the pH is above about 4. In this example, hydroxypropylmethylcellulose phthalate is the enteric coating ingredient, cetyl alcohol is a plasticiser and acetone and alcohol are solvents.

The fourth layer contains an "acid inhibitor" in an effective amount which is released from the dosage form as soon as the film coat dissolves. The acid inhibitor in this example is a proton pump inhibitor, omeprazole, which raises the pH of the gastrointestinal tract to above 4. The typical effective amount of omeprazole in the dosage form may vary from 5 mg to 50 mg. The film coat is applied by conventional pan coating technology and the weight of film coat may vary from 4% to 8% of the core tablet weight. Other ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide, and ammonium hydroxide to adjust the pH of the dispersion. The film coating is thin and rapidly releases omeprazole for absorption. Therefore, omeprazole is released first and then the core erodes and releases naproxen sodium.

Core Tablet Ingredients	**% W/W**	**mg/tablet**
Naproxen sodium, USP	74.075	500.00
Microcrystalline cellulose, NF (Avicel PH 200)	17.165	115.87

Povidone (K29/32), USP	3.450	23.29
Talc, USP	4.350	29.36
Magnesium Stearate, NF	0.960	6.48
Total	100.00	675.00

Naproxen sodium, 50% microcrystalline cellulose and povidone are dry mixed and wet granulated in an appropriate granulator with sufficient purified water. The wet granules are dried, milled, and blended with the remaining 50% microcrystalline cellulose, talc and magnesium stearate. The final granule blend is compressed into tablets.

Barrier Film Coating Ingredients	**%W/W**
Opadry® Clear YS-1-7006	5.00
Purified Water, USP	95.00
Total	100.00

Opadry clear is added slowly to purified water and mixing is continued until Opadry is fully dispersed. The solution is sprayed on to the tablet cores in a conventional coating pan until the proper amount of Opadry clear is deposited on the tablets.

Enteric Coating Ingredients	**%W/W**
Methacrylic Acid Copolymer, NF (Eudragit L-100-55)	6.0
Triethyl Citrate, NF	0.6
Talc, USP	3.0
Purified Water, USP	5.0
Isopropyl Alcohol, USP	85.40
Total	100.00

Methacrylic acid copolymer, triethyl citrate, and talc are dissolved in a mixture of isopropyl alcohol and water. The solution is then sprayed on to the tablet bed in a proper coating equipment. A sample of the tablets is tested for gastric resistance and the coating is stopped if the tablets pass the test.

Omeprazole Film Coating Ingredients	%W/W
Omeprazole, USP	5.00
Opadry® Clear YS-1-7006	5.00
Purified Water, USP	10.00
Isopropyl Alcohol, USP	80.00
Total	100.00

Omeprazole is dissolved in a purified water and isopropyl alcohol mixture. After thorough mixing, Opadry clear is added slowly and mixing is continued until Opadry is fully dispersed. The suspension is sprayed on to the tablet cores in a conventional coating pan until proper amount of omeprazole is deposited on the tablets.

Example 7: Naproxen Sodium Delayed Release and Omeprazole Immediate Release Capsule

A coordinated delivery dosage may be used to provide fast release of an acid inhibitor, a proton pump inhibitor, omeprazole which raises the pH of the gastrointestinal tract to above 4, and the delayed release of a non-steroidal anti-inflammatory drug, naproxen sodium. Omeprazole granules modify the pH of the stomach such that the drug readily dissolves and is absorbed in the stomach without significant degradation. The typical effective amount of omeprazole in the dosage form may vary from 5 mg to 50 mg. The release of naproxen sodium is delayed by enteric coating.

Omeprazole granules contain an alkalizing excipient such as sodium bicarbonate. Other soluble alkalizing agents such as potassium bicarbonate, sodium carbonate, sodium hydroxide, or their combinations may also be used. The alkalizing agent helps solubilize and protect omeprazole from degradation before its absorption. Sodium lauryl sulfate helps in the wetting of omeprazole. Other surfactants may be used to perform the same function. In the present example, hydroxypropyl methylcellulose helps in granule formation, sodium starch glycolate is a disintegrant, and magnesium stearate is a lubricant. Other excipients may also be used to perform these functions.

Naproxen sodium pellets as shown in Figure 3 are prepared by the wet massing technique and the conventional extrusion and spheronization process. The excipients used in the formulation are microcrystalline cellulose, and povidone. The pellets after drying and

classification are coated with a protective subcoating containing povidone. Other coating ingredients may also be used such as Opaspray K-1-4210A or Opadry YS-1-7006 (trademarks of Colorcon, West Point, PA). Polymer film coating ingredients such as hydroxypropylmethylcellulose 2910 and polyethylene glycol 8000 in a subcoating suspension are also alternatives. Other ingredients are, plasticisers such as triethyl citrate, dibutyl phthalate, anti-adhering agents such as talc, lubricating ingredients such as magnesium stearate, opacifiers such as, titanium dioxide.

The subcoated pellets are enteric coated using enteric coating polymers. In this example, the enteric coating polymer is methacrylic acid copolymer and the plasticizer is dibutyl phthalate which are dissolved in a mixture of acetone and alcohol. The enteric film does not dissolve in the acidic pH but dissolves when the pH in the gut is above about pH 6 and releases naproxen sodium.

Omeprazole Granules	**% W/W**	**mg/capsule**
Omeprazole, USP	12.9	20.00
Sodium Bicarbonate, USP	82.40	127.72
Hydroxypropyl methylcellulose, USP	2.00	3.10
Sodium lauryl sulfate, NF	0.20	0.31
Sodium starch glycolate, NF	2.00	3.10
Magnesium stearate, NF	0.50	0.77
Total	100	100

Hydroxypropylmethylcellulose is dissolved in water, then sodium lauryl sulfate is added and the solution is mixed. Omeprazole, microcrystalline cellulose, and sodium bicarbonate are dry mixed together and granulated with the granulating solution. The granulation is mixed until proper granule formation is reached. The granulation is then dried, milled, and blended with magnesium stearate.

Pellet Ingredients	% W/W	mg/tablet
Naproxen sodium, USP	86.80	250.00
Microcrystalline cellulose, NF (Avicel PH 200)	11.10	32.00
Povidone (K90), USP	2.10	6.00
Total	100.00	288.00

Povidone is dissolved in water. Naproxen sodium and microcrystalline cellulose are dry mixed and granulated with povidone solution. The wet mass is mixed until proper consistency is reached. The wet mass is then pressed through an extruder and spheronized to form pellets. The pellets are then dried and classified into suitable particle size range.

Subcoat Ingredients	% W/W
Povidone (K29-32), USP	10.00
Alcohol, USP	90.00
Total	100.00

The pellet cores are coated using povidone solution by a conventional coating pan method to a weight gain of 1-2%.

Enteric Coating Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L-100)	8.20
Diethyl Phthalate, NF	1.70
Acetone, NF	33.30
Isopropyl Alcohol, USP	56.80
Total	100.0

Eudragit L-100 is dissolved in isopropanol and acetone and diethyl phthalate is dissolved. The solution is sprayed on the pellet cores using proper film coating equipment. A sample of the pellets is tested for gastric resistance before stopping the coating process.

Omeprazole fast release granules and naproxen sodium delayed release pellets are blended together and filled into appropriate size capsules to contain 250 mg naproxen sodium and 20 mg omeprazole per capsule.

Example 8: Naproxen Delayed Release and Omeprazole Immediate Release Capsule

The present Example is directed to a coordinated delivery dosage form containing omeprazole and naproxen. The formulation contains 10 mg omeprazole and uses methylcellulose as a binder and croscarmellose sodium as a disintegrant. Naproxen pellets as shown in Figure 3 do not need a subcoating layer and are enteric coated with an aqueous dispersion of methacrylic acid copolymer. Optionally, these pellets could be compressed into a core and film coated with an acid inhibitor and thereby form a bilayer tablet.

Omeprazole Granules	**% W/W**	**mg/capsule**
Omeprazole, USP	6.45	10.00
Sodium Bicarbonate, USP	88.85	137.71
Methylcellulose, USP	2.00	3.10
Sodium lauryl sulfate, NF	0.20	0.31
Croscarmellose sodium, NF	2.00	3.10
Magnesium stearate, NF	0.50	0.78
Total	100	100

Methylcellulose is dissolved in water, then sodium lauryl sulfate is added to the solution and mixed. Omeprazole, microcrystalline cellulose, and sodium bicarbonate are dry mixed together and granulated with the granulating solution. The granulation is mixed until proper granule formation is reached. The granulation is then dried, milled, and blended with magnesium stearate.

Pellet Ingredients	% W/W	mg/tablet
Naproxen, USP	76.22	250.00
Microcrystalline cellulose, NF (Avicel PH 200)	21.78	71.44
Povidone (K90), USP	2.00	6.56
Total	100.00	328.00

Povidone is dissolved in water. Naproxen and microcrystalline cellulose are dry mixed and granulated with povidone solution. The wet mass is mixed until proper consistency is reached. The wet mass is then pressed through an extruder and spheronized to form pellets. The pellets are then dried and classified into a suitable particle size range.

Enteric Coating Ingredients	% W/W
Methacrylic Acid Copolymer, NF (Eudragit L30D 30% dispersion)	15.60
Talc, USP	7.60
Triethyl citrate, NF	1.60
Simethicone Emulsion, USP (Silicone antifoam emulsion SE 2)	0.20
Purified Water, USP	74.80

Eudragit 30D is dispersed in purified water and simethicone emulsion. Talc and triethyl citrate are then dispersed. The suspension is sprayed on the pellet cores using proper film coating equipment. A sample of the pellets is tested for gastric resistance before stopping the coating process. Omeprazole fast release granules and naproxen sodium delayed release pellets are blended together and filled into appropriate size capsules to contain 250 mg naproxen and 10 mg omeprazole per capsule.

Example 9: Clinical Study of the Relationship of Gastric pH to NSAID-induced Gastric Ulcers

Sixty-two subjects were enrolled in a clinical study and randomly assigned to three groups. The following three groups were administered study medication twice daily for five

days: (a) 550 mg naproxen sodium (n=10), (b) 40 mg famotidine given with 550 mg of naproxen or famotidine followed 90 minutes later by 550 mg naproxen, (n=39) or (c) 20 mg omeprazole followed by 550 mg naproxen sodium (n=13). Gastric pH was measured hourly beginning at the time of dosing of the final daily dose of study medication and for 8 – 10 hours thereafter. Subjects had a gastric endoscopy performed at the beginning and on Day 5 prior to the morning dose of study medication to identify gastric and duodenal irritation; no subjects were admitted to the study if gastric irritation was present at the time of initial endoscopy.

Five patients, three (33%) in the naproxen alone group and two (5%) in the famotidine/naproxen group, presented with gastroduodenal ulcers at the end of the study. In the naproxen alone group, the pH was greater than 4 only 4% of the time, and in the famotidine/naproxen group the pH was greater than 4 forty-nine percent of the time during the 8 – 10 hours following naproxen sodium dosing. Additionally, Lanza grade 3 or 4 damage was present in 28% (n=11) of the subjects receiving famotidine/naproxen sodium, and present 100% (n=10) in the naproxen sodium treatment group. Monitoring of gastric acidity on day 5 indicated that patients with Lanza scores of greater than 2 had integrated gastric acidity of greater than 100 mmol-hr./L. Only 20 – 40% of patients with integrated gastric acidity of less than 100 mmol-hr/L had gastric pathology, whereas all patients with integrated gastric acidity greater than 100 mmol-hr/L had pathology.

Example 10. Famotidine and Enteric Coated Naproxen Reduce Gastroduodenal Damage Due to NSAID Therapy

Forty patients are randomized to two groups for a one week study of twice-daily dosing of: 500mg enteric coated naproxen, and 500mg enteric coated naproxen preceded by 40mg famotidine. Endoscopies are conducted on all patients prior to first dosing and on the final day of the study. No subjects have any evidence of gastroduodenal damage at the beginning of the study (at first endoscopy).

At the second endoscopy, Lanza scores for gastroduodenal damage are assessed for all subjects. Subjects in the enteric coated naproxen 500mg group have a lower incidence of grade 3-4 gastroduodenal damage than subjects previously treated with non-enteric coated naproxen 500mg. Importantly, subjects administered 500mg enteric coated naproxen and

40mg famotidine have substantially lower incidence of grade 3 – 4 gastroduodenal damage than subjects who had previously taken naproxen alone (either naked or enteric coated) which demonstrates the need for and the value of combining acid inhibition with enteric coating to minimize the gastrointestinal damage of NSAID.

5

What is Claimed is:

1. A pharmaceutical composition in unit dose form suitable for oral administration to a patient, comprising:

(a) an acid inhibitor present in an amount effective to raise the gastric pH of said patient to at least 3.5 upon the administration of one or more of said unit dosage forms;

(b) a non-steroidal anti-inflammatory drug (NSAID) in an amount effective to reduce or eliminate pain or inflammation in said patient upon administration of one or more of said unit dosage forms;

and wherein said unit dosage form provides for the coordinated release of said acid inhibitor followed by said NSAID.

2. The pharmaceutical composition of claim 1, wherein said acid inhibitor is selected from: a proton pump inhibitor and an H2 blocker.

3. The pharmaceutical composition of claim 2, wherein said acid inhibitor is an H2 blocker selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

4. The pharmaceutical composition of claim 3, wherein said H2 blocker is famotidine, present in said unit dosage form in an amount of between 5 mg and 100 mg.

5. The pharmaceutical composition of claim 1, wherein said acid inhibitor is a proton pump inhibitor selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole.

6. The pharmaceutical composition of claim 5, wherein said proton pump inhibitor is pantoprazole, present in said unit dosage form in an amount of between 10 mg and 200 mg.

7. The pharmaceutical composition of claim 1, wherein said NSAID is a cyclooxygenese-2 (COX-2) inhibitor.

8. The pharmaceutical composition of claim 7, wherein said COX-2 inhibitor is selected from the group consisting of celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

9. The pharmaceutical composition of claim 1, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

10. The pharmaceutical composition of claim 9, wherein said NSAID is naproxen present in an amount of between 50 mg and 1500 mg.

11. The pharmaceutical composition of claim 10, wherein said naproxen is present in an amount of between 200 mg and 600 mg.

12. The pharmaceutical composition of claim 1, wherein said unit dosage form is a multilayer tablet.

13. The pharmaceutical composition of claim 12, wherein said unit dosage form is a trilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID.

14. The pharmaceutical composition of claim 12, wherein said unit dosage form is a bilayer tablet having an outer layer of said acid inhibitor and an inner core of said NSAID.

15. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of the surrounding medium is 3.5 or greater.

16. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of the surrounding medium is 4 or greater.

17. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that does not dissolve unless the pH of the surrounding medium is 5 or greater.

18. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 3.5 or greater.

19. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not released until the pH of the surrounding medium is 4 or greater.

20. The pharmaceutical composition of any one of claims 12-14, wherein said tablet has an inner core of said NSAID surrounded by a barrier coating that dissolves at a rate such that said NSAID is not not released until the pH of the surrounding medium is 5 or greater.

21. The phamaceutical composition of claim 1, wherein said unit dosage form is a capsule.

22. A method of treating a patient for pain or inflammation, comprising administering to said patient the pharmaceutical composition of any one of claims 1-14.

23. The method of claim 22, wherein said patient is treated for either osteoarthritis or rheumatoid arthritis.

24. A method of treating a patient for pain or inflammation, comprising:

(a) orally administering to said patient an acid inhibitor at a dose effective to raise the gastric pH of said patient to at least 3.5; and

(b) orally administering to said patient an NSAID that is coated in a polymer that only dissolves at a pH of 3.5 or greater.

25. The method of claim 24, wherein said acid inhibitor is an H2 blocker.

26. The method of claim 25, wherein said H-2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

27. The method of claim 26, wherein said H2 blocker is famotidine administered at a dose of between 5 mg and 100 mg.

28. The method of claim 24, wherein said acid inhibitor is a proton pump inhibitor.

29. The method of claim 28, wherein said proton pump inhibitor is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole.

30. The method of claim 29, wherein said proton pump inhibitor is pantoprazole administered at a dose of between10 mg and 200 mg.

31. The method of any one of claims 24 - 30, wherein said NSAID is a COX-2 inhibitor selected from the group consisting of: celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

32. The method of any one of claims 24 – 30, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

33. The method of claim 32, wherein said NSAID is naproxen administered at a dose of between 50 mg and 1500 mg.

34. The method of claim 33, wherein said naproxen is administered at a dose of between 200 mg and 600 mg.

35. The method of claim 24, wherein said acid inhibitor and said NSAID are delivered as part of a single dosage form providing for the coordinated release of therapeutic agents.

36. The method of claim 35, wherein said single dosage form is a bilayer tablet with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

37. A method of treating a patient for pain or inflammation, comprising:

(a) orally administering to said patient an acid inhibitor at a dose effective to raise the gastric pH of said patient to at least 3.5; and

(b) concurrently administering to said patient an NSAID that is coated in a polymer that dissolves at a rate such that said NSAID is not released until said gastric pH is at 3.5 or higher.

38. The method of claim 37, wherein said acid inhibitor is an H2 blocker.

39. The method of claim 38, wherein said H-2 blocker is selected from the group consisting of: cimetidine; ranitidine; ebrotidine; pabutidine; lafutidine; loxtidine and famotidine.

40. The method of claim 39, wherein said H2 blocker is famotidine administered at a dose of between 5 mg and 100 mg.

41. The method of claim 37, wherein said acid inhibitor is a proton pump inhibitor.

42. The method of claim 41, wherein said proton pump inhibitor is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, rabeprazole and pantoprazole.

43. The method of claim 42, wherein said proton pump inhibitor is pantoprazole administered at a dose of between 10 mg and 200 mg.

44. The method of any one of claims 37 - 43, wherein said NSAID is a COX-2 inhibitor selected from the group consisting of: celecoxib; rofecoxib; meloxicam; piroxicam; valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522; L-745,337; and NS398.

45. The method of any one of claims 37 – 43, wherein said NSAID is selected from the group consisting of: aspirin; acetaminophen; ibuprofen; flurbiprofen; ketoprofen; lornoxicam; naproxen; oxaprozin; etodolac; indomethacin; ketorolac; and nabumetone.

46. The method of claim 45, wherein said NSAID is naproxen administered at a dose of between 50 mg and 1500 mg.

47. The method of claim 46, wherein said naproxen is administered at a dose of between 200 mg and 600 mg.

48. The method of claim 47, wherein said acid inhibitor and said NSAID are delivered as part of a single dosage form providing for the coordinated release of therapeutic agents.

49. The method of claim 48, wherein said single dosage form is a bilayer tablet with an outer layer comprising an H2 blocker and an inner core comprising an NSAID.

50. A method of improving compliance in patients requiring frequent daily dosages of an acid inhibitor and an NSAID comprising administering said dosages in a coordinated unit dosage form in accordance with claim 1.

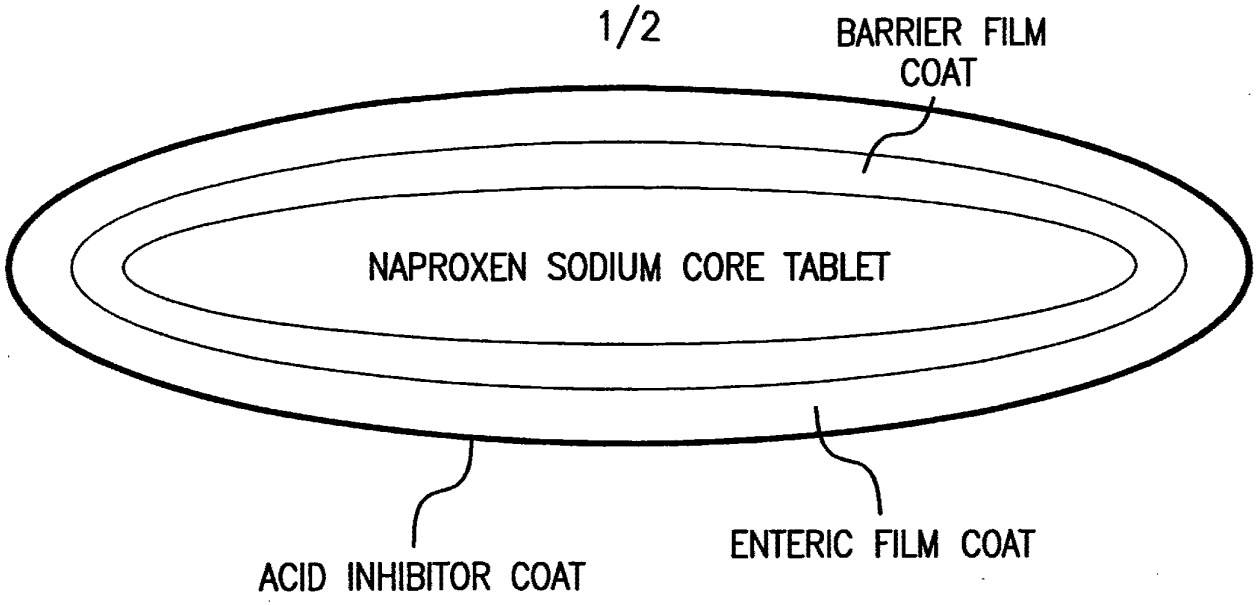
BARRIER FILM COAT
NAPROXEN SODIUM CORE TABLET
ACID INHIBITOR COAT
ENTERIC FILM COAT

FIG.1

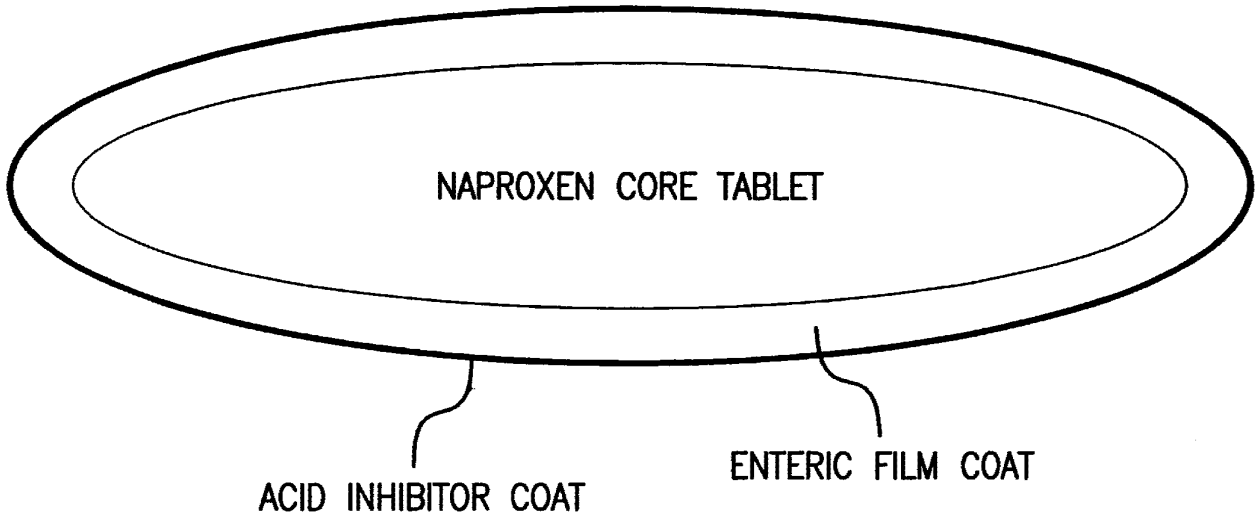
NAPROXEN CORE TABLET
ACID INHIBITOR COAT
ENTERIC FILM COAT

FIG.2

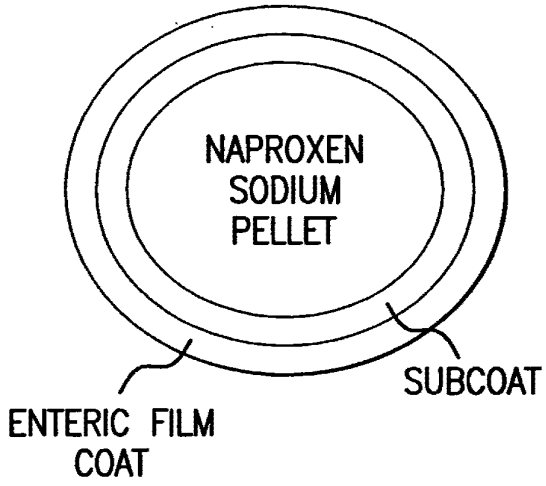

FIG.3

PATENT COOPERATION TREATY

ADVANCE E-MAIL

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.1(c))

To:

ANDREW, Mcaleavey
Law Office Of Michael A. Sanzo, Llc
15400 Calhoun Drive
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ETATS-UNIS D'AMERIQUE

Date of mailing *(day month year)* 09 December 2010 (09.12.2010)	
Applicant's or agent's file reference 7569/20700PC	IMPORTANT NOTICE

International application No.	International filing date *(day month year)*	Priority date *(day month year)*
PCT/US2009/003281	29 May 2009 (29.05.2009)	30 May 2008 (30.05.2008)

Applicant
POZEN INC. et al

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 7569/20700PC	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2009/003281	International filing date *(day/month/year)* 29 May 2009 (29.05.2009)	Priority date *(day/month/year)* 30 May 2008 (30.05.2008)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant POZEN INC.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 30 November 2010 (30.11.2010)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Nora Lindner e-mail: pt11.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	14 JUL 2009
Applicant's or agent's file reference 7569/20700PC	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 09/03281	29 May 2009 (29.05.2009)	30 May 2008 (30.05.2008)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 9/48; A01N 43/40 (2009.01)
USPC - 514/452; 514/338

Applicant POZEN INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	6 July 2009 (06.07.2009)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 09/03281

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 09/03281

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	17-29	YES
	Claims	1-16, 20	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-20	NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-16 and 20 lack novelty under PCT Article 33(2) as being anticipated by US 2008/0103169 A1 to Phillips.

As per claim 1, Phillips discloses a pharmaceutical composition in unit dosage form for oral administration to a patient (para [0230], [0235]) comprising: a therapeutically effective amount of a proton pump inhibitor (ppi) (para [0016]), and a therapeutically effective amount of an H2 blocker (para [0022], [0057]-[0058]), wherein:
a) at least 10% of both said ppi and said H2 blocker are released from said dosage form into the stomach of said patient within fifteen minutes after ingestion (para [0124]-[0127], [0350]) and/or at least 1 mg of said ppi and said H2 blocker are released from said dosage form into the stomach of said patient within fifteen minutes after ingestion (para [0124]-[0127], [0350]);
b) at least a portion of both said ppi and said H2 blocker are not surrounded by an enteric coating (para [0122], [0350]);
c) said dosage form contains no more than 15 mg of buffer (para [0125], [0161], [0187], e.g., ppi amount 1 mg, total buffer being sodium hydroxide with molecular weight of 40 g/mol and valence of 1 and at 0.1 mEq/mg of ppi, thus buffer amount = (1 mg).(0.1 mEq/mg) (40 g/mol)/1 = 4 mg).

As per claim 2, Phillips discloses after ingestion by a patient with a gastric pH of 2.5 or less (para [0275]-[0276]), said gastric pH rises to at least 3.5 within 45 minutes and remains at or above 3.5 for at least 6 hours (para [0029], [0435]; Fig 3).

As per claim 3, Phillips discloses said gastric pH rises to at least 3.5 within 30 minutes after ingestion and remains at or above 3.5 for at least 24 hours (para [0029]-[0030], [0435]-[0438]; Fig 3-4).

As per claim 4, Phillips discloses none of the ppi and none of the H2 blocker in said dosage form are surrounded by an enteric coating (para [0133], [0350]).

As per claim 5, Phillips discloses: a) at least 20% of both said ppi and said H2 blocker are released from said dosage form into the stomach of said patient within ten minutes after ingestion (para [0124]-[0127], [0350]); and
b) after ingestion by a patient with a gastric pH of 2.5 or less (para [0275]-[0276]), said gastric pH rises to at least 3.5 within 45 minutes and remains at or above 3.5 for at least 12 hours (para [0029]-[0030], [0435]-[0438]; Fig 3-4).

As per claim 6, Phillips discloses said gastric pH rises to at least 3.5 within 30 minutes after ingestion and remains at or above 3.5 for at least 24 hours (para [0029]-[0030], [0435]-[0438]; Fig 3-4).

As per claim 7, Phillips discloses: a) at least 5 mg of both said ppi and said H2 blocker are released from said dosage form into the stomach of said patient within five minutes after ingestion (para [0124]-[0127], [0350]); and
b) after ingestion by a patient with a gastric pH of 2.5 or less, said gastric pH rises to at least 3.5 within 45 minutes and remains at or above 3.5 for at least 16 hours (para [0029]-[0030], [0435]-[0438]; Fig 3-4).

As per claim 8, Phillips discloses said gastric pH rises to at least 3.5 within 30 minutes after ingestion and remains at or above 3.5 for at least 24 hours (para [0029]-[0030], [0435]-[0438]; Fig 3-4).

As per claim 9, Phillips discloses said ppi is present in said dosage form at 1-200 mg and is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, pantoprazole, tenatoprazole and rabeprazole (para [0074], [0125]).

As per claim 10, Phillips discloses said ppi is selected from the group consisting of: omeprazole, present in said dosage form at between 5 mg and 50 mg; esomeprazole, present in said dosage form at 5-100 mg; lansoprazole, present in said dosage form at 15-150 mg; pantoprazole, present in said dosage form at between 10 mg and 200 mg; and rabeprazole, present in said dosage form at between 5 mg and 100 mg (para [0074], [0125]).

As per claim 11, Phillips discloses said H2 blocker is present in said dosage form at 1-300 mg and is selected from the group consisting of: cimetidine; ranitidine; famotidine; ebrotidine; pabutidine; lafutidine; and nizatidine (para [0126]-[0127]).

As per claim 12, Phillips discloses said ppi is present in said dosage form at 1-200 mg and is selected from the group consisting of: omeprazole, esomeprazole, lansoprazole, pantoprazole, tenatoprazole and rabeprazole (para [0074], [0125]).

continued in Supplemental Box

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 09/03281

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:
Box No. V 2. Citations and explanations

As per claim 13, Phillips discloses said ppi is selected from the group consisting of: omeprazole, present in said dosage form at between 5 mg and 50 mg; esomeprazole, present in said dosage form at 5-100 mg; lansoprazole, present in said dosage form at 15-150 mg; pantoprazole, present in said dosage form at between 10 mg and 200 mg; and rabeprazole, present in said dosage form at between 5 mg and 100 mg (para [0074], [0125]).

As per claim 14, Phillips discloses a) said ppi is selected from the group consisting of: omeprazole, present in said dosage form at between 5 mg and 50 mg; esomeprazole, present in said dosage form at 5-100 mg; lansoprazole, present in said dosage form at 15-150 mg; pantoprazole, present in said dosage form at between 10 mg and 200 mg; and rabeprazole, present in said dosage form at between 5 mg and 100 mg (para [0074], [0125]); and
b) said H2 blocker is selected from the group consisting of: cimetidine present in said dosage form at 100 to 800 mg; ranitidine present in said dosage form at 50-300 mg; famotidine present in said dosage form at 5-100 mg; etrotidine present in said dosage form at 400 - 800 mg; pabutidine present in said dosage form at 40 mg; lafutidine present in said dosage form at 5-20 mg; and nizatidine present in said dosage form at 50-600 mg (para [0126]-[0127]).

As per claim 15, Phillips discloses said gastric pH rises to at least 3.5 within 30 minutes after ingestion and remains at or above 3.5 for at least 24 hours (para [0029]-[0030], [0435]-[0438]; Fig 3-4).

As per claim 16, Phillips discloses said dosage form is a tablet, capsule or powder and wherein said ppi and said H2 blocker are in admixture (para [0212], [0236]-[0238]).

As per claim 20, Phillips discloses a method of treating a patient for a disease or condition characterized by abnormal gastric acid production comprising administering to said patient the pharmaceutical composition of anyone of claims 1-19 (para [0060], [0275]-[0276]).

Claims 17-19 lack an inventive step under PCT Article 33(3) as being obvious over Phillips in view of US 2008/0031941 A1 to Pettersson.

As per claim 17, claim 1 is anticipated as above. Phillips discloses said dosage form is a tablet (para [0235]). Phillips does not disclose the limitation taught by Pettersson, namely essentially all of said ppi is in one layer and essentially all of said H2 blocker is in a separate layer (para [0035]). It would have been obvious to one skilled in the art to modify Phillips with Pettersson to obtain rapid onset of action and good long-term efficacy (para [0021]).

As per claim 18, claim 17 would have been obvious as above. Pettersson discloses the layer containing said ppi and/or the layer containing said H2 blocker also comprise at least one disintegrant (para [0037]) and/or a compound that causes effervescence (para [0034]).

As per claim 19, claim 17 would have been obvious as above. Pettersson discloses said dosage form comprises a disintegrant selected from the group consisting of: croscarmellose sodium, crospovidone, sodium starch glycolate, povidone, crosslinked polyvinylpyrrolidone, starch, low substituted hydroxymethylcellulose, methylcellulose, microcrystalline cellulose (para [0069]).

Claims 1-20 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used by industry.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
MICHAEL A. SANZO
LAW OFFICE OF MICHAEL A. SANZO, LLC
15400 CALHOUN DRIVE, SUITE 125
ROCKVILLE, MD 20855

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 30 AUG 2010
Applicant's or agent's file reference 7569/22925PC	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 10/39864	International filing date *(day/month/year)* 24 June 2010 (24.06.2010)
Applicant POZEN INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 338 8270

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 7569/22925PC	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/39864	International filing date *(day/month/year)* 24 June 2010 (24.06.2010)	(Earliest) Priority Date *(day/month/year)* 25 June 2009 (25.06.2009)
Applicant . POZEN INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 1

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/39864

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-10, 14-15 and 20
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/39864

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/40; A61K 31/44 (2010.01)
USPC - 514/338
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/338

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 546/272.7, 273.7, 274.4 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB,USPT,USOC,EPAB,JPAB); Google
Search Terms Used: omeprazole, aspirin, ulcer, unit dosage, gastric, pH, independent, risk, age

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2005/0249811 A1 (Plachetka) 10 November 2005 (10.11.2005) para [0011]-[0019], [0045], [0080]-[0100]	1-3, 11-13, 16-19
Y	US 2002/0160048 A1 (Robinson et al.) 31 October 2002 (31.10.2002) para [0003]-[0011], [0032]	1-3, 11-13, 16-19
Y	US 2004/0022846 A1 (Depui et al.) 05 February 2004 (05.02.2004) para [0007]-[0014]	3, 11
A	US 2007/0237820 A1 (Cheng et al.) 11 October 2007 (11.10.2007) entire disclosure	1
A	US 6,869,615 B2 (Chen et al.) 22 March 2005 (22.03.2005) entire disclosure	1

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 August 2010 (15.08.2010)	30 AUG 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: MICHAEL A. SANZO
LAW OFFICE OF MICHAEL A. SANZO, LLC
15400 CALHOUN DRIVE, SUITE 125
ROCKVILLE, MD 20855

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	30 AUG 2010
Applicant's or agent's file reference 7569/22925PC	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 10/39864	24 June 2010 (24.06.2010)	25 June 2009 (25.06.2009)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A01N 43/40; A61K 31/44 (2010.01)
USPC - 514/338

Applicant POZEN INC.

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	15 August 2010 (15.08.2010)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/39864

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

   ☐ on paper

   ☐ in electronic form

   b. (time)

   ☐ in the international application as filed

   ☐ together with the international application in electronic form

   ☐ subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US 10/39864

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 4-10, 14-15 and 20

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 4-10, 14-15 and 20 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 4-10, 14-15 and 20 are improper multiple dependent claims because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 4-10, 14-15 and 20

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/39864

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-3, 11-13, 16-19	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-3, 11-13, 16-19	NO
Industrial applicability (IA)	Claims	1-3, 11-13, 16-19	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-2, 12-13 and 16-19 lack inventive step under PCT Article 33(3) as being obvious over US 2005/0249811 A1 to Plachetka in view of US 2002/0160046 A1 to Robinson et al. (hereinafter 'Robinson').

As per claim 1, Plachetka discloses a method of treating a patient at risk of developing an NSAID-associated ulcer for a disease or disorder that responds to aspirin (para [0011]), comprising administering to said patient a pharmaceutical composition in unit dosage form (para [0011]) comprising:
a) omeprazole or pharmaceutically acceptable salt thereof (para [0013]), that is immediately soluble when the dosage form is placed in an aqueous medium (para [0080]-[0100], Examples 6-8), in an amount effective to raise the gastric pH of the patient to at least 3.5 upon administration of one or more of the unit dosage forms (para [0012]), and
b) aspirin or a pharmaceutically acceptable salt thereof (para [0018]), wherein the aspirin or a pharmaceutically acceptable salt thereof is surrounded by a coating that is substantially insoluble in an aqueous medium at a pH below 3.5 (para [0018]) and at a temperature of 37C (para [0018], i.e., in the patient's stomach, with normal body temperature being 37C). Plachetka does not disclose the limitations taught by Robinson, namely omeprazole release is independent of pH (para [0032]), wherein said administration is continued for a period of at least *14 days* (para [0003], e.g., 4-8 weeks). It would have been obvious to one skilled in the art to modify Plachetka with Robinson so as to provide pH-independent rapid release of omeprazole (para [0009]-[0011]).

As per claim 2, claim 1 would have been obvious as above. Robinson discloses said patient is administered one or more of said unit dosage forms daily for a period of at least 28 days (para [0003]).

As per claim 12, claims 1 would have been obvious as above. Plachetka discloses the unit dosage form is a tablet comprising a core and two or more layers (para [0018]), in which:
a) the core comprises aspirin or a pharmaceutically acceptable salt thereof (para [0018]);
b) a first layer surrounds the core and has a coating substantially insoluble in aqueous medium at a pH below 3.5 (para [0018]); and
c) at least one second layer (para [0018]) comprising the omeprazole or pharmaceutically acceptable salt thereof (para [0013]) said second layer surrounding the coating of said first layer (para [0018]).

As per claim 13, claim 12 would have been obvious as above. Plachetka discloses the amount of omeprazole, or a pharmaceutically acceptable salt thereof, is present in said unit dosage form at 15-40 mg (para [0013], [0046]) and the amount of aspirin, or a pharmaceutically acceptable salt thereof, is present in said unit dosage form at 81 - 650 mg (para [0014]).

As per claim 16, claim 1 would have been obvious as above. Robinson discloses a) said administration continues for a period of at least 28 days (para [0003]). Plachetka discloses b) the amount of omeprazole, or a pharmaceutically acceptable salt thereof, is 15-40 mg (para [0013], [0046]); and c) the amount of aspirin, or a pharmaceutically acceptable salt thereof, is 81 - 650 mg (para [0014]).

As per claim 17, claim 16 would have been obvious as above. Plachetka discloses said patient is treated for pain or inflammation (para [0015]).

As per claim 18, claim 17 would have been obvious as above. Plachetka discloses said pain or inflammation is associated with osteoarthritis; rheumatoid arthritis; ankylosing spondylitis; headache; toothache; common cold; muscle ache; cardiovascular disease; cancer; cerebrovascular disease; or a combination thereof (para [0019]).

As per claim 19, claims 16-18 would have been obvious as above. Plachetka discloses the unit dosage form is a tablet comprising a core and two or more layers (para [0018]), in which:
a) the core comprises aspirin or a pharmaceutically acceptable salt thereof (para [0018]);
b) a first layer surrounds the core and has a coating substantially insoluble in aqueous medium at a pH below 3.5 (para [0018]); and
c) at least one second layer (para [0018]) comprising the omeprazole or pharmaceutically acceptable salt thereof (para [0013]) said second layer surrounding the coating of said first layer (para [0018]).

----------continued in Supplemental Box----------

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 10/39864

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
Box No. V 2. Citations and explanations:

Claims 3 and 11 lack inventive step under PCT Article 33(3) as being obvious over Plachetka in view of Robinson and further in view of US 2004/0022846 A1 to Depui et al. (hereinafter 'Depui').

As per claim 3, claims 1-2 would have been obvious as above. Plachetka and Robinson do not disclose the limitation taught by Depui, namely said patient is at increased risk of ulcer formation due to said patient's age (para [0007). It would have been obvious to one skilled in the art to modify Plachetka and Robinson with Depui so as to simplify treatment regimen and improve patient compliance (para [0014]).

As per claim 11, claim 1 would have been obvious as above. Plachetka and Robinson do not disclose the limitation taught by Depui, namely the pharmaceutical composition in unit dosage form reduces heartburn or dyspepsia associated symptoms in said patient (para [0009]). It would have been obvious to one skilled in the art to modify Plachetka and Robinson with Depui so as to simplify treatment regimen and improve patient compliance (para [0014]).

Claims 1-3, 11-13 and 16-19 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used by industry.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: MICHAEL A. SANZO
PILLSBURY WINTHROP LLP
1600 TYSONS BOULEVARD
MCLEAN, VIRGINIA 22102

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 71896/141467	Date of Mailing *(day/month/year)* 14 MAR 2003 FOR FURTHER ACTION **See paragraphs 1 and 4 below**
International application No. PCT/US02/17105	International filing date *(day/month/year)* 31 MAY 2002
Applicant POZEN INC.	

1. [X] The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 *bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicants's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JAMES M. SPEAR Telephone No. (703) 308-1235

Form PCT/ISA/220 (April 2002)*

(See notes on accompanying sheet)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 71896/141467	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US02/17105	International filing date *(day/month/year)* 31 MAY 2002	(Earliest) Priority Date *(day/month/year)* 01 JUNE 2001
Applicant POZEN INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has b een furnished.

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (See Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/17105

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7): A61K 9/22, 9/24, 9/26, 9/32, 9/36, 9/52, 9/58, 9/62

US CL: 424/457, 458, 461, 462, 468, 469, 472, 474, 480, 482

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/457, 458, 461, 462, 468, 469, 472, 474, 480, 482

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, search terms: nsaid, antiinflammatory, tablet, proton pump inhibitor, histamine H 2 receptor antagonists, H-2 blockers, acid inhibitor, ph

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,716,648 A (HALSKOV et al) 10 February 1998 (10.02.1998), see entire document, especially column 1, column 2, lines 24-48, column 4, lines 52-68, column 6, lines 9-23, column 8, lines 19-68, examples 4 and 5, claims 1 and 23-30.	1, 21, 50

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 26 JANUARY 2003	Date of mailing of the international search report 14 MAR 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Felicia D. Roberts for JAMES M. SPEAR Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)★

Electronic Patent Application Fee Transmittal

Application Number:	12822612
Filing Date:	24-Jun-2010
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Filer:	Steven Lee Highlander/Richard Ortiz
Attorney Docket Number:	103786-1 US/NS

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1290	1290

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**1470**

Electronic Acknowledgement Receipt

EFS ID:	15222212
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	22466
Filer:	Steven Lee Highlander/Richard Ortiz
Filer Authorized By:	Steven Lee Highlander
Attorney Docket Number:	103786-1 US/NS
Receipt Date:	14-MAR-2013
Filing Date:	24-JUN-2010
Time Stamp:	13:37:20
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1470
RAM confirmation Number	24913
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1		PZAZP0002US_RESPONSE-OA.pdf	6295469 dfba71127a72debd2705decdf2af64a458941778	yes	22

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Amendment/Req. Reconsideration-After Non-Final Reject	1	2
Claims	3	11
Applicant Arguments/Remarks Made in an Amendment	12	21
Extension of Time	22	22

Warnings:

Information:

2		PZAZP0002US_POAs.pdf	259755 965f5560a6e4d8c8e7d4b8169fce4fe620cf2977	yes	5

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Assignee showing of ownership per 37 CFR 3.73.	1	1
Power of Attorney	2	2
Assignee showing of ownership per 37 CFR 3.73.	3	4
Power of Attorney	5	5

Warnings:

Information:

3		PZAZP0002US_SIDS.pdf	227366 2108ef0e345e687594417604a413a479802c5642	yes	6

Multipart Description/PDF files in .zip description		
Document Description	**Start**	**End**
Transmittal Letter	1	2
Information Disclosure Statement (IDS) Form (SB08)	3	6

Warnings:

Information:

4	Foreign Reference	PZAZP0002US_REFB1.pdf	890742 b181974128619659a608c54e5750b31630fccb0a	no	29
Warnings:					
Information:					
5	Foreign Reference	PZAZP0002US_REFB2.pdf	386350 a30499e177be54739a9dfd4499b7a35f07f1a58a	no	17
Warnings:					
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6	Foreign Reference	PZAZP0002US_REFB3.pdf	1625955 9f5137ada7a385e1c76fd9ea91aa6c253d81d86a	no	68
Warnings:					
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7	Foreign Reference	PZAZP0002US_REFB4.pdf	272936 c8611d04c8679c2ca1172416e1b40e5b3f37ead6	no	11
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8	Foreign Reference	PZAZP0002US_REFB5.pdf	585574 680710626d7cdb7fa0c147214aea9573a08304f0	no	23
Warnings:					
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9	Foreign Reference	PZAZP0002US_REFB6.pdf	947067 adeb4910bca65bacd720ad32e5cbdaa161a25d7d	no	28
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Information:					
10	Foreign Reference	PZAZP0002US_REFB7.pdf	1217974 a421f476ddd3672877422b9f76c44e36e7cda323	no	22
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Information:					
11	Foreign Reference	PZAZP0002US_REFB8.pdf	593966 935d4f4253267ad2884608e982759086ce7dab9a	no	8
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12	Foreign Reference	PZAZP0002US_REFB9.pdf	464450 c43b9fe6ee3d2671fff8359d76b35dfcb24e4bf7	no	7
Warnings:					
Information:					

13	Foreign Reference	PZAZP0002US_REFB10.pdf	746580 7365f35fe8ac09cb81c929e7f0138ff660079886	no	14
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14	Foreign Reference	PZAZP0002US_REFB11.pdf	261861 98a58d71c3603803e21ba7f5a75269e4777f2e8a	no	4
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Information:					
15	Foreign Reference	PZAZP0002US_REFB12.pdf	1619140 c86ba29bcdb7b88ea668da60f3e4d855ee9e87c4	no	39
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16	Non Patent Literature	PZAZP0002US_REFC1.pdf	512316 ce368cbc3cceb68e48d2942a50591f5c66ef119d	no	87
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17	Non Patent Literature	PZAZP0002US_REFC3.pdf	21928560 04424b52c5fa5cdf5252e29ab34b569619c59f2b	no	80
Warnings:					
Information:					
18	Non Patent Literature	PZAZP0002US_REFC4.pdf	22380761 5ad866f9bedcad6decd18aff2df37471c8bf92b2	no	25
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19	Non Patent Literature	PZAZP0002US_REFC5.pdf	181593 0b5ab1f08ff473515eaca3c2cd525d63cddf6656	no	22
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20	Non Patent Literature	PZAZP0002US_REFC2.pdf	5257438 1bd8981756e14b11c07e9d105f85d93afc2982f9	no	84
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Information:					
21	Non Patent Literature	PZAZP0002US_REFC6.pdf	1434993 3318186473aa833515f56cc8503cbd2135b7ee6a	no	37
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Information:					

22	Non Patent Literature	PZAZP0002US_REFC7.pdf	788003 a98f8612dfe2d8c85f7831bc973da0b039c6048d	no	10
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23	Non Patent Literature	PZAZP0002US_REFC8.pdf	561961 d8760b7275e39a08464b30a404f0b7ca5c91c70c	no	14
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24	Non Patent Literature	PZAZP0002US_REFC9.pdf	854127 b369e868bc6981b66b47e457b0d2edda96a4f396	no	22
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25	Non Patent Literature	PZAZP0002US_REFC10.pdf	1048169 59eb13b47901c201d3f33bf0955dbf120af82b82	no	16
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27	Non Patent Literature	PZAZP0002US_REFC12.pdf	473363 a457981f9a772439397f8e6c3aee4c0e76d41a1a	no	11
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Information:					
28	Non Patent Literature	PZAZP0002US_REFC13.pdf	3939495 a0b4f91f964a57068e551032bef6abf34ce29ae0	no	38
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Information:					
29	Non Patent Literature	PZAZP0002US_REFC14.pdf	113310 4aceaf150e19f222f05ea508226ecf59a14b70a8	no	3
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30	Non Patent Literature	PZAZP0002US_REFC15.pdf	71854 851c520304a271cd337e983e2d7fb422225f5eb9	no	1
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31	Non Patent Literature	PZAZP0002US_REFC16.pdf	1230638 d2a95f237989be87cb67392ab07e979fc3fb322b	no	6
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32	Non Patent Literature	PZAZP0002US_REFC17.pdf	875109 01019ddbcd0fe28763e96578ccc3a9252e4cb5c7	no	9
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33	Non Patent Literature	PZAZP0002US_REFC18.pdf	181607 ce565a4fc67e31d187e0d1223e9ed57dd2540796	no	3
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Warnings:					
Information:					
38	Non Patent Literature	PZAZP0002US_REFC23.pdf	526886 85567cc646d6cba5611c3acf2b343e17042405f8	no	6
Warnings:					
Information:					
39	Fee Worksheet (SB06)	fee-info.pdf	32389 20f5aa30196c25b6c0954865b3d3b939a7ad8a51	no	2
Warnings:					
Information:					

Total Files Size (in bytes):	82868415

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/81 (01-09)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Application Number	12/822,612
Filing Date	June 24, 2010
First Named Inventor	Brian AULT
Title	Method for Treating a Patient at Risk for Developing an NSAID-Associated Ulcer
Art Unit	1612
Examiner Name	Adam C. Milligan
Attorney Docket Number	PZAZ.P0002US

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

108197

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number.

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Applicant/Inventor.

OR

☒ Assignee of record of an interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) (Form PTO/SB/96) submitted herewith or filed on _____.

SIGNATURE of Applicant or Assignee of Record

Signature		Date	March 13, 2013
Name	David Gryte	Telephone	302-885-6609
Title and Company	Authorized Representative	/ASTRAZENECA AB	

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 2 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Brian AULT *et al.*

Serial No.: 12/822,612

Filed: June 24, 2010

For: METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER

Group Art Unit: 1612

Examiner: Adam C. Milligan

Atty. Dkt. No.: PZAZ.P0002US

Confirmation No.: 6136

CERTIFICATE OF ELECTRONIC TRANSMISSION

I hereby certify that this correspondence is being electronically filed with the United States Patent and Trademark Office via EFS-Web on the date below:

March 14, 2013
Date

Steven L. Highlander

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

In compliance with the duty of disclosure under 37 C.F.R. § 1.56, it is respectfully requested that this Supplemental Information Disclosure Statement be entered and the documents listed on attached Form PTO-1449 be considered by the Examiner and made of record. Copies of the listed documents required by 37 C.F.R. § 1.98(a)(2) are enclosed for the convenience of the Examiner.

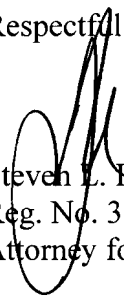
In accordance with 37 C.F.R §§ 1.97(g), (h), this Supplemental Information Disclosure Statement is not to be construed as a representation that a search has been made, and is not to be

construed to be an admission that the information cited is, or is considered to be, material to patentability as defined in 37 C.F.R. § 1.56(b).

A fee as set forth in 37 C.F.R. § 1.17(p) in the amount of $180.00 is enclosed. If an appropriate payment has not been enclosed, or if it is insufficient, the Commissioner is authorized to deduct the appropriate fee from Parker Highlander PLLC Deposit Account No. 50-5902/PZAZ.P0002US.

Applicants respectfully request that the listed documents be made of record in the present case.

Respectfully submitted,



Steven L. Highlander
Reg. No. 37,642
Attorney for Applicants

Parker Highlander PLLC
1120 S. Capital of Texas Highway
Building One, Suite 200
Austin, Texas 78746
512-334-2900 (Telephone)
512-334-2999 (Fax)

Date: March 14, 2013

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☑ Practitioners associated with the Customer Number: 108197

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☑ The address associated with Customer Number: 108197

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

Assignee Name and Address:

POZEN Inc.
1414 Raleigh Road, Suite 400
Chapel Hill, North Carolina 27517

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	Gilda Thomas	Date	8/8/12
Name	Gilda Thomas	Telephone	
Title	Senior Vice President, General Counsel		

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

MODIFIED PTO/SB/96 (04-07)

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Brian AULT, Clara HWANG, Everardus ORLEMANS, Mark SOSTEK and John R. PLACHETKA

Application No./Patent No. 12/822,612 Filed/Issue Date: June 24, 2010

Entitled: METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER

ASTRAZENECA AB, a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☐ the assignee of the entire right, title, and interest;

2. ☐ an assignee of less than the entire right, title and interest.
The extent (by percentage) of its ownership interest is _____ %; or

3. ☒ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

in the patent application/patent identified above by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: Brian AULT, Clara HWANG and Mark SOSTEK To: AstraZeneca PLP
The document was recorded in the United States Patent and Trademark Office at
Reel 028860, Frame 0759, or for which a copy thereof is attached.

2. From: AstraZeneca Pharmaceuticals LP To: AstraZeneca UK Limited
The document was recorded in the United States Patent and Trademark Office at
Reel 028860, Frame 0940, or for which a copy thereof is attached.

3. From: AstraZeneca UK Limited To: AstraZeneca AB
The document was recorded in the United States Patent and Trademark Office at
Reel 028860, Frame 0990, or for which a copy thereof is attached.

☒ Additional documents in the chain of title are listed on a supplemental sheet.

☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being submitted for recordation pursuant to 37 CFR 3.11.
[NOTE: A separate copy *(i.e.,* a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature	March 14, 2013 Date
Steven L. Highlander, Reg. No. 37,642 Printed or Typed Name	(512) 334-2900 Telephone Number
Attorney Title	PZAZ.P0002US File Code

STATEMENT UNDER 37 CFR 3.73(b)

B. (cont) A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

4. From: AstraZeneca AB To: AstraZeneca AB and Pozen Inc.
The document was recorded in the United States Patent and Trademark Office at
Reel 028861, Frame 0066, or for which a copy thereof is attached.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/822,612	06/24/2010	Brian Ault	103786-1 US/NS	6136

22466 7590 09/14/2012

ASTRA ZENECA PHARMACEUTICALS LP
GLOBAL INTELLECTUAL PROPERTY
1800 CONCORD PIKE
WILMINGTON, DE 19850-5437

EXAMINER	
MILLIGAN, ADAM C	
ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
09/14/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/822,612	AULT ET AL.	
	Examiner	Art Unit	
	ADAM C. MILLIGAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-31 and 33-63* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-31 and 33-63* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :12pgs(8/28/2012), 2pgs(8/28/2012), 2pgs(8/28/2012), 18pgs(8/28/2012).

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-31 and 33-63 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pain or inflammation, does not reasonably provide enablement for all diseases and disorders that respond to aspirin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to render the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

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[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to a method of treating a disease or disorder, where the patient population is limited to those at risk developing an NSAID-associated ulcer. As anyone who takes too much NSAID is at risk of developing an ulcer, the claim as presented is directed to treating any disease or disorder. The relative skill of those in the art is high, that of an MD or PhD.

2. The breadth of the claims

The claims are extremely broad given that there is no limitation on which patients are treated or which diseases or conditions are treated. Thus, the claims imply that where a patient is determined to have a risk of developing an NSAID-induced ulcer, but does not currently have an NSAID-induced ulcer, the method would treat the patient. However, no reasonably skill artisan would accept that the method treats a condition that does not exist. Further, no reasonably skilled artisan would accept an assertion that the formulation described herein could be used to treat all known conditions.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning how to treat a condition that does not exist or which conditions can be treated. Rather the specification is drawn to reducing the likelihood of NSAID-induced gastric ulcer occurrence.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to treat all conditions or treat a completely healthy patient as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue

experimentation, with no reasonable expectation of success.

Examiner suggests amending the claims to “a method of reducing the incidence of NSAID-associated ulcers in patients at risk of developing such" or the like.

Claim Rejections - 35 USC § 112 - Indefinite

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-31 and 33-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The term NSAID-associated is not defined in the instant specification and is indefinite because it is unclear what level of association is required between the NSAID and the ulcer to meet the term.

The term "substantially" in claim 18 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 6-9, 13-17, 19, 20, 22, 24, 25, 29, 30, 35, 37, 38, 42, 44, 45, 48-52, 56 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Plachetka (U.S. 6,926,907 – see patent cite #39 on 12 page IDS dated 8/28/2012).

Plachetka teaches non-steroidal anti-inflammatory drugs (NSAIDs) are widely accepted for pain control, but can lead to the development of gastrointestinal (GI) ulcers in susceptible individuals (col.1, lines 21-39 and col.2, lines 64-67). Plachetka states that "the risk of inducing GI ulcers is a recognized problem associated with the administration of NSAIDs" (col.2, lines 64-67). A method for reducing the risk of gastrointestinal side effects for people taking NSAIDs during chronic treatment by administration of a single, coordinated, unit-dose product that combines (a) an agent which actively raises gastric pH to levels associated with less risk of NSAID-induced ulcers and (b) an NSAID that is specially formulated to be released in a coordinated way to minimize adverse effects (col.3, lines 1-17). One specific formulation which is a four layer tablet comprising an inner core of 500mg naproxen sodium and excipients, a second barrier layer to protect the naproxen, a third enteric layer which dissolves only when the pH is above about 4 (Example 6 at col. 14) and a fourth layer comprising immediate release omeprazole in an amount sufficient to raise the pH in the gastrointestinal (GI) tract to above 4 (Example 6 at col. 15).

Note, esomeprazole is the active S-enantiomer of omeprazole. Thus, omeprazole inherently includes esomeprazole and R-omeprazole.

With regard to claims 45 and 48, given that all of the recited structural limitations are disclosed in the prior art, it is reasonably expected that the prior art tablet would exhibit the same functional characteristics as the instantly recited tablet.

With regard to claims 49 and 50 all of the active steps of the method recited are taught by Plachetka given that Plachetka teaches administration of the dosage to the same patient population (i.e. NSAID users at risk of developing ulcers).

With regard to claims 51, 52, 56 and 57, one of skill in the art would expect the method of Plachetka to effectively treat symptoms of heartburn and dyspepsia given that both are associated with pain.

Claim Rejections – 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Claims 2, 4, 5, 10-12, 18, 21, 23, 26-28, 31, 33, 34, 36, 39-41, 43, 53-55 58-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plachetka (U.S. 6,926,907 – see patent cite #39 on 12 page IDS dated 8/28/2012).

Plachetka teaches non-steroidal anti-inflammatory drugs (NSAIDs) are widely accepted for pain control, but can lead to the development of gastrointestinal (GI) ulcers in susceptible individuals (col.1, lines 21-39 and col.2, lines 64-67). Plachetka teaches a method for reducing the risk of gastrointestinal side effects for people taking NSAIDs during chronic treatment by administration of a single, coordinated, unit-dose product that combines an agent which actively raises gastric pH to levels associated with less risk of NSAID-induced ulcers and an NSAID that is specially formulated to be released in a coordinated way to minimize adverse effects (col.3, lines 1-17). Figure 1 and Example 6 demonstrates a dosage having a naproxen (500mg) core layer, which is surrounded by a barrier layer, which is then surrounded by an enteric coating, which is then surrounded by acid inhibitor releasing layer (Example 6). The outermost omeprazole layer raises the gastrointestinal pH to above 4 (col.15, lines 1-16). The third layer prevents the release of the naproxen until the pH is above about 4 (col.14, lines 59-67). The second layer protects the naproxen, and the first layer contains the naproxen and suitable excipients (col.14, lines 40-58). Results demonstrate that after a week of twice a day administration, patients taking the tablet of Plachetka had substantially less grade 3-4 gastrointestinal damage than those taking naked or enteric coated NSAIDs without an acid inhibitor (Example 10). Other than naproxen, which is typically administered at

amounts of 250mg to 500mg, suitable NSAIDs include aspirin (col.1, lines 39-45), which is typically administered in amounts between about 250mg and 1000mg (col 5, lines 55-59). Suitable acid inhibitors include omeprazole (col. 3, lines 18-38 and Examples 6, 7 and 8), which may be administered between about 5mg and 50mg (col.7, lines 1-18) and esomeprazole, which may be administered at 5mg to 100mg. Omeprazole is administered with an alkalizing agent such as sodium bicarbonate, potassium bicarbonate or sodium hydroxide to help solubilize and protect the omeprazole (col.15, lines 34-45). The tablet dosage discussed above may alternatively be formulated as a capsule formulation wherein the capsule contains pellets and granules (See e.g. Example 7).

Plachetka does not teach the administration specific time periods over a week or administration to specific patient subpopulations.

With regard to claims 2, 4, 5, 26-28, 31 and 61-63, it would have been obvious to use the method of Plachetka on any patient who requires prolonged given that NSAIDs are taught to inducing GI ulcers. Accordingly, it would have been obvious to administer the tablets of Plachetka to subsets of these patients where the subsets are included in the group of patients needing prolonged NSAID treatment.

With regard to claims 10-12, 39-41, 53-55 and 58-60, given that the prior art method is demonstrated to lesson gastric ulcers over the course of a week trial and is taught for use by chronic NSAID users, it would have been obvious to

continue the twice per day (BID) regimen for periods of time well beyond a week and up to the lifetime of the patient.

With regard to claim 18, it would have been obvious to one of ordinary skill in the art to substitute sodium bicarbonate for potassium bicarbonate or sodium hydroxide given that each of the above are taught to act as alkalizing agents. MPEP 2144.06(II).

With regard to claims 21, 23, 33 and 34, in the case where the claimed ranges overlap or lie inside ranges disclosed by the prior art, a prima facie case of obviousness exists. *see* MPEP 2144.05. Here, the prior art teaches that naproxen may administered at amounts of 250mg to 500mg and esomeprazole may be administered in amounts of 5mg to 100mg.

With regard to claim 43, the recited “beads or minitablets” recited are interpreted to include the "granules” and “pellets” of Example 7 of the prior art which are placed into the capsule.

Claims 46 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Plachetka (U.S. 6,926,907 – see patent cite #39 on 12 page IDS dated 8/28/2012) in view of Phillips (U.S. 2004/0048896 – see publication cite #12 on 18 page IDS dated 8/28/2012).

Plachetka is discussed above but does not teach the addition of a pharmacologically inert water-soluble coating over the outermost, esomeprazole containing, layer of the tablet.

Phillips teaches that when administering bitter tasting proton pump inhibitors such as omeprazole or esomeprazole, sweeteners such a sucrose and aspartame may be added to the formulation.

Phillips does not teach the addition of naproxen.

It would have been obvious to one of ordinary skill in the art to add a water-soluble coating comprising sucrose or aspartame to the formulation of Plachetka in order to mask the bitter taste associated with esomeprazole as taught by Phillips.

Obvious-Type Nonstatutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-31 and 33-63 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/823082 in view of Plachetka (U.S. 6,926,907 – see IDS dated 8/28/2012).

The copending applications teach a method of treating a patient at risk of developing an NSAID-associated ulcer by administering a unit dose comprising omeprazole in an amount sufficient to raise the gastric pH of the patient to at least 3.5 and the NSAID aspirin surrounded by a coating that is substantially insoluble in an aqueous medium below 3.5.

Plachetka is discussed above and additionally teaches that both aspirin and naproxen are suitable NSAIDs (col.3, lines 18-38) and that both omeprazole and esomeprazole are suitable acid inhibitors (col.3, lines 18-38).

It would have been obvious to one of ordinary skill in the art to substitute aspirin for naproxen given that Plachetka teaches both are substitutable equivalent NSAIDs. See MPEP 2144.06(II). Further, one of ordinary skill in the art would understand that esomeprazole is the S-enantiomer of omeprazole, and thus contained in omeprazole.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-20 of copending Application No. 13/345075 are similarly rejected in view of Plachetka (U.S. 6,926,907 – see IDS dated 8/28/2012) under the same analysis as recited above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ADAM MILLIGAN whose telephone number is (571)270-7674. The examiner can normally be reached on M-F 9:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fred Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ADAM C MILLIGAN/
Examiner, Art Unit 1612

/Benjamin Packard/
Primary Examiner, Art Unit 1612

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12822612
Filing Date	2010-06-24
First Named Inventor	Ault
Art Unit	1614
Examiner Name	
Attorney Docket Number	103786-US-NP/NS

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4198390		1980-04-15	Rider	
	2	4255431		1981-03-10	Junggren et al.	
	3	4344929		1982-08-17	Bonsen et al.	
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	5	4554276		1985-11-19	LaMattina	
	6	4562261		1985-12-31	Hirata et al.	
	7	4619934		1986-10-28	Sunshine et al.	
	8	4676984		1987-06-30	Wu et al.	

/Adam Milligan/ 09/09/2012

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /A.M./

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	9	4704278		1987-11-03	Wu et al.	
	10	4726951		1988-02-23	Panoz et al.	
	11	4738974		1988-04-19	Brandstrom	
	12	4757060		1988-07-12	Lukacsko et al.	
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	20	5026560		1991-06-25	Makino et al.	
	21	5035899		1991-07-30	Saeki et al.	
	22	5037815		1991-08-06	Lukacsko et al.	
	23	5043358		1991-08-27	Lukacsko et al.	
	24	5051262		1991-09-24	Panoz et al.	
	25	5093132		1992-03-03	Makino et al.	
	26	5204118		1993-04-20	Goldman et al.	
	27	5260333		1993-11-09	Lukacsko et al.	
	28	5364616		1994-11-15	Singer et al.	
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	30	5409709		1995-04-25	Ozawa et al. /Adam Milligan/	09/09/2012

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	31	5417980		1995-05-23	Goldman et al.	
	32	5466436		1995-11-14	Stables	
	33	5514663		1996-05-07	Mandel	
	34	5601843		1997-02-11	Gimet et al.	
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	37	5667802		1997-09-16	Grimberg	
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	46	5840737		1998-11-24	Phillips	
	47	5900424		1999-05-04	Kallstrom et al.	
	48	5955451		1999-09-21	Lichtenberger et al.	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20010025107		2001-09-27	Barberich et al.	
	2	20020012676		2002-01-31	Lundberg et al.	

/Adam Milligan/ 09/09/2012

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	4	20020044962		2002-04-18	Cherukuri et al.	
	5	20020045184		2002-04-18	Chen	
	6	20020086029		2002-07-04	Lundberg et al.	
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	9	20030113375		2003-06-19	Lundberg et al.	
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	12	20040048896		2004-03-11	Phillips	
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EAST Search - see attached search history	9/9/2012	AM
STN Search - caplus - esomeprazole, naproxen, NSAID induced GI ulcer, enteric coating	9/9/2012	AM

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L3	1	(John with Plachetka).in. and duodenal ulcer.clm.	US-PGPUB; USPAT	ADJ	OFF	2012/09/09 20:44
L4	1	"6926907".did.	US-PGPUB; USPAT	ADJ	OFF	2012/09/09 21:51
L5	24	L1 and film coat$	US-PGPUB; USPAT	ADJ	OFF	2012/09/09 22:15
L6	14	L1 and (film coat$ and sweet$)	US-PGPUB; USPAT	ADJ	OFF	2012/09/09 22:15
L7	4	L1 and (film coat$ same sweet$)	US-PGPUB; USPAT	ADJ	OFF	2012/09/09 22:17
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S3	25	(John with Plachetka).in. and aspirin	US-PGPUB; USPAT	ADJ	OFF	2012/09/07 22:02
S4	0	(John with Plachetka).in. and "aspirin.clm"	US-PGPUB; USPAT	ADJ	OFF	2012/09/07 22:02
S5	11	(John with Plachetka).in. and aspirin.clm.	US-PGPUB; USPAT	ADJ	OFF	2012/09/07 22:02
S6	9	(John with Plachetka).in. and aspirin and omeprazole	US-PGPUB; USPAT	ADJ	OFF	2012/09/07 22:04

S7	6	(John with Plachetka).in. and aspirin and omeprazole and ulcer	US-PGPUB; USPAT	ADJ	OFF	2012/09/07 22:06
S8	2	(John with Plachetka).in. and aspirin and omeprazole and ulcer.clm.	US-PGPUB; USPAT	ADJ	OFF	2012/09/08 18:49
S9	3	(John with Plachetka).in. and NSAID and ulcer.clm.	US-PGPUB; USPAT	ADJ	OFF	2012/09/08 19:02
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S12	46	aspirin with omeprazole same ulcer and enteric	US-PGPUB; USPAT	ADJ	OFF	2012/09/08 19:44
S13	17	aspirin with omeprazole same ulcer and enteric with tablet	US-PGPUB; USPAT	ADJ	OFF	2012/09/08 19:44
S14	42	aspirin with omeprazole same ulcer and enteric coat$	US-PGPUB; USPAT	ADJ	OFF	2012/09/08 19:45
S15	8	aspirin with omeprazole and ulcer with NSAID and enteric coat$	US-PGPUB; USPAT	ADJ	OFF	2012/09/08 19:46
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EAST Search History (Interference)

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PTO/SB/08a (01-10)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12822612
Filing Date	2010-06-24
First Named Inventor	Ault
Art Unit	1614
Examiner Name	
Attorney Docket Number	103786-US-NP/NS

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4198390		1980-04-15	Rider	
	2	4255431		1981-03-10	Junggren et al.	
	3	4344929		1982-08-17	Bonsen et al.	
	4	4508905		1985-04-02	Junggren et al.	
	5	4554276		1985-11-19	LaMattina	
	6	4562261		1985-12-31	Hirata et al.	
	7	4619934		1986-10-28	Sunshine et al.	
	8	4676984		1987-06-30	Wu et al.	

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	Application Number	12822612
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	First Named Inventor	Ault
	Art Unit	1614
	Examiner Name	
	Attorney Docket Number	103786-US-NP/NS

	9	4704278		1987-11-03	Wu et al.	
	10	4726951		1988-02-23	Panoz et al.	
	11	4738974		1988-04-19	Brandstrom	
	12	4757060		1988-07-12	Lukacsko et al.	
	13	4758579		1988-07-19	Kohl et al.	
	14	4766117		1988-08-23	Crawford et al.	
	15	4786505		1988-11-22	Lovgren et al.	
	16	4853230		1989-08-01	Lovgren et al.	
	17	4865847		1989-09-12	Gosswein	
	18	4948581		1990-08-14	Sawayanagi et al.	
	19	4965065		1990-10-23	Lukacsko et al.	

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	Attorney Docket Number	103786-US-NP/NS

	20	5026560		1991-06-25	Makino et al.	
	21	5035899		1991-07-30	Saeki et al.	
	22	5037815		1991-08-06	Lukacsko et al.	
	23	5043358		1991-08-27	Lukacsko et al.	
	24	5051262		1991-09-24	Panoz et al.	
	25	5093132		1992-03-03	Makino et al.	
	26	5204118		1993-04-20	Goldman et al.	
	27	5260333		1993-11-09	Lukacsko et al.	
	28	5364616		1994-11-15	Singer et al.	
	29	5373022		1994-12-13	Fawzi et al.	
	30	5409709		1995-04-25	Ozawa et al.	

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	Examiner Name	
	Attorney Docket Number	103786-US-NP/NS

	31	5417980		1995-05-23	Goldman et al.	
	32	5466436		1995-11-14	Stables	
	33	5514663		1996-05-07	Mandel	
	34	5601843		1997-02-11	Gimet et al.	
	35	5631022		1997-05-20	Mandel et al.	
	36	5643960		1997-07-01	Breitner et al.	
	37	5667802		1997-09-16	Grimberg	
	38	5679376		1997-10-21	Stevens et al.	
	39	5686105		1997-11-11	Kelm et al.	
	40	5702723		1997-12-30	Griffin	
	41	5714504		1998-02-03	Lindberg et al.	

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	42	5716648		1998-02-10	Halskov et al.	
	43	5750531		1998-05-12	Lee et al.	
	44	5817338		1998-10-06	Bergstrand et al.	
	45	5817340		1998-10-06	Roche et al.	
	46	5840737		1998-11-24	Phillips	
	47	5900424		1999-05-04	Kallstrom et al.	
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20010025107		2001-09-27	Barberich et al.	
	2	20020012676		2002-01-31	Lundberg et al.	

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	Art Unit	1614
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	3	20020042433		2002-04-11	Yelle et al.	
	4	20020044962		2002-04-18	Cherukuri et al.	
	5	20020045184		2002-04-18	Chen	
	6	20020086029		2002-07-04	Lundberg et al.	
	7	20020090395		2002-07-11	Woolfe et al.	
	8	20030008903		2003-01-09	Barberich et al.	
	9	20030113375		2003-06-19	Lundberg et al.	
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	11	20030232080		2003-12-18	Pather et al.	
	12	20040048896		2004-03-11	Phillips	
	13	20040121004		2004-06-24	Taneja	

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	Art Unit	1614
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	Attorney Docket Number	103786-US-NP/NS

	14	20040131676		2004-07-08	Taneja	
	15	20040171646		2004-09-02	Phillips	
	16	20050004171		2005-01-06	Phillips	
	17	20050042304		2005-02-24	Phillips	
	18	20050054682		2005-03-10	Phillips	
	19	20050147668		2005-07-07	Bertelsen et al.	
	20	20050163847		2005-07-28	Cheng et al.	
	21	20050227949		2005-10-13	Edalatpour	
	22	20050249806		2005-11-10	Proehl et al.	
	23	20060165797		2006-07-27	Plachetka	
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	25	20060178348		2006-08-10	Plachetka	
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	27	20060287284		2006-12-21	Schutze et al.	
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	32	20070243251		2007-10-18	Taneja	
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	34	20080031950		2008-02-07	Sesha	
	35	20080103169		2008-05-01	Phillips	

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	36	20090074863		2009-03-19	Taneja	
	37	20100062064		2010-03-11	Ault et al.	
	38	20100172983		2010-07-08	Plachetka	
	39	20100178334		2010-07-15	Johansson et al.	
	40	20120064156		2012-03-15	Plachetka	

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	1	2139653	CA					☐
	2	19801811	DE		2004-12-23	Stada Arzneimittel AG		☒
	3	4035455	DE		1992-05-14	Byk Gulden Lomberg Chemische Fabrik GmbH		☐
	4	0005129	EP		1981-04-29	Aktiebolaget Hassle Fack		☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	12822612
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	First Named Inventor	Ault
	Art Unit	1614
	Examiner Name	
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	6	0166287	EP		1989-08-23	Byk Gulden Lomberg Chemische Fabrik GmbH		☐
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	12	0426479	EP		1994-02-16	McNeil-PPC, Inc.		☐
	13	0550083	EP		1999-03-24	Glaxo Group Limited		☐
	14	1020461	EP		2009-07-22	AstraZeneca AB		☐
	15	1068867	EP		2003-09-24	Sherman, Bernard Charles		☐

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	30	199407541	WO		1994-04-14	Merck & Co., Inc.		☐
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	34	199605177	WO		1996-02-22	Yuhan Corporation		☐
	35	199605199	WO		1996-02-22	Byk Gulden Lomberg Chemische Fabrik GMBH		☐
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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
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	1	Office Action dated 05 January 2012 issued for US Pub No. 2010/0062064	☐
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	3	Office Action dated 22 April 2004 issued for US Patent No. 6,926,907	☐
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	6	Office Action dated 30 March 2009 issued for US Patent No. 8,206,741	☐
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	16	Supplemental ISR issued for WO 2010/151216, October 20, 2011	☐
	17	Written Opinion issued for WO 2010/151216, September 20, 2010	☐
	18	U.S. Appln No. 13/475446, filed on May 18, 2012	☐
	19	Preliminary Amendment for U.S. Appln No. 13/475446, filed on May 18, 2012	☐

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Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	12822612
Filing Date	2010-06-24
First Named Inventor	Ault
Art Unit	1614
Examiner Name	
Attorney Docket Number	103786-US-NP/NS

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/David M Gryte, Reg. No. 41809/	Date (YYYY-MM-DD)	2012-08-28
Name/Print	David Gryte	Registration Number	41809

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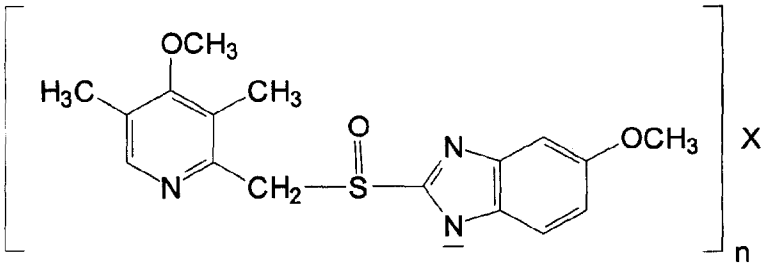
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

23940-831(s)

ABSTRACT

The novel optically pure compounds Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, where R is an alkyl with 1-4 carbon atoms, processes for the preparation thereof and pharmaceutical preparations containing the compounds as active ingredients, as well as the use of the compounds in pharmaceutical preparations and intermediates obtained by preparing the compounds. The novel compounds are represented by:



(Ia, Ib)

Ia (+)-enantiomer

Ib (-)-enantiomer

wherein n is 1 or 2 and X is Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. An optically pure compound characterized in that the compound is a Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole, wherein R is an alkyl group with 1-4 carbon atoms.

2. A compound according to claim 1 characterized in that it is in solid state form.

3. A compound according to claim 2 characterized in that it is in crystalline form.

4. A compound according to claim 1, 2 or 3 characterized in that it is a Na^+, Mg^{2+} or Ca^{2+} salt of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole.

5. A compound according to claim 1, 2 OR 3 characterized in that it is the Mg^{2+} salt of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

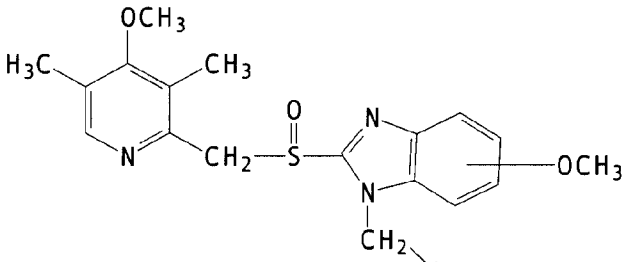
6. A compound according to claim 1 characterized in that it is the Na^+ salt of (-)-5-methoxy-2-[[(4-methoxy-3,5-

dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole in its crystalline form.

7. A compound according to any one of claims 1 to 6 having an optical purity of 98% or greater.

8. A compound according to any one of claims 1 to 6 having an optical purity of 99.8% or greater.

9. A process for the preparation of an optically pure Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, R is defined in claim 1, characterized in that a diastereomeric mixture of an ester of formula IV



(IV)

wherein Acyl designates a chiral acid group having either R or S configuration, is separated to obtain the separated diastereomers, whereafter the diastereomer comprising the acyloxymethyl derivative of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole is dissolved in an alkaline solution wherein the acyloxymethyl group is subjected to solvolysis to give an optically pure compound which is converted to the required Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

10. A process according to claim 9 characterized in that the chiral acyl group is mandeloyl.

11. A process according to claim 9 or 10 characterized in that the diastereomers are separated by chromatography.

12. A process according to claim 9 or 10 characterized in that the diastereomers are separated by fractional crystallization.

13. A process according to claim 9, 10, 11 or 12 characterized in that the solvolysis is performed in an alkaline solution of a base in a protic solvent.

14. A process according to claim 13 characterized in that the protic solvent is an alcohol or water.

15. A process according to claim 9, 10, 11, or 12 characterized in that the solvolysis is performed in an alkaline solution of a base in an aprotic solvent.

16. A process according to claim 15 characterized in that the aprotic solvent is dimethylsulfoxide or dimethylformamide.

17. A process according to any one of claim 9 or 16 characterized in that the product of the solvolysis is neutralized with an acid or an ester, followed by treatment with an appropriate base in non-aqueous solution and recovery of the Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} or $N^+(R)_4$ salt in crystalline form.

18. A process according to claim 17 characterized in that the product of the solvolysis is neutralized with methyl formate.

19. A process according to any one of claims 9 to 18 characterized in that the solvolysis is carried out with NaOH or NaOR′ where R′ is an alkyl or aryl group, the crude sodium salt is neutralized followed by treatment with NaOH in non-aqueous solution to prepare the sodium salt of (-)-5-methoxy-2-

[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

20. A process according to claim 17, 18 or 19 characterized in that the non-aqueous solution comprises 2-butanone or toluene.

21. A process according to any one of claims 9 to 20 characterized in that the product from the solvolysis is neutralised and the obtained (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole is converted into an optionally pure Na^+ salt and the optically pure Na^+ salt is treated with an aqueous solution of an inorganic magnesium salt to precipitate the optically pure Mg^{2+} salt of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

22. A process according to any one of claims 9 to 20 characterized in that the product from the solvolysis is neutralised and the obtained optically pure (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole is reacted with $Mg(OR^3)_2$ in an alcohol of formula R^3OH, wherein R^3 is an alkyl group containing 1 to 4 carbon atoms.

23. A process according to any one of claims 9 to 19 characterized in that the product from the solvolysis is neutralised and the obtained optically pure (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole is reacted with $Mg(OR^3)_2$, wherein R^3 is an alkyl group containing 1 to 4 carbon atoms, in an ether.

24. A pharmaceutical preparation containing an optically pure compound according to any one of claims 1 to 6 together with a pharmaceutically acceptable carrier.

25. An optically pure compound according to any one of claims 1 to 8 for use in therapy.

26. Use of an optically pure compound according to any one of claims 1 to 8 in the preparation of a pharmaceutical formulation for inhibiting gastric acid secretion.

27. Use of an optically pure compound according to any one of claims 1 to 8 for the preparation of a pharmaceutical formulation for the treatment of gastrointestinal inflammatory diseases.

28. Use of an optically pure compound according to any one of claims 1 to 8 in the manufacture of a medicament with a lower degree of interindividual variation in plasma levels.

29. Use of an optically pure compound according to any one of claims 1 to 8 in the manufacture of a medicament with an improved therapeutic profile when treating gastric acid related diseases.

FETHERSTONHAUGH & CO.

OTTAWA, CANADA

PATENT AGENTS

OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

(12) (19) (CA) **Brevet-Patent**

(11) (21) (C) **2,139,653**

(86) 1994/05/27
(87) 1994/12/08
(45) 2001/07/10

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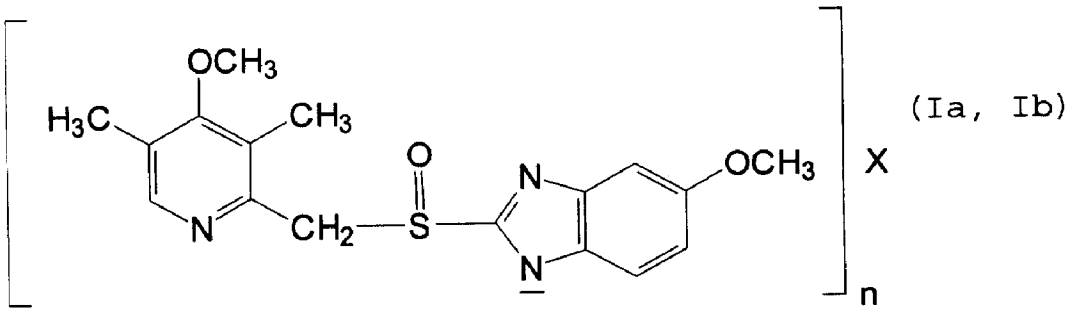
(51) Int.Cl.^{6} C07D 401/12, A61K 31/44
(30) 1993/05/28 (9301830-7) SE

(54) **SELS OPTIQUEMENT PURS DE COMPOSES PYRIDINYLMETHYLSULFINYL-IH-BENZIMIDAZOLE**

(54) **OPTICALLY PURE SALTS OF PYRIDINYLMETHYL SULFINYL-IH-BENZIMIDAZOLE COMPOUNDS**

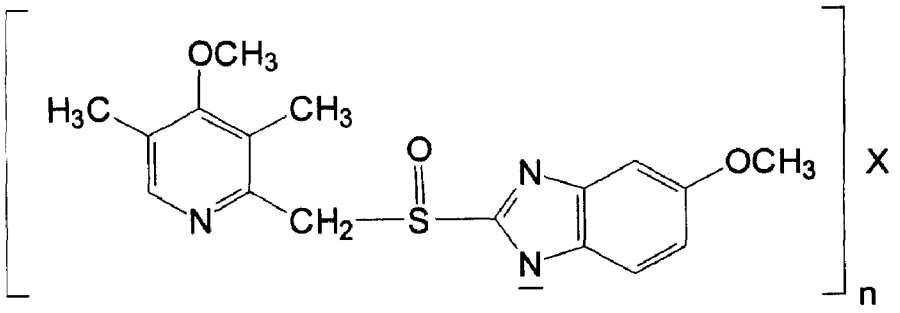


(Ia, Ib)

Ia (+)-enantiomer

Ib (-)-enantiomer

(57) The novel optically pure compounds Na^{+}, Mg^{2+}, Li^{+}, K^{+}, Ca^{2+} and $N^{+}(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole or (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, where R is an alkyl with 1-4 carbon atoms, processes for the preparation thereof and pharmaceutical preparations containing the compounds as active ingredients, as well as the use of the compounds in pharmaceutical preparations and intermediates obtained by preparing the compounds. The novel compounds are represented by: (see above formula) wherein n is 1 or 2 and X is Na^{+}, Mg^{2+}, Li^{+}, K^{+}, Ca^{2+} or $N^{+}(R)_4$.



(Ia, Ib)

Ia (+)-enantiomer

Ib (-)-enantiomer

Optically pure salts of pyridinylmethyl sulfinyl-IH-benzimidazole compounds.

Field of the invention

The present invention is directed to new compounds with high optical purity, their use in medicine, a process for their preparation and their use in the manufacture of pharmaceutical preparation. The invention also relates to novel intermediates in the preparation of the compounds of the invention.

Background of the invention

The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable alkaline salts thereof are described in EP 5129 and EP 124 495, respectively. Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation. The present invention provides such compounds, which are novel salts of single enantiomers of omeprazole.

The separation of the enantiomers of omeprazole in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19 and in a preparative scale in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group, omeprazole is quite sensitive and the acid has to be quickly neutralized with a base to avoid degradation of the acid-sensitive compound. In the above mentioned application

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this is done by adding the reaction mixture containing concentrated sulfuric acid to a concentrated solution of NaOH. This is disadvantageous because there is a great risk of locally reaching pH values between 1-6, which would be devastating for the substance. Moreover, instantaneous neutralisation will create heat which will be difficult to handle in large scale production.

The present invention in a further aspect provides a novel method for preparing the novel compounds of the invention in large scale. This novel method can also be used in large scale to obtain single enantiomers of omeprazole in neutral form.

There is no example known in the prior art of any isolated or characterized salt of optically pure omeprazole, i.e. single enantiomers of omeprazole neither of any isolated or characterized salt of any optically pure omeprazole analogue.

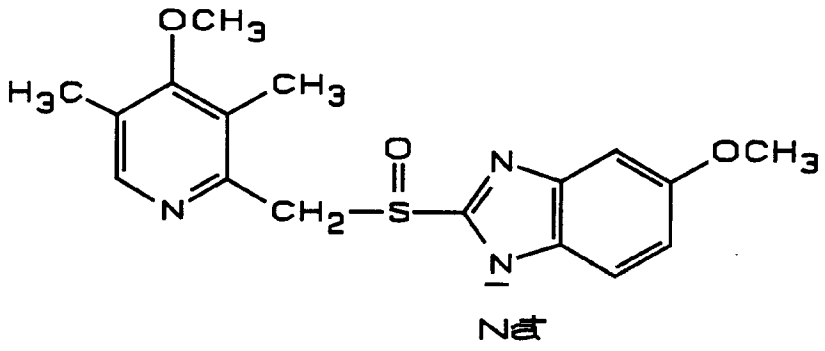
Detailed description of the invention

The present invention refers to the new Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of the single enantiomers of omeprazole, where R is an alkyl with 1-4 carbon atoms, i.e. Na^+, Mg^{2+}, Li^+, K^+, Ca^{2+} and $N^+(R)_4$ salts of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, where R is an alkyl with 1-4 carbon atoms.

Particularly preferred salts according to the invention are the Na^+, Ca^{2+} and Mg^{2+} salts, i.e (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt, (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-

pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt and (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole calcium salt.

Most preferred salts according to the invention are the optically pure Na^+ salts of omeprazole according to compounds Ia and Ib

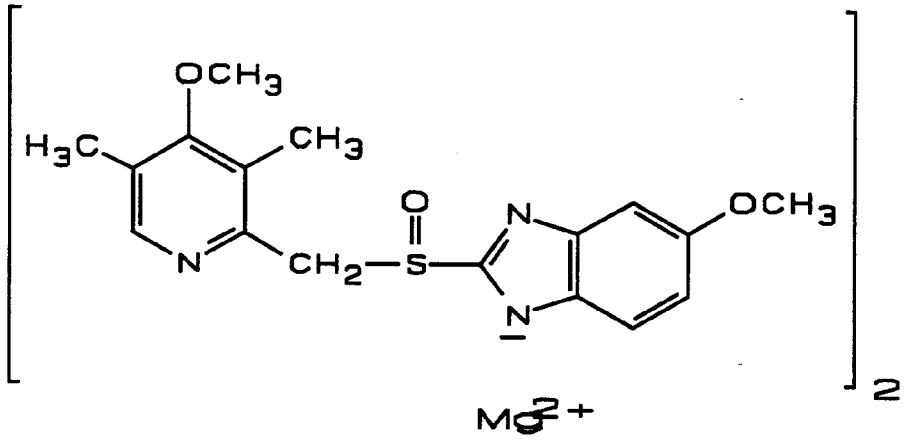


(Ia, Ib)

Ia (+)-enantiomer

Ib (-)-enantiomer

and the optically pure magnesium salts of omeprazole according to compounds IIa and IIb



(IIa, IIb)

IIa (+)-enantiomer

IIb (-)-enantiomer

With the expression "optically pure Na^+ salts of omeprazole" is meant the (+)-enantiomer of omeprazole Na-salt essentially free of the (-)-enantiomer of omeprazole Na-salt and the (-)-enantiomer essentially free of the (+)-enantiomer, respectively. Single enantiomers of omeprazole have hitherto only been obtained as syrups and not as crystalline products. By means of the novel specific method according to one aspect of the invention by preparing the single enantiomers of omeprazole, the salts defined by the present invention are easy to obtain. In addition, the salts, however not the neutral forms, are obtained as crystalline products. Because it is possible to purify optically impure salts of the enantiomers of omeprazole by crystallisation, they can be obtained in very high optical purity, in some instances ≥99.8% enantiomeric excess (e.e.) even from an optically contaminated preparation. Moreover, the optically pure salts are stable towards racemization both in neutral pH and basic pH, which was surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulphur atom was expected to cause racemization under alkaline conditions. This high stability towards racemization makes it possible to use a single enantiomeric salt of the invention in therapy.

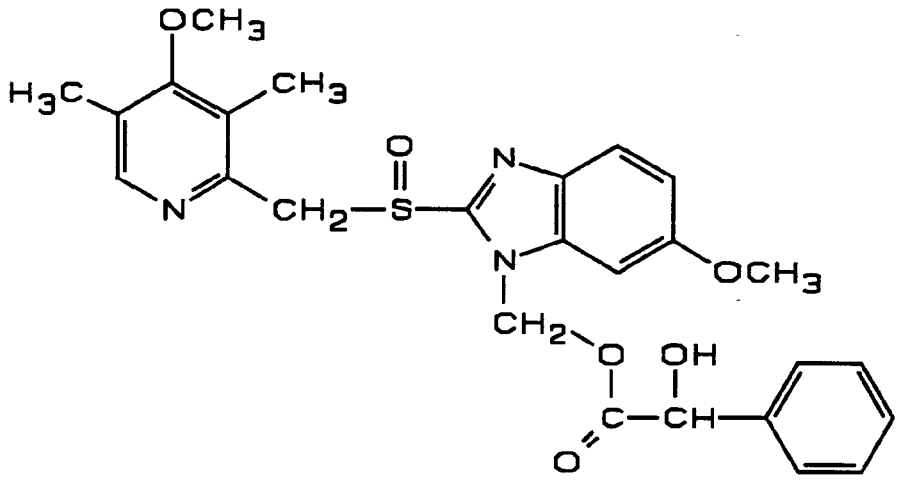
The specific method of preparation of the single enantiomers of omeprazole is a further aspect of the invention as mentioned above and it can be used to obtain the single enantiomers of omeprazole in neutral from as well as the salts thereof.

The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis and gastritis. Furthermore, the compounds may be used for

treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used

in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.

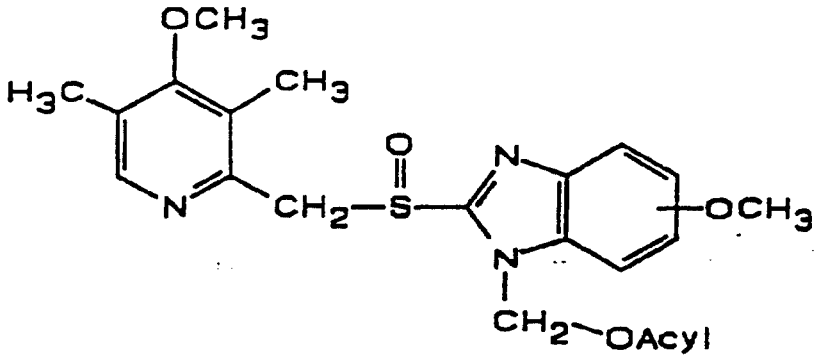
Yet a further aspect of the invention is the compound III, which is an intermediate used in the specific method of preparation.



(III)

Preparation

The optically pure compounds of the invention, i.e. the single enantiomers, are prepared by separating the two stereoisomers of a diastereomeric mixture of the following type, 5- or 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[acyloxymethyl]-1H-benzimidazole, formula IV



(IV)

wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6, and wherein the Acyl radical is as defined below, followed by a solvolysis of each separated diastereomer in an alkaline solution. The formed single enantiomers of omeprazole are then isolated by neutralizing aqueous solutions of the salts of the single enantiomers of omeprazole with a neutralizing agent which can be an acid or an ester such as methyl formate.

The Acyl moiety in the diastereomeric ester may be a chiral acyl group such as mandeloyl, and the asymmetric center in the chiral acyl group can have either R or S configuration.

The diastereomeric esters can be separated either by chromatography or fractional crystallization.

The solvolysis usually takes place together with a base in a protic solvent such as alcohols or water, but the acyl group may also be hydrolysed off by a base in an aprotic solvent such as dimethylsulfoxide or dimethylformamide. The reacting base may be OH^- or R^1O^- where R^1 can be any alkyl or aryl group.

To obtain the optically pure Na^+ salts of the invention, i.e. the single enantiomers of omeprazole Na^+ salts, the compound resulting from the solvolysis is treated with a base, such as

NaOH, in an aqueous or nonaqueous medium, or with $NaOR^2$ wherein R^2 is an alkyl group containing 1-4 carbon atoms, or with $NaNH_2$. Also alkaline salts wherein the cation is Li^+ or K^+ may be prepared using lithium or potassium salts of the above mentioned bases. In order to obtain the crystalline form of the Na^+ salt, addition of NaOH in a non-aqueous medium such as a mixture of 2-butanone and toluene, is preferred.

To obtain the optically pure Mg^{2+} salts of the invention, optically pure Na^+ salts are treated with an aqueous solution of an inorganic magnesium salt such as $MgCl_2$, whereupon the Mg^{2+} salts are precipitated. The optically pure Mg^{2+} salts may also be prepared by treating single enantiomers of omeprazole with a base, such as $Mg(OR^3)_2$, wherein R^3 is an alkyl group containing 1-4 carbon atoms, in a non-aqueous solvent such as alcohol (only for alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran. In an analogous way, also alkaline salts wherein the cation is Ca^{2+} can be prepared, using an aqueous solution of an inorganic calcium salt such as $CaCl_2$.

Alkaline salts of the single enantiomers of the invention are, as mentioned above, beside the sodium salts (compounds Ia and Ib) and the magnesium salts (compound IIa and IIb), exemplified by their salts with Li^+, K^+, Ca^{2+} and $N^+(R)_4$, where R is an alkyl with 1-4 C-atoms.

For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semi-solid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for

parenteral use and between 1-50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalysed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different amounts of the active compound present.

Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above.

Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivates or gelatin. The capsules may be enteric-coated as described above.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administrations may be prepared as solutions of the optically pure compounds of the invention in pharmaceutically acceptable solvents, preferably in a concentration from 0.1 to 10% by weight. These soultions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as dry preparations to be reconstituted with a suitable solvent extemporaneously before use.

The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

The invention is illustrated by the following examples. It will be noted from the examples that the preparation of the optically pure salts of omeprazole will result in a change of direction from (-) to (+) optical rotation when preparing the sodium salt from the non-salt form and vice versa from (+) to (-) optical rotation when preparing the magnesium salt from the sodium salt.

Example 1. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

100 mg (0.3 mmol) of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (+)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 µl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 51 mg (46%) of the title compound as white crystals m.p. (decomposition) 246-248°C. The optical purity (e.e.) which was analyzed by chiral column chromatography was ≥99.8%. $[\alpha]_D^{20}$= +42,8° (c=0.5%, water).

NMR data are given below.

Example 2. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt

100 mg (0.3 mmol) of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (-)-isomer) was dissolved in 1 ml of 2-butanone with stirring. 60 µl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was non-homogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 56 mg (51%) of the title compound as white crystals m.p. (decomposition) 247-249°C.

The optical purity (e.e.) which was analyzed by chiral column chromatography was ≥99.8%. $[\alpha]_D^{20}$= -44.1° (c=0.5%, water).

NMR data are given below.

Example 3. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

2.9 ml of a 0.1 M solution of NaOH was added to 0.10 g (0.29 mmol) (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. To this mixture 2 ml methylene chloride was added, and after mixing in a separatory funnel the aqueous solution was separated off. A solution of 14 mg (0.145 mmol) $MgCl_2$ in water was added dropwise. The formed precipitate was isolated by centrifugation, and 52 mg (50%) of the product was isolated as an amorphous powder. The optical purity (e.e.) was 98%, and thus the same as the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$= +101.2° (c=1%, methanol). The Mg content of the sample was found to be 3.0%, shown by atomic absorption spectroscopy.

Example 4. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

(-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt (0.500 g, 1.36 mmol) was dissolved in water (10 ml). To this mixture 10 ml of an aqueous solution of $MgCl_2xH_2O$ (138 mg, 0.68 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 418 mg (86%) of the product as a white powder. The optical purity (ee) of the product was 99.8% which was the same as the optical purity of the starting material. The optical purity was determined by

chromatography on an analytical chiral column. $[\alpha]_D^{20}$= +129.9° (c=1%, methanol).

Example 5. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

(+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt (0.165 g, 0.45 mmol) was dissolved in water (3 ml). To this mixture 2 ml of an aqueous solution of $MgCl_2xH_2O$ (46 mg, 0.23 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained 85 mg (51%) of the product as a white powder. The optical purity (ee) of the product was 99.9% which was the same or better as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$= -128.2° (c=1%, methanol).

Table 1

Ex.	Solvent	NMR data δ ppm
1.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.37 (d, 1H), 4.75 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H) 7.30 (d, 1H), 8.21 (s, 1H).
2.	DMSO-d_6 500 MHz	2.20 (s, 3H), 2.22 (s, 3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.38 (d, 1H), 4.73 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H), 7.31 (d, 1H), 8.21 (s, 1H).

Preparation of the synthetic intermediates according to the invention will be described in the following examples.

Example 6. Preparation of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

A solution of 3.4 g sodium hydroxide in 40 ml water was added to a mixture of 14.4 g (42 mmol) tetrabutylammonium hydrogen sulphate and 6.4 g (42 mmol) (R)-(-)-mandelic acid. The mixture was extracted with 400 ml chloroform. After separation, the organic extract was heated to reflux with 16.6 g (42 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole. Evaporation of the solvent was followed by dilution with 100 ml dichloromethane and 700 ml ethyl acetate. The mixture was washed with 3 x 200 ml water and the organic solution was dried over $MgSO_4$ and then evaporated. The crude material was purified by recrystallization from 100 ml acetonitrile, giving 8.1 g of the title compound (38%) as a diastereomeric mixture.

NMR data are given below.

Example 7. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound in Example 6 were separated using reversed phase chromatography (HPLC). Approximately 300 mg of the diastereomeric mixture was dissolved in 10 ml hot acetonitrile which was diluted with 10 ml of a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The solution was injected to the column and the compounds were eluted with a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The more hydrophilic isomer was easier to obtain pure than the less hydrophilic one. The work up procedure for the fraction which contained pure isomer was as follows; extraction with dichloromethane, washing the organic solution with aqueous 5 % sodium hydrogen carbonate solution, drying over Na_2SO_4 and

evaporation of the solvent on a rotavapor (at the end of the evaporation the removal of acetonitrile was facilitated by adding more dichloromethane). Using 1.2 g of the diastereomeric mixture with the above mentioned technique, the more hydrophilic isomer, 410 mg, was obtained in a pure state as a colourless syrup.

NMR data are given below.

Example 8. Preparation of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

The product was obtained from 8.1 g (202 mmol) sodium hydroxide in 100 ml water, 34.4 g (101 mmol) tetrabutylammonium hydrogen sulfate, 15.4 g (101 mmol) (S)-(+)-mandelic acid and 39.9 g (101 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole using the same procedure as in Example 6. Recrystallization from 100 ml acetonitrile yielded 21.3 g, i.e. 41% of the title compound as a diastereomeric mixture.

NMR data are given below.

Example 9. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

The diastereomers of the title compound in Example 8 were separated using reversed phase chromatography (HPLC) in the same way as in Example 7, but using the diasteromeric mixture of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloloxymethyl]-1H-benzimidazole instead of the (R)-mandelic ester used in Example 7. Using 2.1 g of the diastereomeric mixture, the more hydrophilic isomer, 760 mg, was obtained in a

pure state as a colourless syrup.

NMR data are given below.

Example 10. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

0.23 g (0.45 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 15 ml methanol. A solution of 36 mg (0.9 mmol) sodium hydroxid in 0.45 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 15 ml water and 15 ml dichloromethane. The organic solution was extracted with 15 ml water and to the combined aqueous solutions was added 85 µl (1.4 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x10 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.12 g (77%) of the title compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 94%. $[\alpha]_D^{20}$= -155° (c=0.5%, chloroform).

NMR data are given below

Example 11. Preparation of (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole

0.76 g (1.5 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 50 ml methanol. A solution of 0.12 mg (3.0 mmol) sodium hydroxid in 1.5 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 25 ml water and

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25 ml dichloromethane. The organic solution was extracted with 25 ml water and to the combined aqueous solutions was added 200 µl (3.2 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x25 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated. There was obtained 0.42 g (81%) of the title compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 98%. $[\alpha]_D^{20}$= +157° (c=0.5%, chloroform).

NMR data are given below

Table 2.

Ex.	Solvent	NMR data δ ppm
6.	$CDCl_3$ 500 MHz	2.18 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.95-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
7.	$CDCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
8.	$CDCl_3$ 500 MHz	2.19 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.96-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d,

1H),7.62(d,1H),7.95(s,1H),7.97(s,1H).

9. $CDCl_3$ 500 MHz — 2.20(s,3H),2.36(s,3H),3.78(s,3H),3.82(s,3H),4.80(d,1H),5.00(d,1H),5.35(d,1H),6.43(d,1H),6.63(d,1H)6.90(d,1H),6.97(dd,1H),7.2-7.3(m,3H),7.37(m,2H),7.62(d,1H),7.97(s,1H).

10. $CDCl_3$ 300 MHz — 2.18,(s,3H),2.22(s,3H),3.68(s,3H),3.83(s,3H),4.77(m,2H),6.93(dd,1H),≈7.0(b,1H),≈7.5(b,1H),8.19(s,1H).

11. $CDCl_3$ — 2.21(s,3H),2.23(s,3H),3.69(s,3H),3.84(s,3H),4.76(m,2H),6.94(dd,1H),≈7.0(b,1H),≈7.5(b,1H),8.20(s,1H).

The best mode of carrying out the invention known at present is to use the sodium salts of the optically pure compounds of the invention, thus the compounds described in Example 1 and Example 2.

Pharmaceutical preparations containing the compounds of the invention as active ingredient are illustrated in the following formulations.

Syrup

A syrup containing 1% (weight per volume) of active substance was prepared from the following ingredients:

Compound according to the invention	1.0 g
Sugar, powder	30.0 g
Saccharine	0.6 g
Glycerol	5.0 g
Flavouring agent	0.05 g

Ethanol 96%	5.0 g
Distilled water q.s. to a final volume of	100 ml

Sugar and saccharine were dissolved in 60 g of warm water. After cooling the active compound was added to the sugar solution and glycerol and a solution of flavouring agents dissolved in ethanol were added. The mixture was diluted with water to a final volume of 100 ml.

Enteric-coated tablets

An enteric coated tablet containing 50 mg of active compound was prepared from the following ingredients:

I	Compound according to the invention as Mg salt	500 g
	Lactose	700 g
	Methyl cellulose	6 g
	Polyvinylpyrrolidone cross-linked	50 g
	Magnesium stearate	15 g
	Sodium carbonate	6 g
	Distilled water	q.s.
II	Cellulose acetate phthalate	200 g
	Cetyl alcohol	15 g
	Isopropanol	2000 g
	Methylene chloride	2000 g

I Compound according to the invention, powder, was mixed with lactose and granulated with a water solution of methyl cellulose and sodium carbonate. The wet mass was forced

through a sieve and the granulate dried in an oven. After drying the granulate was mixed with polyvinylpyrrolidone and magnesium stearate. The dry mixture was pressed into tablet cores (10 000 tablets), each tablet containing 50 mg of active substance, in a tabletting machine using 7 mm diameter punches.

II A solution of cellulose acetate phthalate and cetyl alcohol in isopropanol/methylene chloride was sprayed onto the tablets I in an Accela Cota^{R}, Manesty coating equipment. A final tablet weight of 110 mg was obtained.

Solution for intravenous administration

A parenteral formulation for intravenous use, containing 4 mg of active compound per ml, was prepared from the following ingredients:

Compound according to the invention	4 g
Sterile water to a final volume of	1000 ml

The active compound was dissolved in water to a final volume of 1000 ml. The solution was filtered through a 0.22 µm filter and immediately dispensed into 10 ml sterile ampoules. The ampoules were sealed.

Capsules

Capsules containing 30 mg of active compound were prepared from the following ingredients:

Compound according to the invention	300 g
Lactose	700 g
Microcrystalline cellulose	40 g
Hydroxypropyl cellulose low-substituted	62 g

Disodium hydrogen phosphate	2 g
Purified water	q.s.

The active compound was mixed with the dry ingredients and granulated with a solution of disodium hydrogen phosphate. The wet mass was forced through an extruder and spheronized and dried in a fluidized bed dryer.

500 g of the pellets above were first coated with a solution of hydroxypropyl methylcellulose, 30 g, in water, 750 g, using a fluidized bed coater. Afer drying, the pellets were coated with a second coating as given below:

Coating solution:

Hydroxypropyl methylcellulose phthalate	70 g
Cetyl alcohol	4 g
Acetone	200 g
Ethanol	600 g

The final coated pellets were filled into capsules.

Suppositories

Suppositories were prepared from the following ingredients using a welding procedure. Each suppository contained 40 mg of active compound.

Compound according to the invention	4 g
Witepsol *H-15	180 g

*Trade-mark

The active compound was homogeneously mixed with Witepsol* H-15 at a temperature of 41°C. The molten mass was volume filled into pre-fabricated suppository packages to a net weight of 1.84 g. After cooling the packages were heat sealed. Each suppository contained 40 mg of active compound.

Stability towards racemization at different pHs

The stability of the optically pure compounds of the invention towards racemization has been measured at low concentrations in refrigerator in aqueous buffer solutions at pH 8, 9.3, 10 and 11.2. The stereochemical stability was measured by comparing the optical purity for the (-)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in buffer solution immediately after dissolving and after several days. The measurement was performed by chromatography on an analytical chiral column. The surprising high stereochemical stability in alkaline conditions for the compounds of invention is exemplified by the fact that no racemization for the test compound was obtained at pH 11.2 even after 21 days. At pH 8, 9.3 and 10, the chemical degradation of the compound is more apparent which makes the racemization measurement more difficult to perform, however at none of these pH values a detectable racemization was obtained after 16 days.

In another racemization experiment with the optically pure compounds of the invention, an aqueous phosphate buffer solution (pH=11) of the (+)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole ($c=10^{-5}M$) was warmed for 26 hours at 37°C without any racemization at all being observed.

*Trade-mark

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENT- UND MARKENAMT

(12) **Offenlegungsschrift**

(10) **DE 198 01 811 A 1**

(51) Int. Cl.[6]:
A 61 K 9/50
A 61 J 3/07
// C07D 401/12,A61K 31/44

(21) Aktenzeichen: 198 01 811.8
(22) Anmeldetag: 19. 1. 98
(43) Offenlegungstag: 22. 7. 99

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(56) Entgegenhaltungen:

GB	22 90 965 A
US	53 30 835
EP	4 80 729 A1
EP	4 26 479 A7
EP	1 24 495 A2

Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

Prüfungsantrag gem. § 44 PatG ist gestellt

(54) Pharmazeutische Zubereitung zur oralen Verabreichung

(57) Die Erfindung betrifft eine pharmazeutische Zubereitung zur oralen Verarbeitung, enthaltend als Wirkstoff wenigstens einen Protonenpumpeninhibitor und gegebenenfalls pharmazeutisch akzeptable Trägerstoffe, sowie übliche Zusatz- und Hilfssubstanzen, wobei die Zubereitung eine gefüllte, nahtlose Kapsel ist, enthaltend ein Kapselfüllmaterial umfassend den mindestens einen Wirkstoff, der in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert ist, und mindestens eine Schicht bzw. einen Film zum Beschichten des Kapselfüllmaterials.

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Beschreibung

Die vorliegende Erfindung betrifft eine neue pharmazeutische Zubereitung zur oralen Verabreichung. Sie enthält als Wirkstoff wenigstens eine säurelabile heterozyklische Verbindung, wie einen Protonenpumpeninhibitor, wobei Omeprazol besonders bevorzugt ist. Die erfindungsgemäße pharmazeutische Zubereitung ist insbesondere bestimmt zur Behandlung von Störungen oder Krankheiten des Gastrointestinaltrakts. Weiterhin betrifft die vorliegende Erfindung ein Verfahren zur Herstellung dieser neuen pharmazeutischen Zubereitung.

Protonenpumpeninhibitoren werden allgemein zur Hemmung der Magensäuresekretion sowohl bei Säugetieren als auch bei Menschen eingesetzt.

Allgemein werden sie zur Prävention und Behandlung von Störungen oder Krankheiten, die bei der Magensäuresekretion auftreten, verwendet, einschließlich z. B. Ösophagitis, Gastritis, Duodenitis, gastrischem Ulkus und duodenalem Ulkus. Weiterhin können Protonenpumpeninhibitoren zur Behandlung von anderen gastrointestinalen Störungen eingesetzt werden, bei denen erwünscht ist, daß eine Sekretion der Magensäure unterbleibt, z. B. bei Patienten, die sich einer Therapie mit nichtsteroidalen Antiphlogistika (NSAID) unterziehen. Weiterhin sind Protonenpumpeninhibitoren nützlich bei der Behandlung von Heliobakter-Infektion und damit in Zusammenhang stehenden Krankheiten.

Bekannte Protonenpumpeninhibitoren, die unter ihrem INN Namen bekannt sind, sind z. B. Omeprazol, Lansoprazol, Pantoprazol, Pariprazol, Leminoprazol.

Geeignete Protonenpumpeninhibitoren sind z. B. in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747, WO 90/06925, WO91/19711, WO 91/19712 beschrieben.

Die unter dem generischen Namen Omeprazol bekannte Substanz (5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazol ist in EP-A1-0 005 129 beschrieben. Bestimmte Omeprazolsalze einschließlich alkalischer Omeprazolsalze sind in EP-A-0 124 495 und in WO 95/01977 beschrieben. Weiterhin sind Salze von einzelnen Omeprazolenantiomeren in WO 94/27988 beschrieben.

Protonenpumpeninhibitoren und insbesondere Omeprazol sind jedoch unter Feuchtigkeits- und Säureeinfluß extrem instabil. Z.B. liegt die Halbwertszeit des Abbaus von Omeprazol in wässerigen Lösungen, die ph-Werte von weniger als drei aufweisen, bei weniger als zehn Minuten. Der Abbau von Omeprazol wird von Säuren katalysiert, während alkalische Verbindungen zu einer Stabilisierung führen (siehe WO 96/24338). Die Stabilität von Omeprazol wird ebenfalls durch Wärme, organische Lösungsmittel und in gewisser Weise durch Tageslicht beeinflußt.

Aufgrund der vorgenannten Stabilitätsprobleme muß der Protonenpumpeninhibitor und insbesondere Omeprazol in Form von magensaftresistenten Zubereitungen verabreicht werden. Alle bisherigen Ansätze zur oralen Verabreichung von Protonenpumpeninhibitoren lösen dieses Problem über Dareichungsformen, bei denen der Protonenpumpeninhibitor bzw. das Omeprazol mit Feststoffen zu festen Arzneiformen verarbeitet wird. Beispielsweise seien hier US-4,853,230 sowie WO 96/24338 genannt. Ebenso wie in US-4,786,505, EP-0 277 741 und EP-A-0 342 522 werden in der Patentliteratur Zubereitungen beschrieben, die im wesentlichen aus einem festen Kern bestehen, in dem Omeprazol als stabilisiertes Alkalisalz formuliert ist. Dieser Omeprazol-Kern kann von mehreren Schichten geschützt werden.

WO 96/01623 beschreibt Omeprazoltabletten mit verzögerter Wirkstofffreisetzung, bestehend aus einem Omeprazol-Kernmaterial und darüberliegenden Beschichtungsschichten. Diese Hülle kann aus ein oder mehreren Schichten bestehen, wobei insbesondere eine Methacrylsäurecopolymer (L30D-55)-Schicht verwendet wird.

Daher ist es Aufgabe der Erfindung, eine neue pharmazeutische Zubereitungsform zur oralen Verabreichung, enthaltend als Wirkstoff wenigstens einen Protoneninhibitor und insbesondere Omeprazol, bereitzustellen, wobei der Protonenpumpeninhibitor bzw. Omeprazol nicht mehr mit Feststoffen zu festen Arzneimitteln verarbeitet werden muß. Weiterhin soll ein Verfahren zur Herstellung dieser neuen pharmazeutischen Zubereitung angegeben werden.

Diese Aufgabe wird durch die neue pharmazeutische Zubereitung zur oralen Verabreichung gem. Anspruch 1 gelöst. Die erfindungsgemäße Zubereitung besteht aus einer gefüllten nahtlosen Kapsel, die ein Kapselfüllmaterial d. h. einen Inhalt und einen Film zum Beschichten des Inhalts enthält. Der Inhalt des Kapselfüllmaterials besteht aus dem wenigstens einen Wirkstoff, der in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert ist und ggf. pharmazeutisch akzeptablen Trägerstoffen sowie üblichen Zusatz- und Hilfssubstanzen. Die erfindungsgemäße gefüllte nahtlose Kapsel ist mit mindestens einem Film bzw. einer Schicht beschichtet, so daß die Kapseln die Magenpassage überstehen und erst im Dünndarm den Wirkstoff freisetzen.

Erfindungsgemäß wurde festgestellt, daß Omeprazol erstmals in Form von Lösungen bzw. Suspensionen ebenfalls zu stabilen oralen magensaftresistenten Arzneimitteln verarbeitet werden können.

Die erfindungsgemäße Aufgabe wird weiterhin durch das Verfahren gemäß Anspruch 13 gelöst.

In den Unteransprüchen sind vorteilhafte Ausführungsformen der Erfindung enthalten.

Die Erfindung betrifft daher eine neue pharmazeutische Zubereitungsform zur oralen Verabreichung, enthaltend als Wirkstoff wenigstens einen Protonenpumpeninhibitor und gegebenenfalls pharmazeutische akzeptable Trägerstoffe, sowie übliche Zusatz- und Hilfssubstanzen, wobei die erfindungsgemäße Zubereitung eine gefüllte, nahtlose Kapsel **1** ist, enthaltend ein Kapselfüllamterial **2**, umfassend den mindestens einen Wirkstoff, der in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert ist, und mindestens eine Schicht bzw. einen Film **3** zum Beschichten des Kapselfüllmaterials **2**.

Weiterhin betrifft die vorliegende Erfindung ein Verfahren zur Herstellung der pharmazeutischen Zubereitung wobei man gleichzeitig eine Beschichtungsschicht oder Filmlösung für die nahtlose(n) Kapsel(n) und die Lösung und/oder Suspension des wenigstens einen Wirkstoffes in eine Kühllösung aus einer konzentrisch angeordneten Mehrfachdüse, die wenigstens aus zwei Düsen besteht, extrudiert, wobei die innere Düse einen kleineren Durchmesser als die äußere Düse aufweist, und wobei insbesondere die Kühlflüssigkeit im Bereich des Strahleintritts in diese in den Strahl umhüllende Schwingungen versetzt wird, und der Strahlstrom unter Anwendung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen **1** überführt wird. In einer besonderen Ausführungsform des erfindungsgemäßen Verfahrens kann man eine Mehrfachdüse mit wenigstens drei Düsen einsetzen, bestehend aus einer Außendüse und einer Innendüse und wenigstens einer Zwischendüse, die sich in der Mittelstellung zwischen der Außen- und Innendüse befindet.

Der Durchmesser der drei Düsen steigt graduell in der vorgenannten Reihenfolge an. Gemäß dem erfindungsgemäßen Verfahren wird gleichzeitig eine Filmlösung für die nahtlose Kapsel, die Lösung bzw. die Suspension der Wirksubstanz und eine weitere Filmlösung in eine Kühllösung extrudiert und der Strahlstrom der drei Flüssigkeiten unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen **1** überführt.

Gemäß der Erfindung können die nahtlosen Kapseln **1** eine Größe von 0,3 mm bis 10,0 mm im Durchmesser, insbesondere eine Größe von 0,8 bis 3,0 mm im Durchmesser aufweisen.

Der Protonenpumpeninhibitor im Inneren der Kapsel **1** ist in einer besonderen Ausführungsform durch zwei Schichten **3** und **4** geschützt, einer enterischen Beschichtungsschicht **3** und einer Schicht, die die enterische Besichtungsschicht **4** von den Protonenpumpeninhibitor abtrennt. Erfindungsgemäß kann die vorgenannte Hülle aus einer oder mehreren Schichten bestehen. Die Hüllen sind so gestaltet, daß die Mikrokapseln die Magenpassage überstehen und erst im Dünndarm den Wirkstoff freisetzen. Die so hergestellten Mikrokapseln können in Dosen/Sachets oder Kapseln abgefüllt und/oder unter Zusatz üblicher pharmazeutischer Hilfsstoffe zu Tabletten verpreßt werden.

Als Protonenpumpeninhibitor kommen Stoffe wie Omeprazol, Lansoprazol, Pantoprazol, Pariprazol, Lemiprazol in Betracht, wobei Omeprazol bevorzugt ist. Als Wirkstoff kann gemäß einer besonderen Ausführungsform der Erfindung Omeprazol, ein alkalisches Salz von Omeprazol, ein einzelnes Enantiomer von Omeprazol oder ein alkalisches davon oder ein Magenesiumsalz von S-Omeprazol eingesetzt werden.

Bevor die erfindungsgemäßen nahtlosen Kapseln hergestellt werden, muß Omeprazol in einem geeigneten Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert werden. Als geeignetes Lösungs- und/oder Suspendiermittel kommen Parafinöl, mittelkettige Triglyceride, Isopropylmyristat, Pflanzenöle, niedrigschmelzende Wachse in Betracht. Diesen Lösungs- bzw. Suspendiermitteln können gegebenenfalls alkalisch reagierende Verbindungen zur Stabilisierung des Omeprazols zugesetzt werden. Derartig alkalisch reagierende Verbindungen sind z. B. Aminosäuren wie Lysin, Arginin, Ornitin, Histidin, puffernde Substanzen wie Trometamin, N-Aminozucker wie N-Methyl-D-glukamin (Meglumin), N-Ethyl-D-glukamin (Eglumin), Glukosamin, Dinatrium-N-stearoylglutamat, heterocyclische Aminderivate wie Piperazin, N-Methyl-piperazin, Morpholin, Alkalisalze von Zitronensäure, Weinsäure etc., oder Alkalisalze von Fettsäuren, oder Alkalimetallphosphate, Alkalsilikate oder Alkalikarbonate etc. Besonders bevorzugte alkalisch reagierende Verbindungen zur Stabilisierung sind Harnstoff, Natriumhydrogencarbonat, Natriumhydorgenphosphat und Natriumacetat.

Die Menge der alkalischen Verbindung sollte etwa 0,1 mmol/g Wirkstoff bis zu 15 mmol/g Wirkstoff betragen.

Die Hülle bzw. die Hüllen der erfindungsgemäßen nahtlosen Kapseln können aus Gelatine, Agar und/oder Kombinationen von Gelatine und/oder Agar mit Pektin und/oder Hydroxypropylmethylcellulose und/oder Chitosan und/oder Polyacrylaten bestehen, wobei Methacrylsäurecopolymere (z. B. L30D-55) bevorzugt sein können. Die Menge an verwendeter Gelatine und/oder Agar oder der vorbeschriebenen Gemische beträgt normalerweise 60 bis 90 Gewichtsprozent des Gesamtgewichtes des Kapselfilms. Geeignetes niederes Methoxypectin mit einem Molekulargewicht von nicht mehr als 200 000 und einem Methoxylierungsgrad von 1–6% liegt vorzugsweise in einer Menge von 5–20 Gew.-%, vorzugsweise in einer Menge von 10–15 Gew.-%, bezogen auf das Gesamtgewicht des Films, vor.

Die Beschichtungsschichten können ebenfalls pharmazeutisch akzeptable Weichmacher wie z. B. Phtalsäureestercetylalkohol, Polyethylenglykole etc. enthalten. Die Menge an Weichmacher beträgt üblicherweise 15-50 Gew.-%, bezogen auf das Gesamtgewicht der Beschichtung. Um die säurelabilen Substanzen zu schützen, beträgt die Schichtdicke der Beschichtung wenigstens 10 µm, vorzugsweise 20 µm.

Das Kapselfüllmaterial **2** kann neben dem Wirkstoff noch Bindemittel, oberflächenaktive Substanzen, Füllstoffe und andere bekannte Zusatz- und Hilfsstoffe enthalten. Bindemittel sind zum Beispiel Cellulosen wie Hydroxypropylmethylcellulosen, Hydroxypropylcellulose und Carboxymethylcellulose, Polyvinylpyrolidon, Stärken und andere Substanzen.

Der Protonenpumpeninhibitor kann in einer Menge von 5–80 mg, insbesondere in einer Menge von 10–50 mg in der Kapselfüllung **2** vorliegen. Als Protonenpumpeninhibitor wird Omeprazol besonders bevorzugt.

Neben den nahtlosen Kapseln mit dem Protonenpumpeninhibitor kann zusätzlich mindestens ein weiterer Wirkstoff aus der Gruppe der NSAID wie Ibuprofen, Diclofenac, Piroxicam, Naproxen, Indomethazin, Fenoprofen, Acemetacin, Flurbiprofen, Ketroprofen oder ein pharmazeutisches Salz davon oder ein Enantiomeres davon vorliegen. Vorzugsweise liegt der Wirkstoff aus der Gruppe NSAID in einer Dosierung von 20–1000 mg vor.

In einer anderen Ausführungsform der Erfindung kann neben den nahtlosen Kapseln mit dem Protonenpumpeninhibitor zusätzlich eine oder mehrere antimikrobiell wirksame Substanzen vorliegen.

Geeignete antibakteriell wirksame Substanzen schließen z. B. Antibiotika, Tetracycline, Nitroimidazole, Penicilline, Cephalosporine, Carbopenemene, Aminoglykoside, Macrolid-Antibiotika, Linkosamid-Antibiotika, 4-Quinolone, Rifarnycine, Nitrofurnatoin ein. Beispiele sind: Ampicillin, Amoxicillin, Benzylpenicillin, Phenoxymethylpenicillin, Bacampicillin, Pivampicillin, Carbenicillin, Cloxacillin, Clyclacillin, Dicloxacillin, Methicillin, Oxacillin, p-Peracillin, Ticarcilin, Flucloxacillin, Cefuroxime, Cefetamet, Cefetram, Cefixim, Cefoxitin, Ceftazidim, Ceftizoxim, Latamoxef, Cefoperazon, Ceftriaxon, Cefsulodin, Cefotaxim, Cephalexin, Cefaclor, Cefadroxil, Cefalothin, Cefazolin, Cefpodoxim, Ceftibuten, Aztreonam, Tigemonam, Erythromycin, Dirithromycin, Roxithromycin, Azithromycin, Clarithromycin, Clindamycin, Paldimycin, Lincomycin, Vancomycin, Spectinomycin, Tobramycin, Paromomycin, Metronidazol, Tintidazol, Ornidazol, Amifloxacin, Cinoxacin, Ciprofloxacin, Difloxacin, Enoxacin, Fleroxadin, Norfloxacin, Ofloxacin, Temafloxacin, Doxycyclin, Minoclyclin, Tetracyclin, Chlortetracyclin, Oxytetracyclin, Methacyclin, Rolitracyclin, Nitrofurantoin, Nalidixinsäure, Gentamicin, Rifampicin, Amikacin, Netilmicin, Imipenem, Cilastatin, Chloramphenicol, Furazolidone, Nifuroxazide, Sulfadiazin, Sulfametoxazol, Wismutsubsalizylat, kolloidales Wismutsubcitrat, Gramicidin, Mecillinam, Cloxiquin, Chlorhexidin, Dichlorobenzylalkohol, Methyl-2-pentylphenol, wobei Clarithromycin, Erythromycin, Roxithromycin, Azithromycin, Amoxicillin, Metronidazol, Tinidazol und Tretracylin bevorzugt sind.

Erfindungsgemäß bevorzugt sind folgende Wirkstoffkombinationen:

Omeprazol	20 mg
Clarithormycin	250 bzw. 500 mg
Metronidazol	400 mg

In einer anderen Ausführungsform der Erfindung ist eine Kombination von:

Omeprazol	20 mg
Amoxicillin	1000 mg
Clarithromycin	500 mg

als Füllmaterial **2** bevorzugt. In einer weiteren Ausführungsform der Erfindung wird folgende Kombination als Wirkstoff in die nahtlosen Kapseln eingefüllt:

Omeprazol	20 mg
Clarithromycin	1000 mg
Metronidazol	400 mg

Gemäß einer besonders bevorzugten Ausführungsform der Erfindung, können die nahtlosen Kapseln **1** in Hartgelatinekapseln eingefüllt und konfektioniert werden. In einer anderen Form kann die erfindungsgemäße pharmazeutische Zubereitung die Form einer Tablette aufweisen, die den Protonenpumpeninhibitor in Form von einzelnen, enterisch beschichteten gefüllten nahtlosen Kapseln enthält, wobei die enterisch Beschichtungsschicht **3** die einzelnen nahtlosen Kapseln beschichtet, um ihnen mechanische Festigkeit zu verleihen, so daß beim Tablettieren der gefüllten nahtlosen Kapseln **1** die Säurebeständigkeit der enterischbeschichteten gefüllten nahtlosen Kapseln **1** nicht beeinträchtigt wird.

Die nahtlosen Kapseln mit den Protoneninhibitoren können aber auch als solche oder zusammen mit weiteren Pulvergranulaten, Pellets in Beuteln oder Dosen bzw. Sachets eingefüllt sein.

Die Herstellung der erfindungsgemäßen Kapseln (vergleiche **Fig.** 1 bzw. **Fig.** 2) erfolgt über Zwei- bzw. Dreistoffdüsen, wobei gleichzeitig eine Beschichtungs- oder Filmlösung für die nahtlosen Kapseln und die Lösung und der Suspension des Wirkstoffes in eine Kühllösung aus einer konzentrisch angeordneten Mehrfachdüse extrudiert wird, wobei die innere Düse einen kleineren Durchmesser als die der äußeren Düse aufweist. Die Kühlflüssigkeit wird gegebenenfalls im Bereich des Strahleintritts in diese in umhüllende Schwingungen versetzt und der Strahlstrom wird unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen **1** überführt.

Fig. 1 ist eine schematische Darstellung der erfindungsgemäßen Mikrokapsel **1** mit einer Hülle **3**. Omeprazol befindet sich in Lösung oder Suspension als Kapselfilmmaterial. **Fig.** 2 zeigt eine Omeprazolmikrokapsel **1** mit einer inerten oder magensaftresistenten Hülle **1** (Schicht **3**) oder sowie einer zweiten magensaftresitenten Hülle **2** (Schicht **4**).

Die Herstellung der erfindungsgemäßen nahtlosen Kapsel erfolgt über eine spezielle Technologie. Dabei wird die Lösung des Wirkstoffes **2** in den Düsenteil einer Zwei- bzw. Dreistoffdüse geleitet und aus der inneren Düse extrudiert und eine viskose Flüssigkeit **3** mit einer Hüllsubstanz, die in Wasser unlöslich ist, aus einer ringförmigen zweiten Düse extrudiert. Gleichzeitig wird eine weitere Lösung für die Hülle **4** aus der äußeren dritten Düse extrudiert und der Strahl in eine Kühlflüssigkeit eingedüst, so daß die nahtlosen Kapseln **1** der Erfindung erhalten werden.

Die nahtlosen Kapseln **1** können dann gegebenenfalls getrocknet und gewaschen werden.

Im allgemeinen können Gelatine und/oder Kombinationen von Gelatine mit Pektin usw. als Hüllsubstanzen verwendet werden.

Beispiele

Die folgenden Beispiele sollen die Erfindung näher erläutern, ohne sie einzuschränken.

Beispiel 1

Im folgenden soll die Herstellung der Omeprazolmikrokapseln gemäß **Fig.** 1 beschrieben werden. Die Mikrokapsel hat folgende Zusammensetzung:

Zusammensetzung einer Mikrokapsel

Ausführungsbeispiel zu **Fig.** 1

Füllung: (Lösung (a))	Omeprazol	0,40 mg	Verhältnis 70 %
	Natriumlaurylsulfat	0,001 mg	
	Paraffinöl	8,00 mg	
Hülle: (Lösung (b))	Gelatine	1,823 mg	20 %
	Gummiarab.	0,351 mg	
	Pektin	0,687 mg	
		= 11,262 mg	

50 dieser Mikrokapseln werden in konventionelle Hartgelatinekapseln abgefüllt.

Unter Verwendung einer konzentrischen Doppeldüse wurde eine Omeprazollösung, die Parafinöl und Natriumlaurylsulfat enthielt (Lösung (a)), aus der inneren Düse extrudiert und eine Gelatine/Gummi-Arabikum/Pektinlösung auf 80°C erhitzt (Lösung (b)) und aus einer äußeren Düse zur gleichen Zeit in einem Verhältnis von 70% zu 20% ein Kühlmittel: in Pflanzenöl extrudiert, das eine Temperatur von etwa 12°C aufwies und eine Strömungsgeschwindigkeit von 0,3 m/Sekunde hatte. Die erhaltenen Kapseln wurden getrocknet.

Beispiel 2

Im folgenden wird die Herstellung der in **Fig.** 2 beschriebenen gecoateten Mikrokapseln beschrieben. Die Mikrokapseln hatten folgende Zusammensetzung.

Füllung: (Lösung (a))	Omeprazol	0,44 mg	Verhältnis 65%
	Cetiol HE	1,25 mg	
	Paraffinöl	7,00 mg	
	Dinatriummonohydrogenphosphat	0,05 mg	
	Natriumlaurylsulfat	0,002 mg	
		= 8,742 mg	
Hülle 1: (Lösung (b))	Gelatine	1,537 mg	20%
	Gummiarab.	0,374 mg	
	Pectin	0,483 mg	
		= 2,394 mg	
Hülle 2: (Lösung (c))	Eudragit L100	1,038 mg	15%
	Triethylcitrat	0,085 mg	
	Talkum	0,256 mg	
	Titandioxid	0,132 mg	

Die Mikrokapseln wurden in Hartgelatinekapseln oder Sachets abgefüllt. Im Unterschied zu **Fig.** 1 wurde hier eine Dreistoffdüse verwendet und Lösungen der Hüllen (Lösung (b)), Lösung (c)) sowie Lösungen mit den Wirkstoffen (Lösung (a)) in einem Verhältnis von 65% : 20% :15% gleichzeitig in Pflanzenöl mit einer Temperatur von 12°C extrudiert. Die Mikrogelatinekapseln wurden wie oben beschrieben getrocknet und in Hartgelatinekapseln oder Sachets abgefüllt.

Beispiel 3

Es wurde eine gecoatete Mikrokapsel mit einer Dreistoffdüse, wie dies in Beispiel 2 beschrieben ist, mit den folgenden Zusammensetzungen hergestellt.

Zusammensetzung einer gecoateten Mikrokapsel

Füllung: (Lösung (a))	Omeprazol	0,50 mg	Verhältnis 65%
	Mittelkettige Triglyceride	6,03 mg	
	Natriumhydorgenphosphat	0,0025 mg	
	Natriumlautylsulfat	0,002 mg	
		= 6,5345 mg	
Hülle: (Lösung (b))	Gelatine	1,625 mg	20%
	Gummiarab.	0,234 mg	
	Pectin	0,526 mg	
		= 2,385 mg	
Hülle 2: (Lösung (c))	HPMC phthalat	0,938 mg	15%
	Diethyl phthalat	0,023 mg	
		0,961 mg	
		= 9,8805 mg	

Die Mikrokapseln wurden dann weiter zu einer Tablette weiterverarbeitet mit der folgenden Tablettiermischung:

Omeprazol	
Mikrokapseln 40 Stück	395,22 mg
Maisstärke	225,00 mg
Mikrokristalline Cellulose	375,00 mg
Aerosil 200	5,00 mg
Magnesiumstearat	10,00 mg
	= 1010,22 mg

Bezugszeichenliste

1 nahtlose Kapsel
2 Kapselfüllmaterial
3 Hülle **1** (inert) und/oder magensaftresistent
4 Hülle **2** magensaftresistent
※ Omeprazol in Suspension oder Lösung

Patentansprüche

1. Pharmazeutische Zubereitung zur oralen Verabreichung, enthaltend als Wirkstoff wenigstens einen Protonenpumpeninhibitor und gegebenenfalls pharmazeutisch akzeptable Trägerstoffe, sowie übliche Zusatz- und Hilfssubstanzen, **dadurch gekennzeichnet**, daß die Zubereitung eine gefüllte, nahtlose Kapsel (**1**) ist, enthaltend ein Kapselfüllmaterial (**2**) umfassend den mindestens einen Wirkstoff, der in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert ist, und mindestens eine Schicht bzw. einen Film (**3**) zum Beschichten des Kapselfüllmaterials (**2**).

2. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß Anspruch 1, dadurch gekennzeichnet, daß die Kapseln eine Größe von 0,3 mm bis 10 mm im Durchmesser aufweisen.

3. Pharmazeutische Zubereitung zur oralen Verabreichung nach Anspruch 1, dadurch gekennzeichnet, daß die Kapseln eine Größe von 0,8 mm bis 3 mm im Durchmesser aufweisen.

4. Pharmazeutische Zubereitung zur oralen Verabreichung nach einem der vorhergehenden Ansprüche 1 bis 3, dadurch gekennzeichnet, daß der Protonenpumpeninhibitor durch zwei Schichten (**3**, **4**) geschützt ist, eine enterische Beschichtungsschicht (**4**) und einen Film bzw. eine Schicht (**3**), die die enterische Beschichtungsschicht (**4**) von dem Protonenpumpeninhibitor abtrennt.

5. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 4, dadurch gekennzeichnet, daß der Protonenpumpeninhibitor Omeprazol, ein alkalisches Salz von Omeprazol, ein einzelnes Enantiomer von Omeprazol oder ein alkalisches Salz davon oder das Magnesiumsalz von S-Omeprazol ist.

6. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß der Protonenpumpeninhibitor in einer Menge von 5 mg bis 80 mg, insbesondere in einer Menge von 10 mg bis 50 mg in der Kapselfüllung (**2**) vorliegt.

7. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 6, dadurch gekennzeichnet, daß das Lösungs- und/oder Suspendiermittel eine alkalisch reagierende Verbindung zur Stabilisierung des Protonenpumpeninhibitors enthält.

8. Pharmazeutische Zubereitung einer oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 7, dadurch gekennzeichnet, daß sie neben den nahtlosen Kapseln mit dem Protonenpumpeninhibitor zusätzlich einen oder mehrere Wirkstoffe aus der Gruppe der NSAID wie Ibuprofen, Diclofenac, Piroxicam, Naproxen, Indomethazin, Fenoprofen, Acemetacin, Flurbiprofen, Uetroprofen oder pharmazeutisches Salz oder ein Enantiomeres davon enthält.

9. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 8, daß sie die neben den nahtlosen Kapseln mit dem Protonenpumpeninhibitor zusätzlich ein oder mehrere Antibiotika enthält.

10. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 9, dadurch gekennzeichnet, daß sie in Form einer Hartgelatinekapsel vorliegt, in der die nahtlosen Kapseln (**1**) gemäß einem der vorhergehenden Ansprüche 1 bis 9 enthalten sind.

11. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 9, dadurch gekennzeichnet, daß sie in Form einer Tablette vorliegt, die den Protonenpumpeninhibitor in Form von einzelnen, enterisch beschichteten, gefüllten nahtlosen Kapseln (**1**) enthält, wobei die enterische Beschichtungsschicht (**3**) die einzelnen nahtlosen Kapseln beschichtet, um ihnen mechanische Festigkeit zu verleihen, so daß beim Tablettieren der gefüllten nahtlosen Kapseln (**1**), die Säurebeständigkeit der enterisch beschichteten, gefüllten nahtlosen Kapseln (**1**) nicht beeinträchtigt wird.

12. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 8, dadurch gekennzeichnet daß die nathlosen Kapseln mit dem Protonenpumpeninhibitor als solche oder zusammen mit weiterem Pulvergranulat oder Pellets in Beuteln oder Dosen bzw. Sachets gefüllt sind.

13. Verfahren zum Herstellen der pharmazeutischen Zubereitung gemäß einem der vorhergehenden Ansprüche 1 bis 9, dadurch gekennzeichnet, daß man gleichzeitig eine Beschichtungs- oder Filmlösung für die nahtlose(n) Kapsel(n) (**1**) und die Lösung und/oder Suspension des wenigstens einen Wirkstoffes in eine Kühllösung aus einer konzentrisch angeordneten Mehrfachdüse, die aus wenigstens zwei Düsen besteht, extrudiert, wobei die innere Düse einen kleineren Durchmesser als die äußere Düse aufweist, wobei insbesondere die Kühlflüssigkeit im Bereich des Strahleintritts in diese in den Strahl umhüllende Schwingungen versetzt wird, und der Strahlstrom unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen (**1**) überführt wird.

14. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß die zunächst einfach mikroverkapselte Wirkstofflösung bzw. -suspension im nächsten Schritt in einer Wirbelschicht mit einem weiteren magensaftresistenten Überzug (**4**) versehen wird.

15. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß man eine Mehrfachdüse mit wenigstens drei Düsen einsetzt, bestehend aus einer Außendüse und einer Innendüse und wenigstens einer Zwischendüse, die sich in der Mittelstellung zwischen der Außen- und Innendüse befindet, wobei der Durchmesser der drei Düsen graduell in dieser Reihenfolge ansteigt, und gleichzeitig eine Filmlösung für die nahtlose Kapsel, die Lösung bzw. die Suspension

der Wirksubstanz und eine weitere Filmlösung in eine Kühllösung extrudiert und der Strahlstrom der drei Flüssigkeiten unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische, nahtlose Kapseltropfen (**1**) überführt wird.

Hierzu 1 Seite(n) Zeichnungen

Nummer: **DE 198 01 811 A1**
Int. Cl.[6]: **A 61 K 9/50**
Offenlegungstag: 22. Juli 1999

1

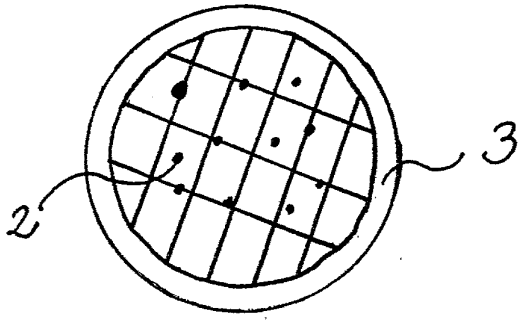

Fig. 1

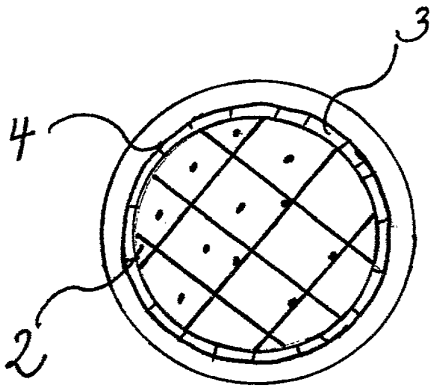

Fig. 2

(19) Bundesrepublik Deutschland
Deutsches Patent- und Markenamt

(10) **DE 198 01 811 B4** 2004.12.23

(12) # Patentschrift

(21) Aktenzeichen: **198 01 811.8**
(22) Anmeldetag: **19.01.1998**
(43) Offenlegungstag: **22.07.1999**
(45) Veröffentlichungstag
der Patenterteilung: **23.12.2004**

(51) Int Cl.[7]: **A61K 9/50**
A61J 3/07
// C07D 401/12,A61K 31/44

Innerhalb von 3 Monaten nach Veröffentlichung der Erteilung kann Einspruch erhoben werden.

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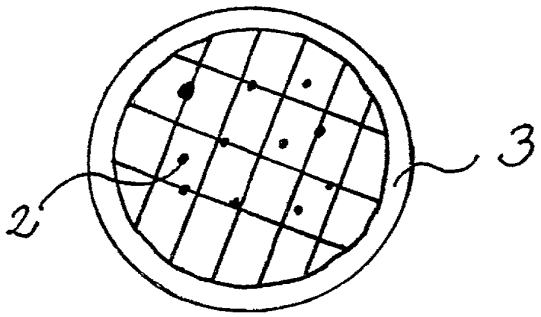
(56) Für die Beurteilung der Patentfähigkeit in Betracht gezogene Druckschriften:
GB 22 90 965 A
US 53 30 835
EP 4 80 729 A1
EP 4 26 479 A1
EP 1 24 495 A2

(54) Bezeichnung: **Pharmazeutische Zubereitung zur oralen Verabreichung**

(57) Hauptanspruch: Pharmazeutische Zubereitung zur oralen Verabreichung, umfassend wenigstens einen Protonenpumpeninhibitor, dadurch gekennzeichnet, dass sie in Form einer Tablette vorliegt, die einzelne, enterisch beschichtete, nahtlose Kapseln (1) umfasst, in denen der mindestens eine Protonenpumpeninhibitor in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert enthalten ist.



Beschreibung

[0001] Die vorliegende Erfindung betrifft eine neue pharmazeutische Zubereitung zur oralen Verabreichung. Sie enthält als Wirkstoff wenigstens einen Protonenpumpeninhibitor als säurelabile heterozyklische Verbindung, wobei Omeprazol besonders bevorzugt ist. Die erfindungsgemäße pharmazeutische Zubereitung ist insbesondere bestimmt zur Behandlung von Störungen oder Krankheiten des Gastrointestinaltrakts. Weiterhin betrifft die vorliegende Erfindung ein Verfahren zur Herstellung dieser neuen pharmazeutischen Zubereitung.

Stand der Technik

[0002] Protonenpumpeninhibitoren werden allgemein zur Hemmung der Magensäuresekretion sowohl bei Säugetieren als auch bei Menschen eingesetzt.

[0003] Allgemein werden sie zur Prävention und Behandlung von Störungen oder Krankheiten, die bei der Magensäuresekretion auftreten, verwendet, einschließlich z. B. Ösophagitis, Gastritis, Duodenitis, gastrischem Ulkus und duodenalem Ulkus. Weiterhin können Protonenpumpeninhibitoren zur Behandlung von anderen gastrointestinalen Störungen eingesetzt werden, bei denen erwünscht ist, daß eine Sekretion der Magensäure unterbleibt, z.B. bei Patienten, die sich einer Therapie mit nichtsteroidalen Antiphlogistika (NSAID) unterziehen. Weiterhin sind Protonenpumpeninhibitoren nützlich bei der Behandlung von Helicobacter Infektion und damit in Zusammenhang stehenden Krankheiten.

[0004] Bekannte Protonenpumpeninhibitoren, die unter ihrem INN Namen bekannt sind, sind z.B. Omeprazol, Lansoprazol, Pantoprazol, Pariprazol, Leminoprazol.

[0005] Geeignete Protonenpumpeninhibitoren sind z. B. in EP-0005129 A1, EP-174 726 A1, EP-166 287 A1, GB 2 163 747 A, WO90/06925 A1, WO91/19711 A1, WO91/19712 A1 beschrieben.

[0006] Die unter dem generischen Namen Omeprazol bekannte Substanz (5-Methoxy-2 [[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazol ist in EP-0005 129 A1 beschrieben. Bestimmte Omeprazolsalze einschließlich alkalischer Omeprazolsalze sind in EP-0 124 495 A2 und in WO95/01977 A1 beschrieben. Weiterhin sind Salze von einzelnen Omeprazolenantiomeren in WO94/27988 A1 beschrieben.

[0007] Protonenpumpeninhibitoren und insbesondere Omeprazol sind jedoch unter Feuchtigkeits- und Säureeinfluß extrem instabil. Z.B. liegt die Halbwertszeit des Abbaus von Omeprazol in wässrigen Lösungen, die ph-Werte von weniger als drei aufweisen, bei weniger als zehn Minuten. Der Abbau von Omeprazol wird von Säuren katalysiert, während alkalische Verbindungen zu einer Stabilisierung führen (siehe WO96/24338 A1). Die Stabilität von Omeprazol wird ebenfalls durch Wärme, organische Lösungsmittel und in gewisser Weise durch Tageslicht beeinflußt.

[0008] Aufgrund der vorgenannten Stabilitätsprobleme muß der Protonenpumpeninhibitor und insbesondere Omeprazol in Form von magensaftresistenten Zubereitungen verabreicht werden. Alle bisherigen Ansätze zur oralen Verabreichung von Protonenpumpeninhibitoren lösen dieses Problem über Dareichungsformen, bei denen der Protonenpumpeninhibitor bzw. das Omeprazol mit Feststoffen zu festen Arzneiformen verarbeitet wird. Beispielsweise seien hier US-4,853,230 A sowie WO96/24338 A1 genannt. Ebenso wie in US-4,786,50 A, EP-0 277 741 A1 und EP-0 342 522 A1 werden in der Patentliteratur Zubereitungen beschrieben, die im wesentlichen aus einem festen Kern bestehen, in dem Omeprazol als stabilisiertes Alkalisalz formuliert ist. Dieser Omeprazol-Kern kann von mehreren Schichten geschützt werden.

[0009] WO96/01623 A1 beschreibt Omeprazoltabletten mit verzögerter Wirkstofffreisetzung, bestehend aus einem Omeprazol-Kernmaterial und darüberliegenden Beschichtungsschichten. Diese Hülle kann aus ein oder mehreren Schichten bestehen, wobei insbesondere eine Methacrylsäurecopolymer (L3OD-55)-Schicht verwendet wird.

Aufgabenstellung

[0010] Daher ist es Aufgabe der Erfindung, eine neue pharmazeutische Zubereitungsform zur oralen Verabreichung, enthaltend als Wirkstoff wenigstens einen Protonenpumpeninhibitor und insbesondere Omeprazol, bereitzustellen, wobei der Protonenpumpeninhibitor bzw. Omeprazol nicht mehr mit Feststoffen zu festen Arnzeimitteln verarbeitet werden muß. Weiterhin soll ein Verfahren zur Herstellung dieser neuen pharmazeutischen Zubereitung angegeben werden.

[0011] Diese Aufgabe wird durch die neue pharmazeutische Zubereitung zur oralen Verabreichung gem. Anspruch 1 gelöst. Die erfindungsgemäße Zubereitung besteht aus einer gefüllten nahtlosen Kapsel, die ein Kapselfüllmaterial d.h. einen Inhalt und einen Film zum Beschichten des Inhalts enthält. Der Inhalt des Kapselfüllmaterials besteht aus dem wenigstens einen Wirkstoff, der in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert ist und ggf. pharmazeutisch akzeptablen Trägerstoffen sowie üblichen Zusatz- und Hilfssubstanzen. Die erfindungsgemäße gefüllte nahtlose Kapsel ist mit mindestens einem Film bzw. einer Schicht beschichtet, so daß die Kapseln die Magenpassage überstehen und erst im Dünndarm den Wirkstoff freisetzen.

[0012] Erfindungsgemäß wurde festgestellt, daß Omeprazol erstmals in Form von Lösungen bzw. Suspensionen ebenfalls zu stabilen oralen magensaftresistenten Arzneimitteln verarbeitet werden kann.

[0013] Die erfindungsgemäße Aufgabe wird weiterhin durch die Verfahren gemäß Ansprüchen 6 und 7 gelöst.

[0014] Die Erfindung betrifft daher eine neue pharmazeutische Zubereitungsform zur oralen Verabreichung, enthaltend als Wirkstoff wenigstens einen Protonenpumpeninhibitor und gegebenenfalls pharmazeutische akzeptable Trägerstoffe, sowie übliche Zusatz- und Hilfssubstanzen, wobei die erfindungsgemäße Zubereitung in Form einer Tablette vorliegt, die einzelne, enterisch beschichtete nahtlose Kapseln (**1**) umfasst, in denene der mindestens eine Protonenpumpeninhibitor in eienm Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert enthalten ist.

[0015] Weiterhin betrifft die vorliegende Erfindung ein Verfahren zur Herstellung der pharmazeutischen Zubereitung, wobei man gleichzeitig eine Beschichtungsschicht oder Filmlösung für die nahtlose(n) Kapsel(n) und die Lösung und/oder Suspension des wenigstens einen Wirkstoffes in eine Kühllösung aus einer konzentrisch angeordneten Mehrfachdüse, die wenigstens aus zwei Düsen besteht, extrudiert, wobei die innere Düse einen kleineren Durchmesser als die äußere Düse aufweist, und wobei insbesondere die Kühlflüssigkeit im Bereich des Strahleintritts in diese in den Strahl umhüllende Schwingungen versetzt wird, und der Strahlstrom unter Anwendung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen **1** überführt wird. In einer besonderen Ausführungsform des erfindungsgemäßen Verfahrens kann man eine Mehrfachdüse mit wenigstens zwei Düsen einsetzen, wobei die zunächst einfach mikroverkapselte Wirkstofflösung bzw. -suspension im nächsten Schritt in einer Wirbelschicht mit einem weiteren enterischen Überzug versehen wird. In einer weiteren besonderen Ausführungsform des erfindungsgemäßen Verfahrens kann man eine Mehrfachdüse mit wenigstens drei Düsen einsetzen, bestehend aus einer Außendüse und einer Innendüse und wenigstens einer Zwischendüse, die sich in der Mittelstellung zwischen der Außen- und Innendüse befindet. Der Durchmesser der drei Düsen nimmt graduell in der vorgenannten Reihenfolge ab. Gemäß dem erfindungsgemäßen Verfahren wird gleichzeitig eine Filmlösung für die nahtlose Kapsel, die Lösung bzw. die Suspension der Wirksubstanz und eine weitere Filmlösung in eine Kühllösung extrudiert und der Strahlstrom der drei Flüßigkeiten unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen **1** überführt.

[0016] Gemäß der Erfindung können die nahtlosen Kapseln **1** eine Größe von 0,3 mm bis 10,0 mm im Durchmesser, insbesondere eine Größe von 0,8 bis 3,0 mm im Durchmesser aufweisen.

[0017] Der Protonenpumpeninhibitor im Inneren der Kapsel **1** ist in einer besonderen Ausführungsform durch zwei Schichten **3** und **4** geschützt, einer enterischen Beschichtungsschicht **4** und einer Schicht **3**, die die enterische Beschichtungsschicht **4** von dem Protonenpumpeninhibitor abtrennt. Erfindungsgemäß kann die vorgenannte Hülle aus einer oder mehreren Schichten bestehen. Die Hüllen sind so gestaltet, daß die Mikrokapseln die Magenpassage überstehen und erst im Dünndarm den Wirkstoff freisetzen. Die so hergestellten Mikrokapseln können unter Zusatz üblicher pharmazeutischer Hilfsstoffe zu Tabletten verpreßt werden.

[0018] Als Protonenpumpeninhibitor kommen Stoffe wie Omeprazol, Lansoprazol, Pantoprazol, Pariprazol, Lemiprazol in Betracht, wobei Omeprazol bevorzugt ist. Als Wirkstoff kann gemäß einer besonderen Ausführungsform der Erfindung Omeprazol, ein alkalisches Salz von Omeprazol, ein einzelnes Enantiomer von Omeprazol oder ein alkalisches davon oder ein magnesiumsalz von S-Omeprazol eingesetzt werden.

[0019] Bevor die erfindungsgemäßen nahtlosen Kapseln hergestellt werden, muß Omeprazol in einem geeigneten Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert werden. Als geeignetes Lösungs- und/oder Suspendiermittel kommen Paraffinöl, mittelkettige Triglyceride, Isopropylmyristat, Pflanzenöle, niedrigschmelzende Wachse in Betracht. Diesen Lösungs- bzw. Suspendiermitteln können gegebenenfalls alkalisch reagierende Verbindungen zur Stabilisierung des Omeprazols zugesetzt werden. Derartig alkalisch reagierende Ver-

bindungen sind z.B. Aminosäuren wie Lysin, Arginin, Ornitin, Histidin, puffernde Substanzen wie Trometamin, N-Aminozucker wie N-Methyl-D-glukamin (Meglumin), N-Ethyl-D-glukamin (Eglumin), Glukosamin, Dinatrium-N-stearoylglutamat, heterocyclische Aminderivate wie Piperazin, N-Methyl-piperazin, Morpholin, Alkalisalze von Zitronensäure, Weinsäure etc., oder Alkalisalze von Fettsäuren, oder Alkalimetallphosphate, Alkallsilikate oder Alkalicarbonate oder etc.. Besonders bevorzugte alkalisch reagierende Verbindungen zur Stabilisierung sind Harnstoff, Natriumhydrogencarbonat, Natriumhydrogenphosphat und Natriumacetat.

[0020] Die Menge der alkalischen Verbindung sollte etwa 0,1 mmol/g Wirkstoff bis zu 15 mmol/g Wirkstoff betragen.

[0021] Die Hülle bzw. die Hüllen der erfindungsgemäßen nahtlosen Kapseln können aus Gelatine, Agar und/oder Kombinationen von Gelatine und/oder Agar mit Pektin und/oder Hydroxypropylmethylcellulose und/oder Chitosan und/oder Polyacrylaten bestehen, wobei Methacrylsäurecopolymere (z.B. L3OD-55) bevorzugt sein können. Die Menge an verwendeter Gelatine und/oder Agar oder der vorbeschriebenen Gemische beträgt normalerweise 60 bis 90 Gewichtsprozent des Gesamtgewichtes des Kapselfilms. Geeignetes niederes Methoxypectin mit einem Molekulargewicht von nicht mehr als 200 000 und einem Methoxylierungsgrad von 1–6 % liegt vorzugsweise in einer Menge von 5–20 Gew.%, vorzugsweise in einer Menge von 10–15 Gew.%, bezogen auf das Gesamtgewicht des Films, vor.

[0022] Die Beschichtungsschichten können ebenfalls pharmazeutisch akzeptable Weichmacher wie z.B. Phtalsäureestercetylalkohol, Polyethylenglykole etc. enthalten. Die Menge an Weichmacher beträgt üblicherweise 15–50 Gew.-%., bezogen auf das Gesamtgewicht der Beschichtung. Um die säurelabilen Substanzen zu schützen, beträgt die Schichtdicke der Beschichtung wenigstens 10 µm, vorzugsweise 20 µm.

[0023] Das Kapselfüllmaterial **2** kann neben dem Wirkstoff noch Bindemittel, oberflächenaktive Substanzen, Füllstoffe und andere bekannte Zusatz- und Hilfsstoffe enthalten. Bindemittel sind zum Beispiel Cellulosen wie Hydroxypropylmethylcellulose, Hydroxypropylcellulose und Carboxymethylcellulose, Polyvinylpyrrollidone, Stärken und andere Substanzen.

[0024] Der Protonenpumpeninhibitor kann in einer Menge von 5–80 mg, insbesondere in einer Menge von 10–50 mg in der Kapselfüllung **2** vorliegen. Als Protonenpumpeninhibitor wird Omeprazol besonders bevorzugt.

[0025] Die nahtlosen Kapseln können neben dem Protonenenpumpeninhibitor zusätzlich mindestens einen weiteren Wirkstoff aus der Gruppe der NSAID wie Ibuprofen, Diclofenac, Piroxicam, Naproxen, Indometacin, Fenoprofen, Acemetacin, Flurbiprofen, Ketoprofen oder ein pharmazeutisches Salz davon oder ein Enantiomeres davon enthalten. Vorzugsweise liegt der Wirkstoff aus der Gruppe NSAID in einer Dosierung von 20–1000 mg vor.

[0026] In einer anderen Ausführungsform der Erfindung können die nahtlosen Kapseln neben dem Protonenpumpeninhibitor zusätzlich eine oder mehrere antimikrobiell wirksame Substanzen enthalten.

[0027] Geeignete antibakteriell wirksame Substanzen schließen z.B. Antibiotika, Tetracycline, Nitroimidazole, Penicilline, Cephalosporine, Carbopenemene, Aminoglykoside, makrolid-Antibiotika, Linkosamid-Antibiotika, 4-Quinolone, Rifamycine, Nitrofurantoin ein. Beispiele sind: Ampicillin, Amoxicillin, Benzylpenicillin, Phenoxymethylpenicillin, Bacampicillin, Pivampicillin, Carbenicillin, Cloxacillin, Clyclacillin, Dicloxacillin, Methicillin, Oxacillin, p-Peracillin, Ticarcillin, Flucloxacillin, Cefuroxim, Cefetamet, Cefetram, Cefixim, Cefoxitin, Ceftazidim, Ceftizoxim, Latamoxef, Cefoperazon, Ceftriaxon, Cefsulodin, Cefotaxim, Cephalexin, Cefaclor, Cefadroxil, Cefalothin, Cefazolin, Cefpodoxim, Ceftibuten, Aztreonam, Tigemonam, Erythromycin, Dirithromycin, Roxithromycin, Azithromycin, Clarithromycin, Clindamycin, Paldimycin, Lincomycin, Vancomycin, Spectinomycin, Tobramycin, Paromomycin, Metronidazol, Tintidazol, Ornidazol, Amifloxacin, Cinoxacin, Ciprofloxacin, Difloxacin, Enoxacin, Fleroxacin, Norfloxacin, Ofloxacin, Temafloxacin, Doxycyclin, Minoclyclin, Tetracyclin, Chlortetracyclin, Oxytetracyclin, Methacyclin, Rolitracyclin, Nitrofurantoin, Nalidixinsäure, Gentamicin, Rifampicin, Amikacin, Netilmicin, Imipenem, Cilastatin, Chloramphenicol, Furazolidone, Nifuroxazide, Sulfadiazin, Sulfametoxazol, Wismutsubsalizylat, kolloidales Wismutsubcitrat, Gramicidin, Mecillinam, Cloxiquin, Chlorhexidin, Dichlorbenzylalkohol, Methyl-2-pentylphenol, wobei Clarithromycin, Erythromycin, Roxithromycin, Azithromycin, Amoxicillin, Metronidazol, Tinidazol und Tretracylin bevorzugt sind.

[0028] In einer weiteren Ausführungsform der Erfindung kann die tablettierte nahtlose mikroverkapselte Wirkstofflösung bzw. -suspension neben dem Protonenpumpeninhibitor eine oder mehrere antimikrobiell wirksame

Substanzen und einen oder mehrere Wirkstoffe aus der Gruppe der NSAID enthalten, wobei geeignete Antibiotika und NSAID die bereits oben ausgeführten Wirkstoffklassen und Wirkstoffe umfassen können.

[0029] Erfindungsgemäß bevorzugt sind folgende Wirkstoffkombinationen:

Omeprazol	20 mg,
Clarithromycin	250 bzw. 500 mg
Metronidazol	400 mg.

[0030] In einer anderen Ausführungsform der Erfindung ist eine Kombination von:

Omeprazol	20 mg
Amoxicillin	1000 mg
Clarithromycin	500 mg

als Füllmaterial **2** bevorzugt. In einer weiteren Ausführungsform der Erfindung wird folgende Kombination als Wirkstoff in die nahtlosen Kapseln eingefüllt:

Omeprazol	20 mg
Clarithromycin	1000 mg
Metronidazol	400 mg

[0031] Gemäß der Erfindung, weist die erfindungsgemäße pharmazeutische Zubereitung die Form einer Tablette auf, die den Protonenpumpeninhibitor in Form von einzelnen, enterisch beschichteten gefüllten nahtlosen Kapseln enthält, wobei die enterische Beschichtungsschicht **4** die einzelnen nahtlosen Kapseln beschichtet, um ihnen mechanische Festigkeit zu verleihen, so daß beim Tablettieren der gefüllten nahtlosen Kapseln **1** die Säurebeständigkeit der enterisch beschichteten gefüllten nahtlosen Kapseln **1** nicht beeinträchtigt wird.

[0032] Die Herstellung der erfindungsgemäßen Kapseln (vergleiche **Fig.** 1 bzw. **Fig.** 2) erfolgt über Zwei- bzw. Dreistoffdüsen, wobei gleichzeitig eine Beschichtungs- oder Filmlösung für die nahtlosen Kapseln und die Lösung und/oder die Suspension des Wirkstoffes in eine Kühllösung aus einer konzentrisch angeordneten Mehrfachdüse extrudiert wird, wobei die innere Düse einen kleineren Durchmesser als die der äußeren Düse aufweist. Die Kühlflüssigkeit wird gegebenenfalls im Bereich des Strahleintritts in diese in umhüllende Schwingungen versetzt und der Strahlstrom wird unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen **1** überführt.

[0033] **Fig.** 1 ist eine schematische Darstellung der erfindungsgemäßen Mikrokapsel **1** mit einer Hülle **3**. Omeprazol befindet sich in Lösung oder Suspension als Kapselfüllmaterial. **Fig.** 2 zeigt eine Omeprazolmikrokapsel **1** mit einer inerten oder magensaftresistenten Hülle **1** (Schicht **3**) sowie einer zweiten magensaftresitenten Hülle **2** (Schicht **4**).

[0034] Die Herstellung der erfindungsgemäßen nahtlosen Kapsel erfolgt über eine spezielle Technologie. Dabei wird die Lösung des Wirkstoffes **2** in den Düsenteil einer Zwei- bzw. Dreistoffdüse geleitet und aus der inneren Düse extrudiert und eine viskose Flüssigkeit **3** mit einer Hüllsubstanz, die in Wasser unlöslich ist, aus einer ringförmigen zweiten Düse extrudiert. Gleichzeitig wird eine weitere Lösung für die Hülle **4** aus der äußeren dritten Düse extrudiert und der Strahl in eine Kühlflüssigkeit eingedüst, so daß die nahtlosen Kapseln **1** der Erfindung erhalten werden.

[0035] Die nahtlosen Kapseln **1** können dann gegebenenfalls getrocknet und gewaschen werden.

[0036] Im allgemeinen können Gelatine und/oder Kombinationen von Gelatine mit Pektin usw. als Hüllsubstanzen verwendet werden.

Ausführungsbeispiel

[0037] Die folgenden Beispiele sollen die Erfindung näher erläutern, ohne sie einzuschränken.

Beispiel 1

[0038] Im folgenden soll die Herstellung der Omeprazolmikrokapseln gemäß **Fig.** 1 beschrieben werden. Die

Mikrokapsel hat folgende Zusammensetzung:

Ausführungsbeispiel zu Figur 1:

Zusammensetzung einer Mikrokapsel:

Füllung: (Lösung (a))	Omeprazol	0,40 mg	Verhältnis 70 %
	Natriumlaurylsulfat	0,001 mg	
	Paraffinöl	8,00 mg	
Hülle: (Lösung (b))	Gelatine	1,823 mg	20 %
	Gummiarab.	0,351 mg	
	Pektin	0,687 mg	
		= 11,262 mg	

[0039] Unter Verwendung einer konzentrischen Doppeldüse wurde eine Omeprazollösung, die Paraffinöl und Natriumlaurylsulfat enthielt (Lösung (a)), aus der inneren Düse extrudiert und eine Gelatine/Gummi-Arabicum/Pektinlösung auf 80°C erhitzt (Lösung (b)) und aus einer äußeren Düse zur gleichen Zeit in einem Verhältnis von 70 % zu 20 % ein Kühlmittel: in Pflanzenöl extrudiert, das eine Temperatur von etwa 12°C aufwies und eine Strömungsgeschwindigkeit von 0,3 m/Sekunde hatte. Die erhaltenen Kapseln wurden getrocknet, im Wirbelbett enterisch beschichtet und zu Tabletten weiterverarbeitet.

Beispiel 2

[0040] Im folgenden wird die Herstellung der in **Fig.** 2 beschriebenen gecoateten Mikrokapseln beschrieben. Die Mikrokapseln hatten folgende Zusammensetzung.

Füllung: (Lösung (a))	Omeprazol	0,44 mg	Verhältnis 65%
	Cetiol HE	1,25 mg	
	Paraffinöl	7,00 mg	
	Dinatriummonohydro-genphosphat	0,05 mg	
	Natriumlaurylsulfat	0,002 mg	
		= 8,742 mg	
Hülle 1: (Lösung (b))	Gelatine	1,537 mg	20%
	Gummiarab.	0,374 mg	
	~~Pectin~~ Pektin	0,483 mg	
		= 2,394 mg	
Hülle 2: (Lösung (c))	Eudragit L100	1,038 mg	15%
	Triethylcitrat	0,085 mg	
	Talkum	0,256 mg	
	Titandioxid	0,132 mg	

[0041] Im Unterschied zu **Fig.** 1 wurde hier eine Dreistoffdüse verwendet und Lösungen der Hüllen (Lösung (b)), Lösung (c)) sowie Lösungen mit den Wirkstoffen (Lösung (a)) in einem Verhältnis von 65 % : 20 % : 15 % gleichzeitig in Pflanzenöl mit einer Temperatur von 12°C extrudiert.

Beispiel 3

[0042] Es wurde eine gecoatete Mikrokapsel mit einer Dreistoffdüse, wie dies in Beispiel 2 beschrieben ist, mit den folgenden Zusammensetzungen hergestellt.

Zusammensetzung einer gecoateten Mikrokapsel:

Füllung: (Lösung (a))	Omeprazol	0,50 mg	Verhältnis 65%
	Mittelkettige Triglyceride	6,03 mg	
	Natriumhydorgenphosphat	0,0025 mg	
	Natrium~~lautyl~~lauryl sulfat	0,002 mg	
		= 6,5345 mg	
Hülle: (Lösung (b))	Gelatine	1,625 mg	20%
	Gummiarab.	0,234 mg	
	~~Pectin~~ Pektin	0,526 mg	
		= 2,385 mg	
Hülle 2: (Lösung (c))	HPMC phthalat	0,938 mg	15%
	Diethyl phthalat	0,023 mg	
		0,961 mg	
		= 9,8805 mg	

[0043] Die Mikrokapseln wurden dann weiter zu einer Tablette weiterverarbeitet mit der folgenden Tablettiermischung:

Omeprazol	
Mikrokapseln 40 Stück	395,22 mg
Maisstärke	225,00 mg
Mikrokristalline Cellulose	375,00 mg
Aerosil 200	5,00 mg
Magnesiumstearat	10,00 mg
	= 1010,22 mg

Bezugszeichenliste

1 nahtlose Kapsel
2 Kapselfüllmaterial
3 Hülle **1** (inert) und/oder magensaftresistent
4 Hülle **2** magensaftresistent
Omeprazol in Suspension oder Lösung

Patentansprüche

1. Pharmazeutische Zubereitung zur oralen Verabreichung, umfassend wenigstens einen Protonenpumpeninhibitor, **dadurch gekennzeichnet**, dass sie in Form einer Tablette vorliegt, die einzelne, enterisch beschichtete, nahtlose Kapseln (**1**) umfasst, in denen der mindestens eine Protonenpumpeninhibitor in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert enthalten ist.

2. Pharmazeutische Zubereitung gemäß Anspruch 1, dadurch gekennzeichnet, dass der Protonenpumpeninhibitor Omeprazol, ein alkalisches Salz von Omeprazol, ein einzelnes Enantiomer von Omeprazol oder ein alkalisches Salz davon oder das Magnesiumsalz von S-Omeprazol ist.

3. Pharmazeutische Zubereitung gemäß einem der Ansprüche 1 bis 2, dadurch gekennzeichnet, dass das Lösungs- und/oder Suspendiermittel eine alkalisch reagierende Verbindung zur Stabilisierung des Protonenpumpeninhibitors enthält.

4. Pharmazeutische Zubereitung gemäß einem der Ansprüche 1 bis 3, dadurch gekennzeichnet, dass die nahtlose Kapsel neben dem Protonenpumpeninhibitor zusätzlich einen oder mehrere Wirkstoffe aus der Gruppe der NSAID wie Ibuprofen, Diclofenac, Piroxicam, Naproxen, Indometacin, Fenoprofen, Acemetacin, Flurbiprofen, Uetroprofen oder ein pharmazeutisches Salz oder ein Enantiomeres davon enthält.

5. Pharmazeutische Zubereitung gemäß einem der Ansprüche 1 bis 4, dadurch gekennzeichnet, dass die nahtlose Kapsel neben dem Protonenpumpeninhibitor zusätzlich ein oder mehrere Antibiotika enthält.

6. Verfahren zum Herstellen der pharmazeutischen Zubereitung gemäß einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, dass man gleichzeitig eine magensaftresistente Filmlösung (**4**), eine Beschichtungs- oder Filmlösung (**3**) und die Lösung und/oder Suspension des wenigstens eines Wirkstoffes (**2**) in eine Kühllösung aus einer konzentrisch angeordneten Mehrfachdüse, die aus wenigstens drei Düsen besteht, extrudiert, wobei die wenigstens drei Düsen aus einer Außen- und einer Innendüse und wenigstens einer Zwischendüse bestehen, die Zwischendüse sich in der Mittelstellung zwischen der Außen- und Innendüse befindet, der Durchmesser der drei Düsen graduell in dieser Reihenfolge abnimmt, wobei gegebenenfalls die Kühlflüssigkeit im Bereich des Strahleintritts in diese in den Strahl umhüllende Schwingungen versetzt wird, und der Strahlstrom unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische enterische nahtlose Kapseltropfen (**1**) überführt wird, und die enterisch beschichteten nahtlosen Kapseln (**1**) zu Tabletten verpresst werden.

7. Verfahren zum Herstellen der pharmazeutischen Zubereitung gemäß einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, dass man gleichzeitig eine Beschichtungs- oder Filmlösung und die Lösung und/oder Suspension des wenigsten einen Wirkstoffes in eine Kühllösung aus einer konzentrisch angeordneten Mehrfachdüse, die aus wenigstens zwei Düsen besteht, extrudiert, wobei die innere Düse einen kleineren Durchmesser als die äußere Düse aufweist, wobei gegebenenfalls die Kühlflüssigkeit im Bereich des Strahleintritts in diese in den Strahl umhüllende Schwingungen versetzt wird, und der Strahlstrom unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische, nahtlose Kapseltropfen (**1**), führt wird, und die zunächst einfach mikroverkapselte Wirkstofflösunge bzw. -suspension im nächsten Schritt in einer Wirbelschicht mit einem weiteren, magensaftresistenten Film überzogen werden, und diese enterisch beschichteten nahtlosen Kapseln zu Tabletten gepresst werden.

Es folgt ein Blatt Zeichnungen

Anhängende Zeichnungen

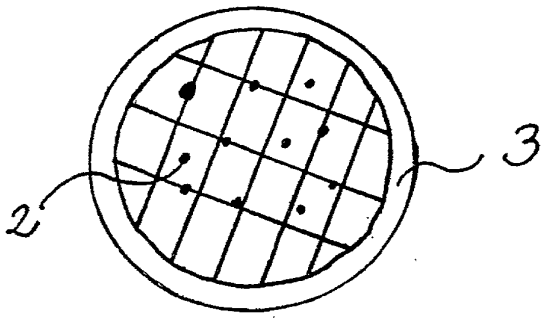


Fig. 1

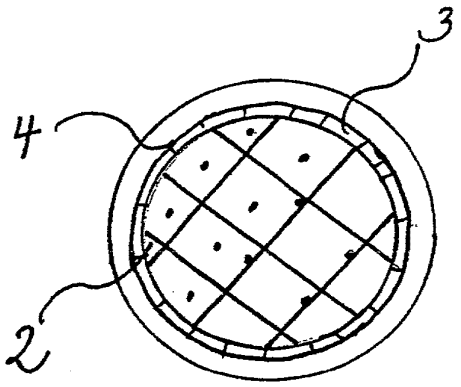


Fig. 2

B2

(19) **Federal Republic of Germany**
German Patent and Trademark Office

(10) **DE 198 01 811 B4** 2004.12.23

(12) **Patent specification**

(21) Filing number: **198 01 811.8**
(22) Date of application: **19.01.1998**
(43) Date laid open for public inspection: **22.07.1999**
(45) Date of publication of the grant of patent: **23.12.2004**

(51) Int. Cl.[7]: **A61K 9/50**
A61J 3/07
// C07D 401/12,
A61K 31/44

Objection can be filed within 3 months after publication of the grant

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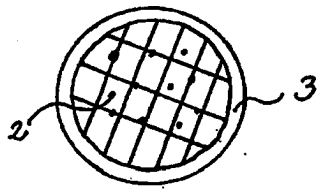
(56) Documents taken into consideration for assessing patentability:
GB 22 90 965 A
US 53 30 835
EP 4 80 729 A1
EP 4 26 479 A1
EP 1 24 495 A2

(54) Title: **Pharmaceutical preparation for oral administration**

(57) Main claim: Pharmaceutical preparation for oral administration, comprising at least one proton pump inhibitor, characterised in that it is present in the form of a tablet which comprises individual, enterically coated, seamless capsules (1) in which the at least one proton pump inhibitor is contained dissolved or suspended in a solvent and/or suspending agent.



Description

[0001] The present invention relates to a novel pharmaceutical preparation for oral administration. It contains as active ingredient at least one proton pump inhibitor as acid-labile heterocyclic compound, wherein omeprazole is particularly preferred. The pharmaceutical preparation according to the invention is in particular intended for the treatment of disorders or diseases of the gastrointestinal tract. The present invention furthermore relates to a process for the production of this novel pharmaceutical preparation.

Prior art

[0002] Proton pump inhibitors are generally used for the inhibition of gastric juice secretion both in mammals and also in humans.

[0003] Generally they are used for the prevention and treatment of disorders or diseases which occur in gastric juice secretion, including e.g. oesophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Proton pump inhibitors can furthermore be used for the treatment of other gastrointestinal disorders in which it is desirable that a secretion of the gastric juice ceases, e.g. in patients who are undergoing therapy with non-steroidal antiphlogistics (NSAID). Proton pump inhibitors are furthermore useful in the treatment of helicobacter infection and diseases connected therewith.

[0004] Known proton pump inhibitors which are known under their INN names are e.g. omeprazole, lansoprazole, pantoprazole, pariprazole and leminoprazole.

[005] Suitable proton pump inhibitors are described e.g. in EP-0005129 A1, EP-174 726 A1, EP-166 287 A1, GB 2 163 747 A, WO90/06925 A1, WO91/19711 A1 and WO91/19712 A1.

[0006] The substance known under the generic name omeprazole (5-methoxy-2 [[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole is described in EP-0005 129 A1. Certain omeprazole salts, including alkaline omeprazole salts, are described in EP-0 124 495 A2 and in WO95/01977 A1. Furthermore, salts of individual omeprazole enantiomers are described in WO94/27988 A1.

[0007] Proton pump inhibitors and in particular omeprazole are, however, extremely unstable under the influence of moisture and acid. For example, the half-life of the degradation of omeprazole in aqueous solutions which have pH values of less than three, is less than ten minutes. The degradation of omeprazole is catalysed by acids, whilst alkaline compounds lead to stabilisation (see WO96/24338 A1). The stability of omeprazole is also influenced by heat, organic solvents and to a certain extent by daylight.

[0008] Due to the above-mentioned stability problems, the proton pump inhibitor and in particular omeprazole must be administered in the form of gastric juice-resistant preparations. All previous formulations for oral administration of proton pump inhibitors resolve this problem by forms of administration in which the proton pump inhibitor or the omeprazole is processed with solids to solid pharmaceutical forms. US-4,853,230 A and WO96/24338 A1, for example, can be named here. Just as in US-4,786,50 A, EP-0 277 741 A1 and EP-0 342 522 A1, preparations which consist substantially of a solid core in which omeprazole is formulated as stabilised alkali salt, are described in the patent literature. This omeprazole core can be protected by several layers.

[0009] WO96/01623 A1 describes omeprazole tablets with delayed active ingredient release, consisting of an omeprazole core material and overlying coating layers. This shell can consist of one or more layers, wherein in particular a methacrylic acid copolymer (L30D-55) layer is used.

Problem

[0010] The problem of the invention is therefore to provide a novel pharmaceutical preparation form for oral administration containing as active ingredient at least one proton pump inhibitor and in particular omeprazole, wherein the proton pump inhibitor or omeprazole no longer has to be processed with solids to solid medicinal products. Furthermore, a process for the production of this novel pharmaceutical preparation will be given.

[0011] This problem is resolved by the novel pharmaceutical preparation for oral administration according to claim 1. The preparation according to the invention consists of a filled, seamless capsule which contains a capsule filling material, i.e. a content and a film to coat the content. The content of the capsule filling material consists of at least one active ingredient which is dissolved or suspended in a solvent and/or suspending agent and optionally pharmaceutically acceptable carriers and conventional additives and excipients. The filled seamless capsule according to the invention is coated with at least one film or a layer so that the capsules survive the gastric passage and release the active ingredient only in the small intestine.

[0012] According to the invention, it was established for the first time that omeprazole in the form of solutions or suspensions can also be processed to stable oral gastric juice-resistant medicinal products.

[0013] The problem according to the invention is furthermore resolved by the processes according to claims 6 and 7.

[0014] The invention therefore relates to a novel pharmaceutical preparation form for oral administration, containing as active ingredient at least one proton pump inhibitor and optionally pharmaceutically acceptable carriers and conventional additives and excipients, wherein the preparation according to the invention is present in the form of a tablet which comprises individual, enterically coated, seamless capsules (**1**) in which at least one proton pump inhibitor is contained dissolved or suspended in a solvent and/or suspending agent.

[0015] The present invention furthermore relates to a process for the production of the pharmaceutical preparation, wherein at the same time a coating layer or film solution for the seamless capsule(s) and the solution and/or suspension of at least one active ingredient is extruded into a cooling solution from a concentrically arranged multi-jet nozzle which consists of at least two nozzles, wherein the inner nozzle has a smaller diameter than the outer nozzle, and wherein in particular the cooling liquid in the area of the jet inlet is passed into these oscillations enveloping the jet, and the jet stream is continuously converted into small spherical seamless capsule drops **1** using the interfacial tension. In a particular embodiment of the process according to the invention, a multi-jet nozzle with at least two nozzles can be used, wherein the in the first instance singly micro-encapsulated active ingredient solution or active ingredient suspension is provided in the next sep in a fluidised bed with a further enteric covering. In a further particular embodiment of the process according to the invention, a multi-jet nozzle with at least three nozzles consisting of an outer nozzle and an inner nozzle and at least one intermediate nozzle which is

located in the intermediate position between the outer nozzle and inner nozzle can be used. The diameter of the three nozzles decreases gradually in the above-named sequence. According to the process according to the invention, a film solution for the seamless capsule, the solution or the suspension of the active ingredient and a further film solution is at the same time extruded into a cooling solution and the jet stream of the three liquids continuously converted into small spherical seamless capsule drops **1** using the interfacial tension.

[0016] According to the invention, the seamless capsules **1** can have a size of 0.3 mm to 10.0 mm in diameter, in particular a size of 0.8 to 3.0 mm in diameter.

[0017] The proton pump inhibitor inside the capsule **1** is protected in a particular embodiment by two layers **3** and **4**, an enteric coating layer **4** and a layer **3** which separates the enteric coating layer **4** from the proton pump inhibitor. According to the invention, the above-mentioned shell can consist of one or more layers. The shells are designed such that the microcapsules survive the gastric passage and release the active ingredient only in the small intestine. The microcapsules produced in this way can be pressed to tablets with addition of conventional pharmaceutical excipients.

[0018] Substances such as omeprazole, lansoprazole, pantoprazole, pariprazole and leminoprazole come into consideration as proton pump inhibitors, wherein omeprazole is preferred. According to a particular embodiment of the invention, omeprazole, an alkali salt of omeprazole, an individual enantiomer of omeprazole or an alkali *salt* thereof or a magnesium salt of S-omeprazole can be used as active ingredient.

[0019] Before the seamless capsules according to the invention are produced, omeprazole must be dissolved or suspended in a suitable solvent and/or suspending agent. Paraffin oil, medium-chain triglycerides, isopropyl myristate, vegetable oils and low-melting waxes come into consideration as suitable solvents and/or suspending agents. Optionally, alkaline-reacting compounds can be added to these solvents or suspending agents to stabilise the omeprazole. Alkaline-reacting compounds of this type are e.g. amino acids such as lysine, arginine, ornithine, histidine, buffering substances such as tromethamine, N-amino sugars such as N-methyl-D-glucamine (meglumine), N-ethyl-D-glucamine (eglumine), glucosamine, disodium-N-stearoyl glutamate, heterocyclic amine derivatives such as piperazine, N-methyl piperazine, morpholine, alkali salts of citric acid, tartaric acid etc or alkali salts of fatty acids, or alkali metal phosphates, alkali silicates or alkali carbonates etc. Particularly preferred alkaline-reacting compounds for stabilisation are urea, sodium hydrogen carbonate, sodium hydrogen phosphate and sodium acetate.

[0020] The quantity of the alkaline compound should be approximately 0.1 mmol/g active ingredient to 15 mmol/g active ingredient.

[0021] The shell or shells of the seamless capsules according to the invention can consist of gelatine, agar and/or combinations of gelatine and/or agar with pectin and/or hydroxypropyl methylcellulose and/or chitosan and/or polyacrylates, wherein methacrylic acid copolymers (e.g. L3OD-55) can be preferred. The quantity of gelatine and/or agar used or of the above-described mixtures is normally 60 to 90 percent by weight of the total weight of the capsule film. Suitable lower methoxypectin with a molecular weight of not more than 200 000 and a degree of methoxylation of 1-6% is preferably in a quantity of 5-20 %w/w, preferably in a quantity of 10-15 %w/w, based on the total weight of the film.

[0022] The coating layers can likewise contain pharmaceutically acceptable plasticisers such as e.g. phthalic acid ester cetyl alcohol, polyethylene glycols, etc. The quantity of plasticiser is conventionally 15-50 %w/w, based on the total weight of the coating. In order to protect the acid-labile substances, the layer thickness of the coating is at least 10 µm, preferably 20 µm.

[0023] The capsule filling material **2** can contain, apart from the active ingredient, also binders, surface-active substances, fillers and other known additives and excipients. Binders are for example celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and carboxymethyl cellulose, polyvinylpyrrolidone, starches and other substances.

[0024] The proton pump inhibitor can be present in the capsule filling **2** in a quantity of 5-80 mg, in particular in a quantity of 10-50 mg. Omeprazole is particularly preferred as proton pump inhibitor.

[0025] The seamless capsules can contain, apart from the proton pump inhibitor, additionally at least one other active ingredient from the NSAID group such as ibuprofen, diclofenac, piroxicam, naproxen, indometacin, fenoprofen, acemetacin, flurbiprofen, ketoprofen or a pharmaceutical salt thereof or an enantiomer thereof. The active ingredient from the NSAID group is preferably present in a dosage of 20-1000 mg.

[0026] In a further embodiment of the invention, the seamless capsules can contain, apart from the proton pump inhibitor, additionally one or more antimicrobially active substances.

[0027] Suitable antibacterially active substances include e.g. antibiotics, tetracyclines, nitroimidazoles, penicillins, cephalosporins, carbopenemens, aminoglycosides, macrolide antibiotics, lincosamide antibiotics, 4-quinolones, rifamycins and nitrofurantoin. Examples are: ampicillin, amoxicillin, benzyl penicillin, phenoxymethylpenicillin, bacampicillin, pivampicillin, carbenicillin, cloxacillin, *cyclacillin*, dicloxacillin, methicillin, oxacillin, *piperacillin*, ticarcillin, flucloxacillin, cefuroxime, cefetamet, cefetram, cefixim, cefoxitin, ceftazidim, ceftizoxime, latamoxef, cefoperazone, ceftriaxone, cefsulodin, cefotaxime, cephalexin, cefaclor, cefadroxil, cefalothin, cefazolin, cefpodoxime, ceftibuten, aztreonam, tigemonam, ethythromycin, dirithromycin, roxithromycin, azithromycin, clarithromycin, clindamycin, paldimycin, lincomycin, vancomycin, spectinomycin, tobramycin, paromomycin, metronidazole, *tinidazole*, ornidazole, amifloxacin, cinoxacin, ciprofloxacin, difloxacin, enoxacin, fleroxacin, norfloxacin, ofloxacin, temafloxacin, doxycycline, *minocycline*, tetracycline, chlortetracycline, oxytetracycline, methacyclin, rolitracycline, nitrofurantoin, nalidixic acid, gentamicin, rifampicin, amikacin, netilmicin, imipenem, cilastatin, chloramphenicol, furazolidone, nifuroxazides, sulfadiazine, sulfamethoxazole, bismuth subsalicylate, colloidal bismuth subcitrate, gramicidin, mecillinam, cloxiquin, chlorhexidine, dichlorobenzyl alcohol, methyl-2-pentylphenol, wherein clarithromycin, erythromycin, roxithromycin, azithromycin, amoxicillin, metronidazole, tinidazole and *tetracycline* are preferred.

[0028] In a further embodiment of the invention, the tabletted, seamless, micro-encapsulated active ingredient solution or suspension can contain, apart from the proton pump inhibitor, one or more antimicrobially active substances and one or more active ingredients from the NSAID group, wherein suitable antibiotics and NSAID can comprise the active ingredient classes and active ingredients already listed above.

[0029] According to the invention, the following active ingredient combinations are preferred:

omeprazole	20 mg
clarithromycin	250 or 500 mg
metronidazole	400 mg.

[0030] In a further embodiment of the invention, a combination of:

omeprazole	20 mg
amoxicillin	1000 mg
clarithromycin	500 mg

is preferred as filler **2**. in a further embodiment of the invention, the following combination is filled into the seamless capsules as active ingredient:

omeprazole	20 mg
clarithromycin	1000 mg
metronidazole	400 mg

[0031] According to the invention, the pharmaceutical preparation according to the invention has the form of a tablet which contains the proton pump inhibitor in the form of individual, enterically coated, filled seamless capsules, wherein the enteric coating layer **4** coats the individual seamless capsules in order to give them mechanical strength, so that during tabletting of the filled seamless capsules **1**, the acid resistance of the enterically coated filled seamless capsules **1** is not affected.

[0032] The production of the capsules according to the invention (cf **Fig.** 1 and **Fig.** 2) is carried out using two- or three-component nozzles, wherein at the same time a coating solution or film solution for the seamless capsules and the solution and/or suspension of the active ingredient is extruded into a cooling solution from a concentrically arranged multi-jet nozzle, wherein the inner nozzle has a smaller diameter than the outer nozzle. The cooling liquid is optionally passed in the area of the jet inlet into these enveloping oscillations and the jet stream is continuously converted into small spherical seamless capsule drops **1** using the interfacial tension.

[0033] **Fig.** 1 is a schematic representation of the microcapsule **1** according to the invention with a shell **3**. Omeprazole is in solution or suspension as capsule filling material. **Fig.** 2 shows an omeprazole microcapsule **1** with an inert or gastric juice-resistant shell **1** (layer **3**) and a second gastric juice-resistant shell **2** (layer **4**).

[0034] The production of the seamless capsule according to the invention is carried out using a special technology. The solution of the active ingredient **2** is thereby led into the nozzle part of a two- or three-component nozzle and extruded from the inner nozzle and a viscous liquid **3** with a shell substance, which is insoluble in water, extruded from an annular second nozzle. At the same time, a further solution for the shell **4** is extruded from the outer third nozzle and the jet is fed into a cooling liquid so that the seamless capsules **1** of the invention are obtained.

[0035] The seamless capsules **1** can then optionally be dried and washed.

[0035] In general, gelatine and/or combinations of gelatine with pectin etc can be used as shell substances.

Practical example

[0037] The following examples will explain the invention in more detail without restricting it.

Example 1

[0038] In the following, the production of the omeprazole microcapsules according to **Fig.** 1 will be described. The microcapsule has the following composition:

Practical example for Figure 1:

Composition of a microcapsule

Filling: (solution (a))	Omeprazole	0.40 mg	Ratio 70%
	Sodium lauryl sulphate	0.001 mg	
	Paraffin oil	8.00 mg	
Shell: (solution (b))	Gelatine	1.823 mg	20%
	Gum arabic	0.351 mg	
	Pectin	0.687 mg	
		= 11.262 mg	

[0039] Using a concentric double nozzle, an omeprazole solution which contains paraffin oil and sodium lauryl sulphate (solution (a)), was extruded from the inner nozzle and a gelatine/gum arabic/pectin solution heated to 80°C (solution (b)) and from an outer nozzle at the same time in a ratio of 70% to 20% a cooling liquid extruded in vegetable oil which had a temperature of approximately 12°C and a flow rate of 0.3 m/second. The capsules obtained were dried, enterically coated in the fluidised bed and further processed to tablets.

Example 2

[0040] In the following, the production of the coated microcapsules described in **Fig.** 2 is described. The microcapsules had the following composition.

Filling: (solution (a))	Omeprazole	0.44 mg	Ratio 65%
	Cetiol HE	1.25 mg	
	Paraffin oil	7.00 mg	
	Disodium monohydrogen phosphate	0.05 mg	
	Sodium lauryl sulphate	0.002 mg	
		= 8.742 mg	
Shell 1: (solution (b))	Gelatine	1.537 mg	20%
	Gum arabic	0.374 mg	
	Pectin	0.483 mg	
		= 2.394 mg	
Shell 2:	Eudragit L100	1.038 mg	

(solution c))			15%
	Triethyl citrate	0.085 mg	
	Talcum	0.256 mg	
	Titanium dioxide	0.132 mg	

[0041] In contrast to **Fig.** 1, a three-component nozzle was used here and solutions of the shells (solution (b)), solution (c)) and solutions with the active ingredients (solution (a)) in a ratio of 65% : 20% : 15% extruded at the same time in vegetable oil with a temperature of 12°C.

Example 3

[0042] A coated microcapsule with a three-component nozzle, as described in Example 2, was produced with the following compositions.

Composition of a coated microcapsule:

Filling: (solution (a))	Omeprazole	0.50 mg	Ratio 65%
	Medium-chain triglycerides	6.03 mg	
	Sodium hydrogen phosphate	0.0025 mg	
	Sodium lauryl sulphate	0.002 mg	
		= 6.5345 mg	
Shell: (solution (b))	Gelatine	1.625 mg	20%
	Gum arabic	0.234 mg	
	Pectin	0.526 mg	
		= 2.385 mg	
Shell 2: (solution c))	HPMC phthalate	0.938 mg	15%
	Diethyl phthalate	0.023 mg	
		0.961 mg	
		= 9.8805 mg	

[0043] The microcapsules were then again further processed to a tablet with the following tabletting mixture:

Omeprazole	
Microcapsules 40 pieces	395.22 mg
Maize starch	225.00 mg
Microcrystalline cellulose	375.00 mg
Aerosol 200	5.00 mg
Magnesium stearate	10.00 mg
	= 1010.22 mg

List of reference numbers

1 seamless capsule
2 capsule filling material
3 shell **1** (inert) and/or gastric juice-resistant
4 shell **2** gastric juice-resistant
omeprazole in suspension or solution

Claims

1. Pharmaceutical preparation for oral administration, comprising at least one proton pump inhibitor, **characterised in that** it is present in the form of a tablet which comprises individual, enterically coated, seamless capsules (**1**) in which the at least one proton pump inhibitor is contained dissolved or suspended in a solvent and/or suspending agent.

2. Pharmaceutical preparation according to claim 1, characterised in that the proton pump inhibitor is omeprazole, an alkali salt of omeprazole, an individual enantiomer of omeprazole or an alkali salt thereof or the magnesium salt of S-omeprazole.

3. Pharmaceutical preparation according to one of claims 1 to 2, characterised in that the solvent and/or suspending agent contains an alkaline-reacting compound for the stabilisation of the proton pump inhibitor.

4. Pharmaceutical preparation according to one of claims 1 to 3, characterised in that the seamless capsule contains, apart from the proton pump inhibitor, additionally one or more active ingredients from the NSAID group such as ibuprofen, diclofenac, piroxicam, naproxen, indometacin, fenoprofen, acemetacin, flurbiprofen, *ketoprofen* or a pharmaceutical salt or an enantiomer thereof.

5. Pharmaceutical preparation according to one of claims 1 to 4, characterised in that the seamless capsule contains, apart from the proton pump inhibitor, additionally one or more antibiotics.

6. Process for producing the pharmaceutical preparation according to one of claims 1 to 5, characterised in that at the same time a gastric juice-resistant film solution (**4**), a coating solution or film solution (**3**) and the solution and/or suspension of at least one active ingredient (**2**) is extruded into a cooling solution from a concentrically arranged multi-jet nozzle which consists of at least three nozzles, wherein the at least three nozzles consist of an outer nozzle and an inner nozzle and at least one intermediate nozzle, the intermediate nozzle is located in the intermediate position between the outer nozzle and inner nozzle, the diameter of the three nozzles gradually decreases in this sequence, wherein optionally the cooling liquid in the area of the jet inlet is passed into these oscillations enveloping the jet, and the jet stream is continuously converted into small spherical, enteric, seamless capsule drops (**1**) using the interfacial tension, and the enterically coated seamless capsules (**1**) are pressed to tablets.

7. Process for producing the pharmaceutical preparation according to one of claims 1 to 5, characterised in that at the same time a coating solution or film solution and the solution and/or suspension of the at least one active ingredient is extruded into a cooling solution from a concentrically arranged multi-jet nozzle which consists of at least two nozzles, wherein the inner nozzle has a smaller diameter than the outer nozzle, wherein optionally the cooling liquid in the area of the jet inlet is passed into these oscillations enveloping the jet, and the jet stream is continuously passed into small spherical, seamless capsule drops (**1**) using the interfacial tension, and the in the first instance singly micro-encapsulated active ingredient solution or suspension is covered in the next step in a fluidised bed with a further gastric juice-resistant film, and these enterically coated seamless capsules are pressed to tablets.

There follows a sheet of drawings

Appended drawings

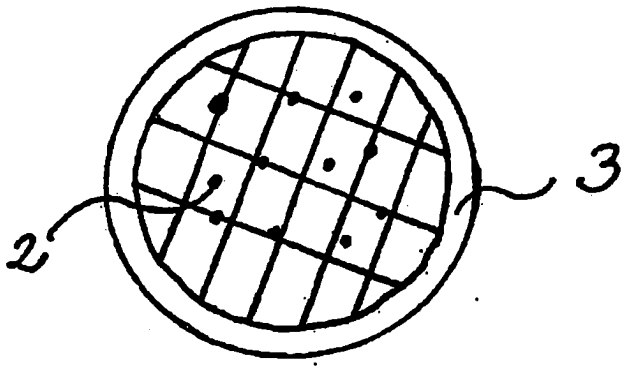


Fig. 1

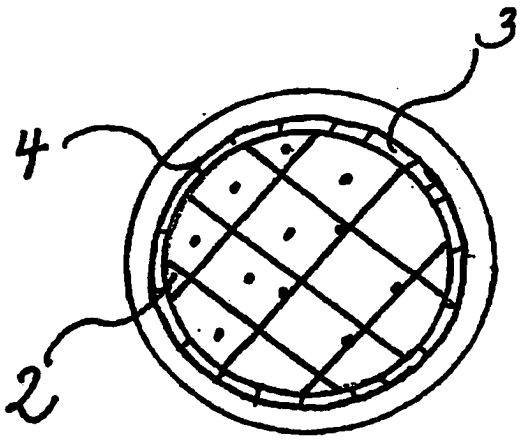


Fig. 2

Translator's notes

There are a number of inconsistencies in the German text, as explained below. All references refer to the German text.

1. Paragraph 0014 – 'denene' (line 4) and 'eienm' (line 5) are assumed to be typing errors and have been corrected in the English translation.
2. Paragraph 0014, line 2 – It has been assumed that 'pharmazeutische' should read 'pharmazeutisch' in line with other places were the phrase occurs (paragraphs 0011 and 0022).
3. Paragraph 0015, line 6; paragraph 0032, line 8; claim 6, line 8 – 'in' (umhüllende Schwingungen) appears to be superfluous and has been omitted in the English translation.
4. Paragraph 0018, line 4 – 'Salz' appears to have been omitted in the German text. 'Salt' has been included in the English translation (in italics).
5. Paragraph 0019, line 5 – 'oder' appears to be superfluous and has been omitted in the English translation.
6. There are several instances in paragraph 0027 where product names have been misspelled in German. These have been checked and corrected (identified in italics).
7. Claim 4, line 4 – No references to 'Uetroprofen' could be found on the internet and it was assumed that this should be 'ketoprofen' (cf the similar list in paragraph 0022).
8. Claim 7, line 8 – It has been assumed that 'Wirkstofflösunge' should be "Wirkstofflösung'

B2

Espacenet
Bibliographic data: DE19801811 (A1) — 1999-07-22

Oral pharmaceutical composition containing antisecretory compound useful for inhibiting stomach acid secretion in treatment of esophagitis, gastritis, duodenitis, gastric ulcers and duodenal ulcers

Inventor(s):	SCHUMANN CHRISTOF [DE] +
Applicant(s):	STADA ARZNEIMITTEL AG [DE] +

Classification:	**- international:**	***A61J3/07; A61K31/44; A61K31/4439; A61K31/54; A61K9/20; A61K9/50;*** (IPC1-7): A61J3/07; A61K31/44; A61K9/50; C07D401/12
	- European:	A61J3/07; A61K31/44; A61K31/4439; A61K31/54; A61K9/20K2B; A61K9/50H6H2; A61K9/50K
Application number:		DE19981001811 19980119
Priority number (s):		DE19981001811 19980119
Also published as:		DE19801811 (B4)

Abstract of DE19801811 (A1)

An orally administered pharmaceutical formulation containing an antisecretory compound, such as omeprazole, comprises a seamless capsule filled with the active compound, which is separated from the capsule by a coating or film. An orally administered pharmaceutical composition contains, as the active ingredient(s), at least one proton pump inhibitor and optional carriers and additives. The composition is in the form of a seamless capsule with a filling comprising the active compound(s), which are suspended or dissolved in a solvent. The filling is separated from the capsule by a coating comprising one or more layers of a film. An independent claim is also included for preparation of the composition.

Last updated: 14.03.2012 Worldwide Database 5.7.36; 92p

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENT- UND MARKENAMT

(12) **Offenlegungsschrift**

(10) **DE 198 01 811 A 1**

(51) Int. Cl.[6]:
A 61 K 9/50
A 61 J 3/07
// C07D 401/12,A61K 31/44

(21) Aktenzeichen: 198 01 811.8
(22) Anmeldetag: 19. 1. 98
(43) Offenlegungstag: 22. 7. 99

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(56) Entgegenhaltungen:

GB	22 90 965 A
US	53 30 835
EP	4 80 729 A1
EP	4 26 479 A7
EP	1 24 495 A2

Die folgenden Angaben sind den vom Anmelder eingereichten Unterlagen entnommen

Prüfungsantrag gem. § 44 PatG ist gestellt

(54) Pharmazeutische Zubereitung zur oralen Verabreichung

(57) Die Erfindung betrifft eine pharmazeutische Zubereitung zur oralen Verarbeitung, enthaltend als Wirkstoff wenigstens einen Protonenpumpeninhibitor und gegebenenfalls pharmazeutisch akzeptable Trägerstoffe, sowie übliche Zusatz- und Hilfssubstanzen, wobei die Zubereitung eine gefüllte, nahtlose Kapsel ist, enthaltend ein Kapselfüllmaterial umfassend den mindestens einen Wirkstoff, der in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert ist, und mindestens eine Schicht bzw. einen Film zum Beschichten des Kapselfüllmaterials.

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DE 198 01 811 A 1

Beschreibung

Die vorliegende Erfindung betrifft eine neue pharmazeutische Zubereitung zur oralen Verabreichung. Sie enthält als Wirkstoff wenigstens eine säurelabile heterozyklische Verbindung, wie einen Protonenpumpeninhibitor, wobei Omeprazol besonders bevorzugt ist. Die erfindungsgemäße pharmazeutische Zubereitung ist insbesondere bestimmt zur Behandlung von Störungen oder Krankheiten des Gastrointestinaltrakts. Weiterhin betrifft die vorliegende Erfindung ein Verfahren zur Herstellung dieser neuen pharmazeutischen Zubereitung.

Protonenpumpeninhibitoren werden allgemein zur Hemmung der Magensäuresekretion sowohl bei Säugetieren als auch bei Menschen eingesetzt.

Allgemein werden sie zur Prävention und Behandlung von Störungen oder Krankheiten, die bei der Magensäuresekretion auftreten, verwendet, einschließlich z. B. Ösophagitis, Gastritis, Duodenitis, gastrischem Ulkus und duodenalem Ulkus. Weiterhin können Protonenpumpeninhibitoren zur Behandlung von anderen gastrointestinalen Störungen eingesetzt werden, bei denen erwünscht ist, daß eine Sekretion der Magensäure unterbleibt, z. B. bei Patienten, die sich einer Therapie mit nichtsteroidalen Antiphlogistika (NSAID) unterziehen. Weiterhin sind Protonenpumpeninhibitoren nützlich bei der Behandlung von Heliobakter-Infektion und damit in Zusammenhang stehenden Krankheiten.

Bekannte Protonenpumpeninhibitoren, die unter ihrem INN Namen bekannt sind, sind z. B. Omeprazol, Lansoprazol, Pantoprazol, Pariprazol, Leminoprazol.

Geeignete Protonenpumpeninhibitoren sind z. B. in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747, WO 90/06925, WO91/19711, WO 91/19712 beschrieben.

Die unter dem generischen Namen Omeprazol bekannte Substanz (5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazol ist in EP-A1-0 005 129 beschrieben. Bestimmte Omeprazolsalze einschließlich alkalischer Omeprazolsalze sind in EP-A-0 124 495 und in WO 95/01977 beschrieben. Weiterhin sind Salze von einzelnen Omeprazolenantiomeren in WO 94/27988 beschrieben.

Protonenpumpeninhibitoren und insbesondere Omeprazol sind jedoch unter Feuchtigkeits- und Säureeinfluß extrem instabil. Z.B. liegt die Halbwertszeit des Abbaus von Omeprazol in wässerigen Lösungen, die ph-Werte von weniger als drei aufweisen, bei weniger als zehn Minuten. Der Abbau von Omeprazol wird von Säuren katalysiert, während alkalische Verbindungen zu einer Stabilisierung führen (siehe WO 96/24338). Die Stabilität von Omeprazol wird ebenfalls durch Wärme, organische Lösungsmittel und in gewisser Weise durch Tageslicht beeinflußt.

Aufgrund der vorgenannten Stabilitätsprobleme muß der Protonenpumpeninhibitor und insbesondere Omeprazol in Form von magensaftresistenten Zubereitungen verabreicht werden. Alle bisherigen Ansätze zur oralen Verabreichung von Protonenpumpeninhibitoren lösen dieses Problem über Darreichungsformen, bei denen der Protonenpumpeninhibitor bzw. das Omeprazol mit Feststoffen zu festen Arzneiformen verarbeitet wird. Beispielsweise seien hier US-4,853,230 sowie WO 96/24338 genannt. Ebenso wie in US-4,786,505, EP-0 277 741 und EP-A-0 342 522 werden in der Patentliteratur Zubereitungen beschrieben, die im wesentlichen aus einem festen Kern bestehen, in dem Omeprazol als stabilisiertes Alkalisalz formuliert ist. Dieser Omeprazol-Kern kann von mehreren Schichten geschützt werden.

WO 96/01623 beschreibt Omeprazoltabletten mit verzögerter Wirkstofffreisetzung, bestehend aus einem Omeprazol-Kernmaterial und darüberliegenden Beschichtungsschichten. Diese Hülle kann aus ein oder mehreren Schichten bestehen, wobei insbesondere eine Methacrylsäurecopolymer (L30D-55)-Schicht verwendet wird.

Daher ist es Aufgabe der Erfindung, eine neue pharmazeutische Zubereitungsform zur oralen Verabreichung, enthaltend als Wirkstoff wenigstens einen Protoneninhibitor und insbesondere Omeprazol, bereitzustellen, wobei der Protonenpumpeninhibitor bzw. Omeprazol nicht mehr mit Feststoffen zu festen Arzneimitteln verarbeitet werden muß. Weiterhin soll ein Verfahren zur Herstellung dieser neuen pharmazeutischen Zubereitung angegeben werden.

Diese Aufgabe wird durch die neue pharmazeutische Zubereitung zur oralen Verabreichung gem. Anspruch 1 gelöst. Die erfindungsgemäße Zubereitung besteht aus einer gefüllten nahtlosen Kapsel, die ein Kapselfüllmaterial d. h. einen Inhalt und einen Film zum Beschichten des Inhalts enthält. Der Inhalt des Kapselfüllmaterials besteht aus dem wenigstens einen Wirkstoff, der in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert ist und ggf. pharmazeutisch akzeptablen Trägerstoffen sowie üblichen Zusatz- und Hilfssubstanzen. Die erfindungsgemäße gefüllte nahtlose Kapsel ist mit mindestens einem Film bzw. einer Schicht beschichtet, so daß die Kapseln die Magenpassage überstehen und erst im Dünndarm den Wirkstoff freisetzen.

Erfindungsgemäß wurde festgestellt, daß Omeprazol erstmals in Form von Lösungen bzw. Suspensionen ebenfalls zu stabilen oralen magensaftresistenten Arzneimitteln verarbeitet werden können.

Die erfindungsgemäße Aufgabe wird weiterhin durch das Verfahren gemäß Anspruch 13 gelöst.

In den Unteransprüchen sind vorteilhafte Ausführungsformen der Erfindung enthalten.

Die Erfindung betrifft daher eine neue pharmazeutische Zubereitungsform zur oralen Verabreichung, enthaltend als Wirkstoff wenigstens einen Protonenpumpeninhibitor und gegebenenfalls pharmazeutische akzeptable Trägerstoffe, sowie übliche Zusatz- und Hilfssubstanzen, wobei die erfindungsgemäße Zubereitung eine gefüllte, nahtlose Kapsel **1** ist, enthaltend ein Kapselfüllamterial **2**, umfassend den mindestens einen Wirkstoff, der in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert ist, und mindestens eine Schicht bzw. einen Film **3** zum Beschichten des Kapselfüllmaterials **2**.

Weiterhin betrifft die vorliegende Erfindung ein Verfahren zur Herstellung der pharmazeutischen Zubereitung wobei man gleichzeitig eine Beschichtungsschicht oder Filmlösung für die nahtlose(n) Kapsel(n) und die Lösung und/oder Suspension des wenigstens einen Wirkstoffes in eine Kühllösung aus einer konzentrisch angeordneten Mehrfachdüse, die wenigstens aus zwei Düsen besteht, extrudiert, wobei die innere Düse einen kleineren Durchmesser als die äußere Düse aufweist, und wobei insbesondere die Kühlflüssigkeit im Bereich des Strahleintritts in diese in den Strahl umhüllende Schwingungen versetzt wird, und der Strahlstrom unter Anwendung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen **1** überführt wird. In einer besonderen Ausführungsform des erfindungsgemäßen Verfahrens kann man eine Mehrfachdüse mit wenigstens drei Düsen einsetzen, bestehend aus einer Außendüse und einer Innendüse und wenigstens einer Zwischendüse, die sich in der Mittelstellung zwischen der Außen- und Innendüse befindet.

Der Durchmesser der drei Düsen steigt graduell in der vorgenannten Reihenfolge an. Gemäß dem erfindungsgemäßen Verfahren wird gleichzeitig eine Filmlösung für die nahtlose Kapsel, die Lösung bzw. die Suspension der Wirksubstanz und eine weitere Filmlösung in eine Kühllösung extrudiert und der Strahlstrom der drei Flüssigkeiten unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen **1** überführt.

Gemäß der Erfindung können die nahtlosen Kapseln **1** eine Größe von 0,3 mm bis 10,0 mm im Durchmesser, insbesondere eine Größe von 0,8 bis 3,0 mm im Durchmesser aufweisen.

Der Protonenpumpeninhibitor im Inneren der Kapsel **1** ist in einer besonderen Ausführungsform durch zwei Schichten **3** und **4** geschützt, einer enterischen Beschichtungsschicht **3** und einer Schicht, die die enterische Besichtungsschicht **4** von den Protonenpumpeninhibitor abtrennt. Erfindungsgemäß kann die vorgenannte Hülle aus einer oder mehreren Schichten bestehen. Die Hüllen sind so gestaltet, daß die Mikrokapseln die Magenpassage überstehen und erst im Dünndarm den Wirkstoff freisetzen. Die so hergestellten Mikrokapseln können in Dosen/Sachets oder Kapseln abgefüllt und/oder unter Zusatz üblicher pharmazeutischer Hilfsstoffe zu Tabletten verpreßt werden.

Als Protonenpumpeninhibitor kommen Stoffe wie Omeprazol, Lansoprazol, Pantoprazol, Pariprazol, Lemiprazol in Betracht, wobei Omeprazol bevorzugt ist. Als Wirkstoff kann gemäß einer besonderen Ausführungsform der Erfindung Omeprazol, ein alkalisches Salz von Omeprazol, ein einzelnes Enantiomer von Omeprazol oder ein alkalisches davon oder ein Magenesiumsalz von S-Omeprazol eingesetzt werden.

Bevor die erfindungsgemäßen nahtlosen Kapseln hergestellt werden, muß Omeprazol in einem geeigneten Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert werden. Als geeignetes Lösungs- und/oder Suspendiermittel kommen Parafinöl, mittelkettige Triglyceride, Isopropylmyristat, Pflanzenöle, niedrigschmelzende Wachse in Betracht. Diesen Lösungs- bzw. Suspendiermitteln können gegebenenfalls alkalisch reagierende Verbindungen zur Stabilisierung des Omeprazols zugesetzt werden. Derartig alkalisch reagierende Verbindungen sind z. B. Aminosäuren wie Lysin, Arginin, Ornitin, Histidin, puffernde Substanzen wie Trometamin, N-Aminozucker wie N-Methyl-D-glukamin (Meglumin), N-Ethyl-D-glukamin (Eglumin), Glukosamin, Dinatrium-N-stearoylglutamat, heterocyclische Aminderivate wie Piperazin, N-Methyl-piperazin, Morpholin, Alkalisalze von Zitronensäure, Weinsäure etc., oder Alkalisalze von Fettsäuren, oder Alkalimetallphosphate, Alkalsilikate oder Alkalikarbonate etc. Besonders bevorzugte alkalisch reagierende Verbindungen zur Stabilisierung sind Harnstoff, Natriumhydrogencarbonat, Natriumhydorgenphosphat und Natriumacetat.

Die Menge der alkalischen Verbindung sollte etwa 0,1 mmol/g Wirkstoff bis zu 15 mmol/g Wirkstoff betragen.

Die Hülle bzw. die Hüllen der erfindungsgemäßen nahtlosen Kapseln können aus Gelatine, Agar und/oder Kombinationen von Gelatine und/oder Agar mit Pektin und/oder Hydroxypropylmethylcellulose und/oder Chitosan und/oder Polyacrylaten bestehen, wobei Methacrylsäurecopolymere (z. B. L30D-55) bevorzugt sein können. Die Menge an verwendeter Gelatine und/oder Agar oder der vorbeschriebenen Gemische beträgt normalerweise 60 bis 90 Gewichtsprozent des Gesamtgewichtes des Kapselfilms. Geeignetes niederes Methoxypectin mit einem Molekulargewicht von nicht mehr als 200 000 und einem Methoxylierungsgrad von 1–6% liegt vorzugsweise in einer Menge von 5–20 Gew.-%, vorzugsweise in einer Menge von 10–15 Gew.-%, bezogen auf das Gesamtgewicht des Films, vor.

Die Beschichtungsschichten können ebenfalls pharmazeutisch akzeptable Weichmacher wie z. B. Phtalsäureestercetylalkohol, Polyethylenglykole etc. enthalten. Die Menge an Weichmacher beträgt üblicherweise 15-50 Gew.-%, bezogen auf das Gesamtgewicht der Beschichtung. Um die säurelabilen Substanzen zu schützen, beträgt die Schichtdicke der Beschichtung wenigstens 10 µm, vorzugsweise 20 µm.

Das Kapselfüllmaterial **2** kann neben dem Wirkstoff noch Bindemittel, oberflächenaktive Substanzen, Füllstoffe und andere bekannte Zusatz- und Hilfsstoffe enthalten. Bindemittel sind zum Beispiel Cellulosen wie Hydroxypropylmethylcellulosen, Hydroxypropylcellulose und Carboxymethylcellulose, Polyvinylpyrolidon, Stärken und andere Substanzen.

Der Protonenpumpeninhibitor kann in einer Menge von 5–80 mg, insbesondere in einer Menge von 10–50 mg in der Kapselfüllung **2** vorliegen. Als Protonenpumpeninhibitor wird Omeprazol besonders bevorzugt.

Neben den nahtlosen Kapseln mit dem Protonenpumpeninhibitor kann zusätzlich mindestens ein weiterer Wirkstoff aus der Gruppe der NSAID wie Ibuprofen, Diclofenac, Piroxicam, Naproxen, Indomethazin, Fenoprofen, Acemetacin, Flurbiprofen, Ketroprofen oder ein pharmazeutisches Salz davon oder ein Enantiomeres davon vorliegen. Vorzugsweise liegt der Wirkstoff aus der Gruppe NSAID in einer Dosierung von 20–1000 mg vor.

In einer anderen Ausführungsform der Erfindung kann neben den nahtlosen Kapseln mit dem Protonenpumpeninhibitor zusätzlich eine oder mehrere antimikrobiell wirksame Substanzen vorliegen.

Geeignete antibakteriell wirksame Substanzen schließen z. B. Antibiotika, Tetracycline, Nitroimidazole, Penicilline, Cephalosporine, Carbopenemene, Aminoglykoside, Macrolid-Antibiotika, Linkosamid-Antibiotika, 4-Quinolone, Rifarnycine, Nitrofurnatoin ein. Beispiele sind: Ampicillin, Amoxicillin, Benzylpenicillin, Phenoxymethylpenicillin, Bacampicillin, Pivampicillin, Carbenicillin, Cloxacillin, Clyclacillin, Dicloxacillin, Methicillin, Oxacillin, p-Peracillin, Ticarcilin, Flucloxacillin, Cefuroxime, Cefetamet, Cefetram, Cefixim, Cefoxitin, Ceftazidim, Ceftizoxim, Latamoxef, Cefoperazon, Ceftriaxon, Cefsulodin, Cefotaxim, Cephalexin, Cefaclor, Cefadroxil, Cefalothin, Cefazolin, Cefpodoxim, Ceftibuten, Aztreonam, Tigemonam, Erythromycin, Dirithromycin, Roxithromycin, Azithromycin, Clarithromycin, Clindamycin, Paldimycin, Lincomycin, Vancomycin, Spectinomycin, Tobramycin, Paromomycin, Metronidazol, Tinidazol, Ornidazol, Amifloxacin, Cinoxacin, Ciprofloxacin, Difloxacin, Enoxacin, Fleroxadin, Norfloxacin, Ofloxacin, Temafloxacin, Doxycyclin, Minoclyclin, Tetracyclin, Chlortetracyclin, Oxytetracyclin, Methacyclin, Rolitracyclin, Nitrofurantoin, Nalidixinsäure, Gentamicin, Rifampicin, Amikacin, Netilmicin, Imipenem, Cilastatin, Chloramphenicol, Furazolidone, Nifuroxazide, Sulfadiazin, Sulfametoxazol, Wismutsubsalizylat, kolloidales Wismutsubcitrat, Gramicidin, Mecillinam, Cloxiquin, Chlorhexidin, Dichlorobenzylalkohol, Methyl-2-pentylphenol, wobei Clarithromycin, Erythromycin, Roxithromycin, Azithromycin, Amoxicillin, Metronidazol, Tinidazol und Tretracylin bevorzugt sind.

Erfindungsgemäß bevorzugt sind folgende Wirkstoffkombinationen:

Omeprazol	20 mg
Clarithormycin	250 bzw. 500 mg
Metronidazol	400 mg

In einer anderen Ausführungsform der Erfindung ist eine Kombination von:

Omeprazol	20 mg
Amoxicillin	1000 mg
Clarithromycin	500 mg

als Füllmaterial **2** bevorzugt. In einer weiteren Ausführungsform der Erfindung wird folgende Kombination als Wirkstoff in die nahtlosen Kapseln eingefüllt:

Omeprazol	20 mg
Clarithromycin	1000 mg
Metronidazol	400 mg

Gemäß einer besonders bevorzugten Ausführungsform der Erfindung, können die nahtlosen Kapseln **1** in Hartgelatinekapseln eingefüllt und konfektioniert werden. In einer anderen Form kann die erfindungsgemäße pharmazeutische Zubereitung die Form einer Tablette aufweisen, die den Protonenpumpeninhibitor in Form von einzelnen, enterisch beschichteten gefüllten nahtlosen Kapseln enthält, wobei die enterisch Beschichtungsschicht **3** die einzelnen nahtlosen Kapseln beschichtet, um ihnen mechanische Festigkeit zu verleihen, so daß beim Tablettieren der gefüllten nahtlosen Kapseln **1** die Säurebeständigkeit der enterischbeschichteten gefüllten nahtlosen Kapseln **1** nicht beeinträchtigt wird.

Die nahtlosen Kapseln mit den Protoneninhibitoren können aber auch als solche oder zusammen mit weiteren Pulvergranulaten, Pellets in Beuteln oder Dosen bzw. Sachets eingefüllt sein.

Die Herstellung der erfindungsgemäßen Kapseln (vergleiche **Fig.** 1 bzw. **Fig.** 2) erfolgt über Zwei- bzw. Dreistoffdüsen, wobei gleichzeitig eine Beschichtungs- oder Filmlösung für die nahtlosen Kapseln und die Lösung und der Suspension des Wirkstoffes in eine Kühllösung aus einer konzentrisch angeordneten Mehrfachdüse extrudiert wird, wobei die innere Düse einen kleineren Durchmesser als die der äußeren Düse aufweist. Die Kühlflüssigkeit wird gegebenenfalls im Bereich des Strahleintritts in diese in umhüllende Schwingungen versetzt und der Strahlstrom wird unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen **1** überführt.

Fig. 1 ist eine schematische Darstellung der erfindungsgemäßen Mikrokapsel **1** mit einer Hülle **3**. Omeprazol befindet sich in Lösung oder Suspension als Kapselfilmmaterial. **Fig.** 2 zeigt eine Omeprazolmikrokapsel **1** mit einer inerten oder magensaftresistenten Hülle **1** (Schicht **3**) oder sowie einer zweiten magensaftresitenten Hülle **2** (Schicht **4**).

Die Herstellung der erfindungsgemäßen nahtlosen Kapsel erfolgt über eine spezielle Technologie. Dabei wird die Lösung des Wirkstoffes **2** in den Düsenteil einer Zwei- bzw. Dreistoffdüse geleitet und aus der inneren Düse extrudiert und eine viskose Flüssigkeit **3** mit einer Hüllsubstanz, die in Wasser unlöslich ist, aus einer ringförmigen zweiten Düse extrudiert. Gleichzeitig wird eine weitere Lösung für die Hülle **4** aus der äußeren dritten Düse extrudiert und der Strahl in eine Kühlflüssigkeit eingedüst, so daß die nahtlosen Kapseln **1** der Erfindung erhalten werden.

Die nahtlosen Kapseln **1** können dann gegebenenfalls getrocknet und gewaschen werden.

Im allgemeinen können Gelatine und/oder Kombinationen von Gelatine mit Pektin usw. als Hüllsubstanzen verwendet werden.

Beispiele

Die folgenden Beispiele sollen die Erfindung näher erläutern, ohne sie einzuschränken.

Beispiel 1

Im folgenden soll die Herstellung der Omeprazolmikrokapseln gemäß **Fig.** 1 beschrieben werden. Die Mikrokapsel hat folgende Zusammensetzung:

Zusammensetzung einer Mikrokapsel

Ausführungsbeispiel zu **Fig.** 1

Füllung: (Lösung (a))	Omeprazol	0,40 mg	Verhältnis 70 %
	Natriumlaurylsulfat	0,001 mg	
	Paraffinöl	8,00 mg	
Hülle: (Lösung (b))	Gelatine	1,823 mg	20 %
	Gummiarab.	0,351 mg	
	Pektin	0,687 mg	
		= 11,262 mg	

50 dieser Mikrokapseln werden in konventionelle Hartgelatinekapseln abgefüllt.

Unter Verwendung einer konzentrischen Doppeldüse wurde eine Omeprazollösung, die Parafinöl und Natriumlaurylsulfat enthielt (Lösung (a)), aus der inneren Düse extrudiert und eine Gelatine/Gummi-Arabikum/Pektinlösung auf 80°C erhitzt (Lösung (b)) und aus einer äußeren Düse zur gleichen Zeit in einem Verhältnis von 70% zu 20% ein Kühlmittel: in Pflanzenöl extrudiert, das eine Temperatur von etwa 12°C aufwies und eine Strömungsgeschwindigkeit von 0,3 m/Sekunde hatte. Die erhaltenen Kapseln wurden getrocknet.

Beispiel 2

Im folgenden wird die Herstellung der in **Fig.** 2 beschriebenen gecoateten Mikrokapseln beschrieben. Die Mikrokapseln hatten folgende Zusammensetzung.

Füllung: (Lösung (a))	Omeprazol	0,44 mg	Verhältnis 65%
	Cetiol HE	1,25 mg	
	Paraffinöl	7,00 mg	
	Dinatriummonohydrogenphosphat	0,05 mg	
	Natriumlaurylsulfat	0,002 mg	
		= 8,742 mg	
Hülle 1: (Lösung (b))	Gelatine	1,537 mg	20%
	Gummiarab.	0,374 mg	
	Pectin	0,483 mg	
		= 2,394 mg	
Hülle 2: (Lösung (c))	Eudragit L100	1,038 mg	15%
	Triethylcitrat	0,085 mg	
	Talkum	0,256 mg	
	Titandioxid	0,132 mg	

Die Mikrokapseln wurden in Hartgelatinekapseln oder Sachets abgefüllt. Im Unterschied zu **Fig.** 1 wurde hier eine Dreistoffdüse verwendet und Lösungen der Hüllen (Lösung (b)), Lösung (c)) sowie Lösungen mit den Wirkstoffen (Lösung (a)) in einem Verhältnis von 65% : 20% :15% gleichzeitig in Pflanzenöl mit einer Temperatur von 12°C extrudiert. Die Mikrogelatinekapseln wurden wie oben beschrieben getrocknet und in Hartgelatinekapseln oder Sachets abgefüllt.

Beispiel 3

Es wurde eine gecoatete Mikrokapsel mit einer Dreistoffdüse, wie dies in Beispiel 2 beschrieben ist, mit den folgenden Zusammensetzungen hergestellt.

Zusammensetzung einer gecoateten Mikrokapsel

Füllung: (Lösung (a))	Omeprazol	0,50 mg	Verhältnis 65%
	Mittelkettige Triglyceride	6,03 mg	
	Natriumhydorgenphosphat	0,0025 mg	
	Natriumlautylsulfat	0,002 mg	
		= 6,5345 mg	
Hülle: (Lösung (b))	Gelatine	1,625 mg	20%
	Gummiarab.	0,234 mg	
	Pectin	0,526 mg	
		= 2,385 mg	
Hülle 2: (Lösung (c))	HPMC phthalat	0,938 mg	15%
	Diethyl phthalat	0,023 mg	
		0,961 mg	
		= 9,8805 mg	

Die Mikrokapseln wurden dann weiter zu einer Tablette weiterverarbeitet mit der folgenden Tablettiermischung:

Omeprazol	
Mikrokapseln 40 Stück	395,22 mg
Maisstärke	225,00 mg
Mikrokristalline Cellulose	375,00 mg
Aerosil 200	5,00 mg
Magnesiumstearat	10,00 mg
	= 1010,22 mg

Bezugszeichenliste

1 nahtlose Kapsel
2 Kapselfüllmaterial
3 Hülle **1** (inert) und/oder magensaftresistent
4 Hülle **2** magensaftresistent
※ Omeprazol in Suspension oder Lösung

Patentansprüche

1. Pharmazeutische Zubereitung zur oralen Verabreichung, enthaltend als Wirkstoff wenigstens einen Protonenpumpeninhibitor und gegebenenfalls pharmazeutisch akzeptable Trägerstoffe, sowie übliche Zusatz- und Hilfssubstanzen, **dadurch gekennzeichnet**, daß die Zubereitung eine gefüllte, nahtlose Kapsel (**1**) ist, enthaltend ein Kapselfüllmaterial (**2**) umfassend den mindestens einen Wirkstoff, der in einem Lösungs- und/oder Suspendiermittel gelöst bzw. suspendiert ist, und mindestens eine Schicht bzw. einen Film (**3**) zum Beschichten des Kapselfüllmaterials (**2**).

2. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß Anspruch 1, dadurch gekennzeichnet, daß die Kapseln eine Größe von 0,3 mm bis 10 mm im Durchmesser aufweisen.

3. Pharmazeutische Zubereitung zur oralen Verabreichung nach Anspruch 1, dadurch gekennzeichnet, daß die Kapseln eine Größe von 0,8 mm bis 3 mm im Durchmesser aufweisen.

4. Pharmazeutische Zubereitung zur oralen Verabreichung nach einem der vorhergehenden Ansprüche 1 bis 3, dadurch gekennzeichnet, daß der Protonenpumpeninhibitor durch zwei Schichten (**3**, **4**) geschützt ist, eine enterische Beschichtungsschicht (**4**) und einen Film bzw. eine Schicht (**3**), die die enterische Beschichtungsschicht (**4**) von dem Protonenpumpeninhibitor abtrennt.

5. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 4, dadurch gekennzeichnet, daß der Protonenpumpeninhibitor Omeprazol, ein alkalisches Salz von Omeprazol, ein einzelnes Enantiomer von Omeprazol oder ein alkalisches Salz davon oder das Magnesiumsalz von S-Omeprazol ist.

6. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der Ansprüche 1 bis 5, dadurch gekennzeichnet, daß der Protonenpumpeninhibitor in einer Menge von 5 mg bis 80 mg, insbesondere in einer Menge von 10 mg bis 50 mg in der Kapselfüllung (**2**) vorliegt.

7. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 6, dadurch gekennzeichnet, daß das Lösungs- und/oder Suspendiermittel eine alkalisch reagierende Verbindung zur Stabilisierung des Protonenpumpeninhibitors enthält.

8. Pharmazeutische Zubereitung einer oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 7, dadurch gekennzeichnet, daß sie neben den nahtlosen Kapseln mit dem Protonenpumpeninhibitor zusätzlich einen oder mehrere Wirkstoffe aus der Gruppe der NSAID wie Ibuprofen, Diclofenac, Piroxicam, Naproxen, Indomethazin, Fenoprofen, Acemetacin, Flurbiprofen, Uetroprofen oder pharmazeutisches Salz oder ein Enantiomeres davon enthält.

9. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 8, daß sie die neben den nahtlosen Kapseln mit dem Protonenpumpeninhibitor zusätzlich ein oder mehrere Antibiotika enthält.

10. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 9, dadurch gekennzeichnet, daß sie in Form einer Hartgelatinekapsel vorliegt, in der die nahtlosen Kapseln (**1**) gemäß einem der vorhergehenden Ansprüche 1 bis 9 enthalten sind.

11. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 9, dadurch gekennzeichnet, daß sie in Form einer Tablette vorliegt, die den Protonenpumpeninhibitor in Form von einzelnen, enterisch beschichteten, gefüllten nahtlosen Kapseln (**1**) enthält, wobei die enterische Beschichtungsschicht (**3**) die einzelnen nahtlosen Kapseln beschichtet, um ihnen mechanische Festigkeit zu verleihen, so daß beim Tablettieren der gefüllten nahtlosen Kapseln (**1**), die Säurebeständigkeit der enterisch beschichteten, gefüllten nahtlosen Kapseln (**1**) nicht beeinträchtigt wird.

12. Pharmazeutische Zubereitung zur oralen Verabreichung gemäß einem der vorhergehenden Ansprüche 1 bis 8, dadurch gekennzeichnet daß die nathlosen Kapseln mit dem Protonenpumpeninhibitor als solche oder zusammen mit weiterem Pulvergranulat oder Pellets in Beuteln oder Dosen bzw. Sachets gefüllt sind.

13. Verfähren zum Herstellen der pharmazeutischen Zubereitung gemäß einem der vorhergehenden Ansprüche 1 bis 9, dadurch gekennzeichnet, daß man gleichzeitig eine Beschichtungs- oder Filmlösung für die nahtlose(n) Kapsel(n) (**1**) und die Lösung und/oder Suspension des wenigstens einen Wirkstoffes in eine Kühllösung aus einer konzentrisch angeordneten Mehrfachdüse, die aus wenigstens zwei Düsen besteht, extrudiert, wobei die innere Düse einen kleineren Durchmesser als die äußere Düse aufweist, wobei insbesondere die Kühlflüssigkeit im Bereich des Strahleintritts in diese in den Strahl umhüllende Schwingungen versetzt wird, und der Strahlstrom unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische nahtlose Kapseltropfen (**1**) überführt wird.

14. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß die zunächst einfach mikroverkapselte Wirkstofflösung bzw. -suspension im nächsten Schritt in einer Wirbelschicht mit einem weiteren magensaftresistenten Überzug (**4**) versehen wird.

15. Verfahren nach Anspruch 13, dadurch gekennzeichnet, daß man eine Mehrfachdüse mit wenigstens drei Düsen einsetzt, bestehend aus einer Außendüse und einer Innendüse und wenigstens einer Zwischendüse, die sich in der Mittelstellung zwischen der Außen- und Innendüse befindet, wobei der Durchmesser der drei Düsen graduell in dieser Reihenfolge ansteigt, und gleichzeitig eine Filmlösung für die nahtlose Kapsel, die Lösung bzw. die Suspension

der Wirksubstanz und eine weitere Filmlösung in eine Kühllösung extrudiert und der Strahlstrom der drei Flüssigkeiten unter Ausnutzung der Grenzflächenspannung kontinuierlich in kleine sphärische, nahtlose Kapseltropfen (**1**) überführt wird.

Hierzu 1 Seite(n) Zeichnungen

Nummer: **DE 198 01 811 A1**
Int. Cl.[6]: **A 61 K 9/50**
Offenlegungstag: 22. Juli 1999

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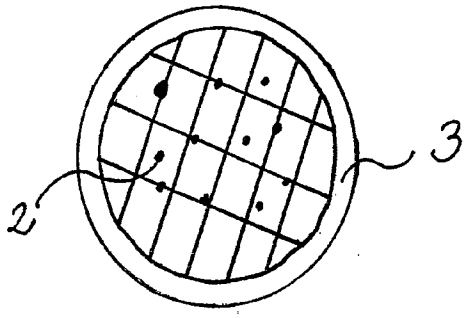

Fig. 1

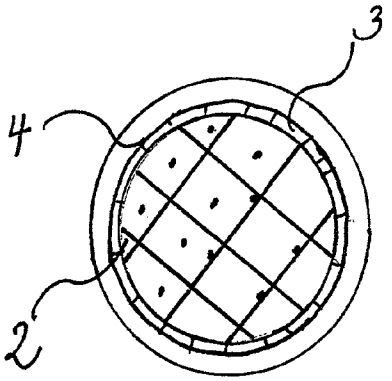

Fig. 2

(19) BUNDESREPUBLIK DEUTSCHLAND

DEUTSCHES PATENTAMT

(12) **Offenlegungsschrift**

(10) **DE 40 35 455 A 1**

(21) Aktenzeichen: P 40 35 455.5
(22) Anmeldetag: 8. 11. 90
(43) Offenlegungstag: 14. 5. 92

(51) Int. Cl.[5]:
C 07 D 401/12
C 07 D 491/056
C 07 H 15/18
// (C07D 401/12, 235:28,213:34) (C07D 491/056,235:00, 325:00)

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(54) Enantiomerentrennung

(57) Die Erfindung betrifft konfigurativ einheitliche, enantiomer reine Pyridylmethylsulfinyl-1H-benzimidazole, ein Verfahren zu ihrer Herstellung und neue Zwischenprodukte, die in dem Verfahren benötigt werden.

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Beschreibung

Anwendungsgebiet der Erfindung

Die Erfindung betrifft ein Verfahren zur Auftrennung von chiralen Pyridylmethylsulfinyl-1H-benzimidazolen in ihre Enantiomeren. Die Enantiomeren werden in der pharmazeutischen Industrie zur Herstellung von Medikamenten verwendet.

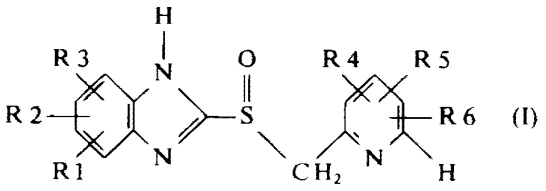
Stand der Technik

In einer Vielzahl von Patentanmeldungen und Patenten werden Pyridylmethylsulfinyl-1H-benzimidazole beschrieben, die magensäuresekretionshemmende Eigenschaften besitzen. Im Zusammenhang mit der vorliegenden Erfindung seien hier beispielsweise die folgenden Patentanmeldungen und Patente erwähnt: EP-B-5 129, EP-A-1 34 400 (= USP 45 55 518), EP-A-1 27 763 (=USP 45 60 693), EP-B-1 66-287 (=USP 47 58 579), EP-A-1 74 726, EP-A-2 01 575 (=USP 46 86 230), WO89/05 299 und WO89/11 479. — Es ist weiterhin bekannt, daß diese Pyridylmethylsulfinyl-1H-benzimidazole ein Chiralitätszentrum besitzen und daß sie daher in ihre Enantiomeren trennbar sein sollten. Trotz der Vielzahl von Patentanmeldungen auf dem Gebiet der Pyridylmethylsulfinyl-1H-benzimidazole ist bisher jedoch noch kein Verfahren beschrieben worden, mit dessen Hilfe die Pyridylmethylsulfinyl-1H-benzimidazole in die optischen Antipoden getrennt werden könnten. Auch die Enantiomeren der Pyridylmethylsulfinyl-1H-benzimidazole sind bisher (mangels eines geeigneten Trennverfahrens) noch nicht isoliert und charakterisiert worden.

Beschreibung der Erfindung

Es wurde nun ein Verfahren gefunden, mit dessen Hilfe die nachstehend näher bezeichneten Pyridylmethylsulfinyl-1H-benzimidazole in ihre optischen Antipoden gespalten werden können.

Das Verfahren ist dadurch gekennzeichnet, daß man Verbindungen der Formel I,



(I)

worin

R1 Wasserstoff, 1-4C-Alkyl oder 1-4C-Alkoxy bedeutet,

R2 Wasserstoff, Trifluormethyl, 1-4C-Alkyl, 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy. Chlordifluormethoxy, 2-Chlor-1,1,2-trifluormethoxy oder gemeinsam mit R3 gewünschtenfalls ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeutet,

R3 Wasserstoff, 1-4C-Alkyl, 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy, Chlordifluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R2 gewünschtenfalls ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeutet,

R4 Wasserstoff oder 1-4C-Alkyl bedeutet,

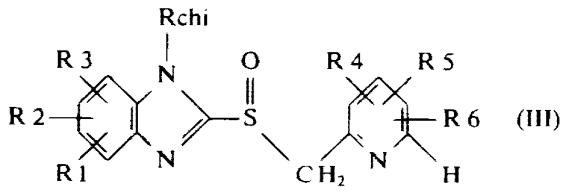
R5 Wasserstoff, 1-4C-Alkyl oder 1-4C-Alkoxy bedeutet und

R6 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy oder Benzyloxy bedeutet,

oder ihre Salze mit Basen mit konfigurativ einheitlich chiralen Verbindungen der Formel II,

Rchi—X (II)

worin Rchi einen konfigurativ einheitlichen, chiralen Rest und X eine Abgangsgruppe darstellt, umsetzt, das erhaltene Isomeren- bzw. Diastereomerengemisch III,



(III)

worin R1, R2, R3, R4, R5 und R6 die oben angegebenen Bedeutungen haben und Rchi einen konfigurativ einheitlichen, chiralen Rest darstellt, trennt und aus den optisch reinen Diastereomeren die konfigurativ einheitlichen, optisch reinen Verbindungen I durch Solvolyse in stark saurem Medium freisetzt.

1-4C-Alkyl steht für geradkettige oder verzweigte Alkylreste; beispielsweise seien der Butyl-, i-Butyl-, sec.-Butyl-, t-Butyl-, Propyl-, Isopropyl-, Ethyl- und insbesondere der Methylrest genannt.

1-4C-Alkoxy steht für geradkettige oder verzweigte Alkoxyreste; beispielsweise seien genannt der Butoxy-, i-Butoxy-, sec.-Butoxy-, t-Butoxy-, Propoxy-, Isopropoxy-, Ethoxy- und insbesondere der Methoxyrest.

Als ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy seien beispielsweise der 1,2,2,-Trifluorethoxy-, der 2,2,3,3,3-Pentafluorpropoxy-, der Perfluorethoxy- und insbesondere der 1,1,2,2-Tetrafluorethoxy-, der Trifluormethoxy-, der 2,2,2-Trifluorethoxy- und der Difluormethoxyrest genannt.

Wenn R2 und R3 gemeinsam ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeuten, so sind die Substituenten R2 oder R3 in Nachbarpositionen am Benzoteil des Benzimidazolringes gebunden.

Als ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy seien beispielsweise der 1,1-Difluorethylendioxy- ($-O-CF_2-CH_2-O-$), der 1,1,2,2-Tetrafluorethylendioxy- ($-O-CF_2-CF_2-O-$) und insbesondere der Difluormethylendioxy- ($-O-CF_2-O-$) und der 1,1,2-Trifluorethylendioxyrest ($-O-CF_2-CHF-O-$) genannt.

Als Verbindungen der Formel II kommen prizipiell alle chiralen, konfigurativ einheitlichen Verbindungen in Frage, die mit der Verbindung I oder ihrem Anion unter Abspaltung der Abgangsgruppe X zu reagieren in der Lage sind und deren Rest Rchi nach der Diastereomerentrennung glatt und ohne unerwünschte Nebenreaktion wieder abgespalten werden kann.

Als Abgangsgruppen X kommen insbesondere alle nucleophil ablösbaren Atome oder Gruppen, wie beispielsweise Halogenatome (J, Br oder insbesondere Cl) oder durch Veresterung (z. B. mit Sulfonsäuren) aktivierte Hydroxylgruppen ($-O-SO_2-CH_3$, $-O-SO_2-CF_3$ oder $-O-SO_2-C_6H_4-p-CH_2$) in Frage.

Als Reste Rchi kommen alle konfigurativ einheitlichen Reste in Frage, die sich von natürlich vorkommenden oder synthetisch zugänglichen chiralen Verbindungen ableiten lassen und die solvolytisch unter sauren Bedingungen aus den Verbindungen III abgespalten werden können. Als Reste Rchi seien insbesondere genannt

- Glycosylreste, die sich von Glycopyranosen, Glycofuranosen oder Oligosacchariden ableiten und die gewünschtenfalls mit in der Kohlenhydratchemie üblichen Schutzgruppen teilweise oder vollständig geschützt sind, oder
- chirale, über das Sauerstoffatom verknüpfte Terpenalkoholreste, oder
- andere chirale, über das Sauerstoffatom verknüpfte Alkoholreste,

die jeweils an dem als Verknüpfungsglied fungierenden Sauerstoffatom eine Carbonylgruppe oder insbesondere eine Methylengruppe tragen.

Bevorzuge Reste Rchi sind Reste der Formel IV

$$R'-O-CH_2- \quad (IV)$$

worin R' gemeinsam mit dem Sauerstoffatom, woran es gebunden ist, einen Glycosylrest, einen chiralen Terpenalkoholrest, oder einen sonstigen chiralen Alkoholrest darstellt.

Als Glycosylreste $R'-O-$ seien beispielsweise die Reste genannt, die sich von natürlich vorkommenden Mono- oder Disacchariden, wie Arabinose, Fructose, Galactose, Glucose, Lactose, Mannose, Ribose, Xylose, Maltose, Sorbose oder N-Acetyl-D-glucosamin herleiten.

Als chirale Terpenalkoholreste $R'-O-$ seien insbesondere solche Reste genannt, die sich von einem natürlich vorkommenden oder synthetisch leicht zugänglichen Terpenalkohol herleiten. Als beispielhafte Terpenalkohole seien hierbei genannt: Isopulegol, Neomenthol, Isomenthol, Menthol, Carveol, Dihydrocarveol, Terpinen-4-ol, Mirtenol, Citronellol, Isoborneol, Borneol, Isopinocampheol und insbesondere Fenchol.

Als sonstige chirale Alkoholreste $R'-O-$ seien beispielsweise die Reste genannt, die sich von folgenden Alkoholen herleiten: Mandelsäureester, Cinchonidin, Cinchonin, Ephedrin, Serinmethylester, Sitosterol, 3-Hydroxy-2-methyl-propionsäuremethylester und Milchsäureethylester.

Ein besonders bevorzugter Rest Rchi ist der Fenchyloxymethylrest.

Die Umsetzung der Verbindung I mit der Verbindung II erfolgt auf eine dem Fachmann vertraute Weise. Zur Erhöhung der Nucleophilie der Verbindungen I ist es zweckmäßig, diese zu deprotonieren, d. h. von den Salzen der Verbindungen I mit Basen auszugehen. Als Beispiele für basische Salze seien Natrium-, Kalium-, Calcium-, Aluminium-, Magnesium-, Titan-, Ammonium- oder Guanidiniumsalze erwähnt, die beispielsweise durch Umsetzung der Verbindungen I mit den entsprechenden Hydroxiden (z. B. Natriumhydroxid oder Kaliumhydroxid) auf übliche Weise erhalten werden können.

Die Umsetzung der Verbindungen I mit Verbindungen II wird in inerten, protischen oder aprotischen Lösungsmitteln durchgeführt. Als solche eignen sich beispielsweise Methanol, Isopropanol, Dimethylsulfoxid, Aceton, Acetonitril, Dioxan, Dimethylformamid und vorzugsweise N-Methylpyrrolidon.

Die Umsetzung wird — in Abhängigkeit von der Reaktivität der Verbindung II — vorzugsweise bei Temperaturen zwischen $-30°C$ und $+100°C$, insbesondere bei Temperaturen zwischen $0°C$ und $50°C$ durchgeführt.

Die Trennung des nach der Umsetzung von I mit II erhaltenen Diastereomerengemisches erfolgt in an sich bekannter Weise, beispielsweise durch Chromatographie an geeigneten Säulen oder vorzugsweise durch fraktionierte Kristallisation.

Aufgrund der Prototropie im Benzimidazolteil der Verbindungen I (die 5- und 6-Positionen einerseits bzw. die 4- und 7-Positionen andererseits sind zueinander identisch) entstehen bei der Umsetzung mit den Verbindungen II bei entsprechendem Substitutionsmuster im Benzimidazol Isomerengemische. Zweckmäßigerweise werden die Isomeren noch vor Trennung der Diastereomeren voneinander getrennt, beispielsweise durch Säulen-

chromatographie an geeignetem Trägermaterial (z. B. Kieselgel) und mit geeigneten Elutionsmitteln (z. B. Ethylacetat).

Die Freisetzung der konformativ einheitlichen Verbindungen I aus den optisch reinen Diastereomeren III erfolgt durch Solvolyse unter stark sauren Bedingungen. Als für die Solvolyse geeignete Reagenzien seien beispielsweise starke höherkonzentrierte Säuren (z. B. 60—100%ige Schwefelsäure, konzentrierte Salzsäure, wasserfreie oder wasserhaltige Tetrafluorborsäure, Methansulfonsäure, Trifluormethansulfonsäure, Phosphorsäure oder Perchlorsäure), bevorzugt ca. 90%ige Schwefelsäure genannt. Die Freisetzung erfolgt vorzugsweise bei Temperaturen zwischen 0° und 40° C. Bei der auf die Freisetzung folgenden Aufarbeitung wird vorteilhafterweise so verfahren, daß der pH-Wert möglichst rasch erhöht wird, beispielsweise durch Einbringen der stark sauren Lösung in Pufferlösung oder bevorzugt in Lauge.

Die Verbindungen der Formel II sind bekannt bzw. sie sind auf eine für den Fachmann vertraute Weise aus bekannten Verbindungen auf analoge Weise zugänglich. So können beispielsweise die Verbindungen II, in denen Rchi die Bedeutung der Formel IV hat und X ein Chloratom darstellt, durch Chlormethylierung entsprechender Alkohole [z. B. in Analogie zu R. C. Ronald et. al., J. Org. Chem. 45 (1980) 2224] hergestellt werden.

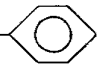
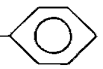
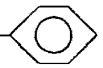
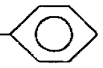
Die Verbindungen der Formel III sind neu und ebenfalls Gegenstand der Erfindung.

Die konfigurativ einheitlichen, optisch reinen Verbindungen der Formel I sind ebenfalls neu und daher auch Gegenstand der Erfindung.

Als beispielhafte, durch das erfindungsgemäße Verfahren herstellbare, optisch reine Verbindungen der Formel I und als dazugehörige erfindungsgemäße Zwischenprodukte III seien anhand der Substituentenbedeutungen in den obenstehenden Formeln I bzw. III die folgenden Verbindungen der nachstehenden Tabelle 1 besonders erwähnt:

Tabelle 1

R1	R2, R3		R4	R5	R6
H	5-CF_3	H	H	H	4-OCH_3
H	5-CF_3	H	3-CH_3	H	4-OCH_3
H	5-CF_3	H	3-CH_3	5-CH_3	4-OCH_3
H	5-OCH_3	H	3-CH_3	5-CH_3	4-OCH_3
H	5,6-O—CH_2—O—		H	H	4-OCH_3
H	5,6-O—CH_2—CH_2—O—		H	H	4-OCH_3
H	H	5-OCF_3	H	H	4-OCH_3
H	H	5-OCF_3	3-CH_3	H	4-OCH_3
H	H	5-OCF_3	H	5-CH_3	4-OCH_3
H	H	5-OCF_2CF_2H	H	H	4-OCH_3
H	H	5-OCF_2CF_2H	3-CH_3	H	4-OCH_3
H	H	5-OCF_3	3-CH_3	5-CH_3	4-OCH_3
H	H	5-OCH_2CF_3	3-CH_3	H	4-OCH_3
H	H	5-OCF_2H	3-CH_3	H	4-OCH_3
H	5-OCF_2H	6-OCF_2H	H	H	4-OCH_3
H	5-OCF_2H	6-OCF_2H	3-CH_3	H	4-OCH_3
H	5-OCH_3	6-OCF_2H	3-CH_3	H	4-OCH_3
H	H	5-OCF_2Cl	H	H	4-OCH_3
H	5,6-O—CF_2—O—		H	H	4-OCH_3
H	5,6-O—CF_2—O—		3-CH_3	H	4-OCH_3
H	5,6-O—CF_2—CHF—O—		H	H	4-OCH_3
H	5,6-O—CF_2—CHF—O—		3-CH_3	H	4-OCH_3
H	5,6-O—CF_2—O—		H	5-CH_3	4-OCH_3
H	5,6-O—CF_2—CHF—O—		3-CH_3	5-CH_3	4-OCH_3
H	5,6-O—CF_2—CFCl—O—		3-CH_3	H	4-OCH_3
4-CH_3	6-CH_3	5-OCF_2H	3-CH_3	H	4-OCH_3
H	5-OCH_3	6-OCF_2H	H	H	4-OCH_3
H	H	5-OCF_2CF_2H	H	H	4-OCH_3
H	5,6-O—CF_2—O—		H	H	4-OCH_3
H	H	5-OCF_2CClFH	H	H	4-OCH_3
H	H	5-OCF_2CClFH	H	H	4-OCH_3
H	H	5-OCF_2CClFH	3-CH_3	H	4-OCH_3
4-CH_3	6-CH_3	5-OCF_2H	H	3-CH_3	4-OCH_3
H	H	5-OCF_2H	H	3-OCH_3	4-OCH_3
H	H	5-OCF_2H	3-CH_3	5-OCH_3	4-OCH_3
H	H	5-OCF_3	3-CH_3	5-OCH_3	4-OCH_3
H	H	5-OCF_2CF_2H	H	3-OCH_3	4-OCH_3
H	H	5-OCH_2CF_3	H	3-OCH_3	4-OCH_3
H	5-OCH_3	6-OCF_2H	H	3-OCH_3	4-OCH_3

R1	R2, R3	R4	R5	R6
H	5,6-O—CF_2—O—	H	3-OCH_3	4-OCH_3
H	5,6-O—CF_2—CHF—O—	H	3-OCH_3	4-OCH_3
H	H 5-OCF_3	H	5-OCH_3	4-OCH_3
H	H 5-OCF_2CF_2H	H	5-OCH_3	4-OCH_3
H	5,6-O—CF_2—O—	H	5-OCH_3	4-OCH_3
H	5,6-O—CF_2—O—	H	4-OCH_3	5-OCH_2— 
H	H 5-OCF_2H	H	3-OCH_3	4-OCH_2— 
H	H 5-OCF_2H	H	4-OCH_3	3-OCH_2— 
H	H 5-OCF_2H	3-CH_3	4-OCH_3	5-OCH_2— 
H	H 5-OCF_2H	H	3-OCH_3	4-OCH_2CF_3
H	H 5-OCF_2H	H	3-CH_3	4-OCH_2CF_3
H	H 5-OCH_2CF_3	H	3-CH_3	4-OCH_2CF_3
H	5,6-O—CF_2—O—	H	3-CH_3	4-OCH_2CF_3

Besonders bevorzugte, durch das erfindungsgemäße Verfahren herstellbare Verbindungen sind die Verbindungen

(+)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(−)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(+)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(−)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(+)-2-{[(3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl]methyl}sulfinyl-1H-benzimidazol, und
(−)-2-{[(3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl]methyl}sulfinyl-1H-benzimidazol,

und ihre Salze mit Basen.

Die folgenden Beispiele dienen der näheren Erläuterung der Erfindung. Die Abkürzung h steht für Stunde(n), Schmp. für Schmelzpunkt.

Beispiele

1. (+)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1-[(+)-fenchyloxymethyl]-benzimidazol

Zu einer Lösung von 50 g (0,123 Mol) (±)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol-Na-Salz in 125 ml N-Methylpyrrolidon tropft man bei einer Temperatur von 25—35°C innerhalb einer Stunde 27,5 g (0,136 Mol) (+)-Fenchyl-chlormethylether zu. Nach 6 h wird mit 500 ml Wasser verdünnt, der pH-Wert auf 9,0 gestellt und dreimal mit je 100 ml Dichlormethan extrahiert. Die vereinigten organischen Phasen werden mit Wasser gewaschen, getrocknet und im Vakuum vollständig eingeengt. Der ölige Rückstand wird an Kieselgel chromatographiert (Laufmittel: Ethylacetat). Man isoliert 25,2 g (74%) eines Diastereomerengemisches aus (+)- und (−)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1-[(+)-fenchyloxymethyl]-benzimidazol als blaßgelbes, allmählich kristallisierendes Öl (Rf.-Wert in Ethylacetat ca. 0,85). Viermalige Umkristallisation aus Ethylacetat/Diisopropylether liefert die Titelverbindung (9,0 g 71,4%) in Form farbloser Kristalle vom Schmp. 138—139°C {$[\alpha]_D^{22} = +155{,}2°$ (c = 1, Chloroform)}.

2. (+)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol

1,0 g (1,8 mMol) (+)-4-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]-sulfinyl}-1-[(+)-fenchyloxymethyl]-benzimidazol werden portionsweise bei 5—10°C unter Rühren in 7 ml 90%ige Schwefelsäure eingetragen. Nach vollständiger Auflösung wird das Reaktionsgemisch unter Kühlung in 8N Natronlauge eingetropft, der pH auf 7,5 gestellt und mehrmals mit Dichlormethan extrahiert. Die vereinigten Extrakte werden mit Wasser gewaschen, über Magnesiumsulfat getrocknet und im Vakuum vollständig eingeengt. Der rote ölige Rückstand

wird über Kieselgel chromatographiert (Dichlormethan/Methanol) und anschließend aus Diisopropylether kristallisiert. Man erhält 0,3 g (44%) der Titelverbindung als farbloses Kristallisat vom Schmp. 147—148°C (Zers.) {$[\alpha]_D^{22} = +146{,}0°$ (c=0,5, Acetonitril/Methanol 1 : 1)}.

3.
(—)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1-[(—)-fenchyloxymethyl]-benzimidazol

Nach der in Beispiel 1 beschriebenen Arbeitsweise erhält man durch Umsetzung von 28 g (0,069 Mol) (±)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl-methyl]sulfinyl}-1H-benzimidazol-Na-Salz mit 16,5 g (0,084 Mol) (—)-Fenchylchlormethylether in 75 ml N-Methylpyrrolidon nach Chromatographie an Kieselgel (Dichlormethan/Methanol) 11,0 (58%) eines Diastereomerengemisches aus (+)- und (—)-5-Difluormethoxy--2-{[(3,4-dimethoxy-2-pyridinyl)-methyl]sulfinyl}-1-[(—)-fenchyloxymethyl]-benzimidazol. Mehrmalige Umkristallisation aus Ethylacetat/Diisopropylether liefert die Titelverbindung in Form farbloser Kristalle (4,0 g, 72%) vom Schmp. 138—139°C {$[\alpha]_D^{22} = -152{,}8°$ (c=1, Chloroform)}.

4. (—)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol

Nach der in Beispiel 2 beschriebenen Arbeitsweise erhält man aus 1 g (1,8 mMol) (—)-5-Difluormethoxy--2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1-[(—)-fenchyloxymethyl]-benzimidazol in 7 ml 90%iger Schwefelsäure 0,25 g (36%) der Titelverbindung vom Schmp. 144—145°C (Zers.) {$[\alpha]_D^{22} = -144{,}4°$ (c=0,5, Acetonitril/Methanol 1 : 1)}.

5.
(+)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1-[(+)-fenchyloxymethyl]-benzimidazol

Nach der in Beispiel 1 beschriebenen Arbeitsweise erhält man aus (±)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol-Na-Salz (60 mMol) in 80 ml N-Methylpyrrolidon nach Chromatographie an Kieselgel (Ethylacetat) nach mehrmaliger Umkristallisation aus Ethylacetat/Diisopropylether 3,1 g (40%) der Titelverbindung in Form farbloser Kristalle vom Schmp. 161°C (Zers.) {$[\alpha]_D^{22} = +103{,}0°$ (c=1, Chloroform)}.

6. (+)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol

Nach der in Beispiel 2 beschriebenen Arbeitsweise erhält man aus 0,51 g (1 mMol) (+)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-[(+)-fenchyloxymethyl]-benzimidzol in 4 ml 90%iger Schwefelsäure 0,15 g (43%) der Titelverbindung als amorphen Feststoff {$[\alpha]_D^{22} = +165°$ (c=0,5, Chloroform)}.

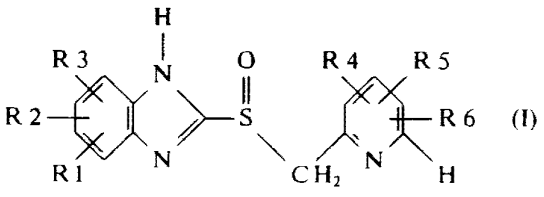
Gewerbliche Anwendbarkeit

Nach dem erfindungsgemäßen Verfahren können Pyridylmethylsulfinyl-1H-benzimidazole erstmals in ihre optischen Antipoden aufgespalten werden. Als besonders überraschend ist hierbei die Tatsache zu werten, daß die Freisetzung der optisch reinen Verbindungen aus den Diastereomeren mit Hilfe hochkonzentrierter Mineralsäuren vorgenommen wird, obwohl bekannt ist, daß es sich bei den Pyridylmethylsulfinyl-1H-benzimidazolen um sehr säurelabile Verbindungen handelt.

Die erfindungsgemäß hergestellten Verbindungen werden als Wirkstoffe in Arzneimitteln für die Behandlung von Magen- und Darmerkrankungen eingesetzt. Bezüglich der Anwendungsweise und Dosierung der Wirkstoffe wird z. B. auf das europäische Patent 1 66 287 verwiesen.

Patentansprüche

1. Konfigurativ einheitliche, optisch reine Verbindungen der Formel I



(I)

worin

R1 Wasserstoff, 1-4C-Alkyl oder 1-4C-Alkoxy bedeutet,

R2 Wasserstoff, Trifluormethyl, 1-4C-Alkyl, 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy. Chlordifluormethoxy, 2-Chlor-1,1,2-trifluormethoxy oder gemeinsam mit R3 gewünschtenfalls ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeutet,

R3 Wasserstoff, 1-4C-Alkyl, 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy,

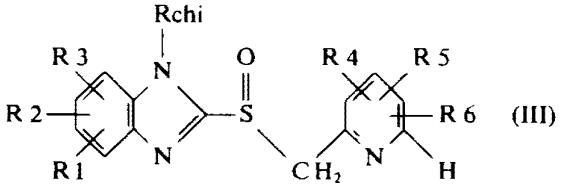
Chlordifluormethoxy, 2-Chlor-1,1,2-trifluorethoxy oder gemeinsam mit R2 gewünschtenfalls ganz oder teilweise durch Fluor substituiertes 1-2C-Alkylendioxy oder Chlortrifluorethylendioxy bedeutet,
R4 Wasserstoff oder 1-4C-Alkyl bedeutet,
R5 Wasserstoff, 1-4C-Alkyl oder 1-4C-Alkoxy bedeutet und
R6 1-4C-Alkoxy, ganz oder überwiegend durch Fluor substituiertes 1-4C-Alkoxy oder Benzyloxy bedeutet,
und ihre Salze mit Basen.

2. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus
(+)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(−)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(+)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(−)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(+)-2-{[(3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl]methyl}sulfinyl-1H-benzimidazol, und
(−)-2-{[(3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl]methyl}sulfinyl-1H-benzimidazol,
und ihren Salze mit Basen.

3. Verfahren zur Herstellung von konfigurativ einheitlichen, optisch reinen Vebindungen der Formel I nach Anspruch 1 und ihren Salzen, dadurch gekennzeichnet, daß man Racemate von Verbindungen der Formel I, worin R1, R2, R3, R4, R5 und R6 die in Anspruch 1 angegebenen Bedeutungen haben, oder ihre Salze mit Basen, mit konfigurativ einheitlichen, chiralen Verbindungen der Formel II,

Rchi—X (II)

worin Rchi einen konfigurativ einheitlichen, chiralen Rest und X eine Abgangsgruppe darstellt, umsetzt, das erhaltene Isomeren- bzw. Diastereomerengemisch III,

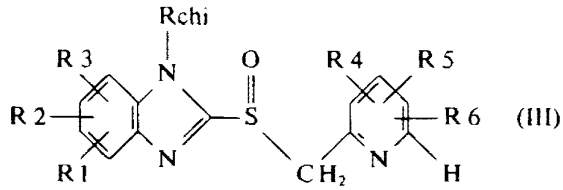


(III)

worin R1, R2, R3, R4, R5 und R6 die in Anspruch 1 angegebenen Bedeutungen haben und Rchi einen konfigurativ einheitlichen, chiralen Rest darstellt, trennt und aus den optisch reinen Diastereomeren die konfigurativ einheitlichen, optisch reinen Verbindungen I durch Solvolyse in stark saurem Medium freisetzt und gewünschtenfalls anschließend in die Salze mit Basen überführt.

4. Verfahren nach Anspruch 3, dadurch gekennzeichnet, daß man eine Verbindung ausgewählt aus der Gruppe bestehend aus
(+)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(−)-5-Difluormethoxy-2-{[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(+)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(−)-5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazol,
(+)-2-{[(3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl]methyl}sulfinyl-1H-benzimidazol, und
(−)-2-{[(3-Methyl-4-(2,2,2-trifluorethoxy)-2-pyridinyl]methyl}sulfinyl-1H-benzimidazol,
oder ihr Salz mit Basen herstellt.

5. Zwischenprodukte der Formel III,



(III)

worin R1, R2, R3, R4, R5 und R6 die in Anspruch 1 angegebenen Bedeutungen haben und Rchi einen konfigurativ einheitlichen, chiralen Rest darstellt.

6. Zwischenprodukte nach Anspruch 5, worin Rchi einen Fenchyloxymethylrest darstellt.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 005 129**
A1

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: **79850022.9**

(22) Date of filing: **03.04.79**

(51) Int. Cl.²: **C 07 D 403/12**
A 61 K 31/44

(30) Priority: **14.04.78 SE 7804231**

(43) Date of publication of application:
31.10.79 Bulletin 79/22

(84) Designated Contracting States:
BE CH DE FR GB IT LU NL SE

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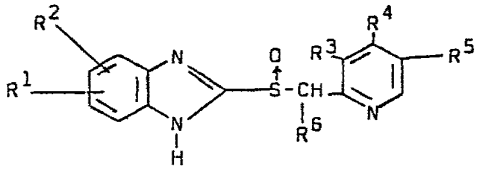
(54) **Substituted pyridylsulfinylbenzimidazoles having gastric acid secretion properties, pharmaceutical preparations containing same, and intermediates for their preparation.**

(57) The present invention relates to novel compounds of the formula



wherein R^1 and R^2 are same or different and are each hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, or alkanoyl, R^6 is hydrogen, methyl or ethyl, R^3, R^4 and R^5 are same or different and are each hydrogen, methyl, methoxy, ethoxy, methoxyethoxy or ethoxyethoxy whereby R^3, R^4 and R^5 are not all hydrogen, and whereby when two of R^3, R^4 and R^5 are hydrogen the third of R^3, R^4 and R^5 is not methyl. The compounds are potent gastric acid secretion inhibitors.

EP 0 005 129 A1

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KH 575-1
79-03-07
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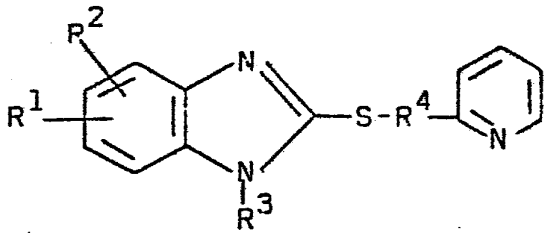
Substituted pyridylsulfinylbenzimidazoles having gastric acid secretion properties, pharmaceutical preparations containing same, and intermediates for their preparation

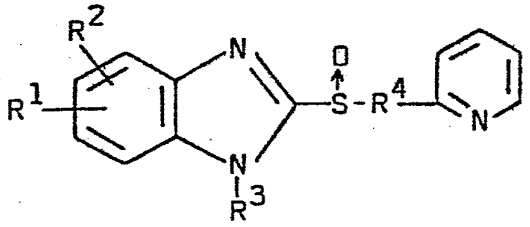
The present invention relates to new compounds having valuable properties in affecting gastric acid secretion in mammals, including man, as well as the process for their preparation, method of affecting gastric acid secretion and pharmaceutical preparations containing said novel compounds.

The object of the present invention is to obtain compounds which affect gastric acid secretion, and which inhibit exogenously or endogenously stimulated gastric acid secretion. These compounds can be used in the treatment of peptic ulcer disease.

It is previously known that compounds of the formulas I and II



(I)

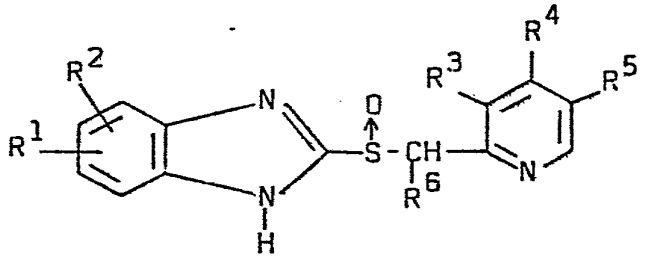


(II)

wherein R^1 and R^2 are each selected from the group consisting of hydrogen, alkyl, halogen, cyano, carboxy, carboxyalkyl, carboalkoxy, carboalkoxyalkyl, carbamoyl, carbamoyloxy, hydroxy, alkoxy, hydroxyalkyl, trifluoromethyl and acyl in any position, R^3 is selected from the group consisting of hydrogen, alkyl, acyl, carboalkoxy, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, alkylcarbonylmethyl, alkoxycarbonylmethyl, and alkylsulphonyl, and R^4 is selected from the group consisting of straight and branched alkylene groups having 1 to 4 carbon atoms, whereby at most one methylene group is present between S and the pyridyl group, and whereby the pyridyl group may be further substituted with alkyl or halogen, possess inhibiting effect of gastric acid secretion.

It has now, however, surprisingly been found that the compounds defined below possess a still greater inhibiting effect than those given above.

Compounds of the invention are those of the general formula III



(III)

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, and R^3, R^4 and R^5 are same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4 and R^5 is not methyl.

Alkyl R^1 and R^2 of formula III are suitably alkyl having up to 7 carbon atoms, preferably up to 4 carbon atoms. Thus, alkyl R may be methyl, ethyl, n-propyl, isopropyl, n-butyl or isobutyl.

Halogen R^1 and R^2 is chloro, bromo, fluoro, or iodo.

Alkoxy R^1 and R^2 are suitably alkoxy groups having up to 5 carbon atoms, preferably up to 3 carbon atoms, as methoxy, ethoxy, n-propoxy, or isopropoxy.

Alkanoyl R^1 and R^2 have preferably up to 4 carbon atoms and are e.g. formyl, acetyl, or propionyl, preferably acetyl.

A preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, alkoxy, and alkanoyl, whereby R^1 and R^2 are not both hydrogen, R^6 is hydrogen, and R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, and ethoxy, whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen the third of R^3, R^4, and R^5 is not methyl.

A second preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, R^3 is methyl, R^4 is methoxy, and R^5 is methyl.

A third preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 is hydrogen, R^4 is methoxy and R^5 is methyl or R^3 is methyl, R^4 is methoxy and R^5 is hydrogen.

A fourth preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, R^3 and R^5 are hydrogen and R^4 is methoxy.

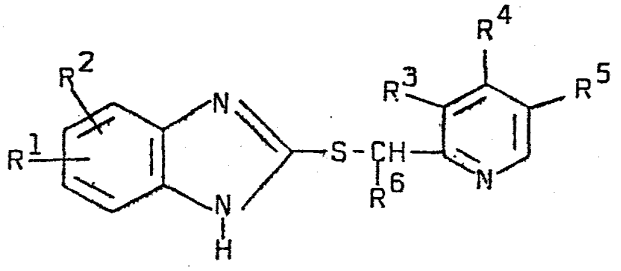
A fifth preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 and R^5 are methyl and R^4 is hydrogen.

A sixth preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, R^3 and R^5 are hydrogen and R^4 is ethoxy, methoxyethoxy or ethoxyethoxy.

A seventh preferred group of compounds of the general formula III are those wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, R^3, R^4, and R^5 are all methyl.

Compounds of formula III above may be prepared according to the following methods:

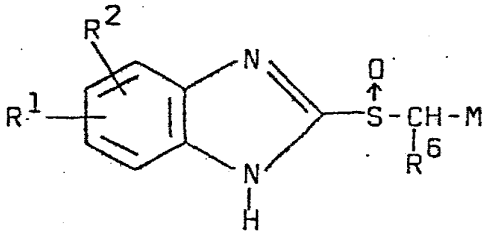
a) oxidizing a compound of formula IV



(IV)

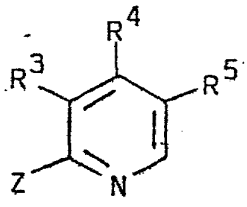
wherein R^1, R^2, R^6, R^3, R^4, and R^5 have the meanings given, to the formation of a compound of formula III.

b) reacting a compound of the formula V



(V)

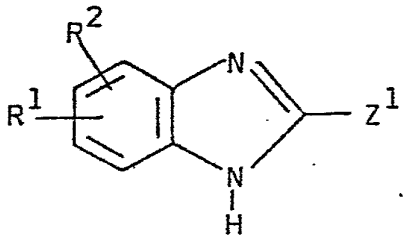
wherein R^1, R^2, and R^6 have the meanings given above and M is a metal selected from the group consisting of K, Na and Li, with a compound of formula VI.



(VII)

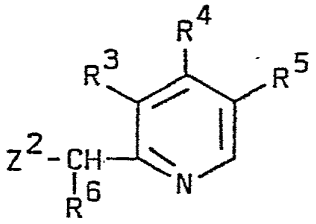
wherein R^3, R^4, and R^5 have the same meanings as given above, Z is a reactive esterified hydroxy group, to the formation of a compound of formula III;

c) reacting a compound of the formula VII



(VII)

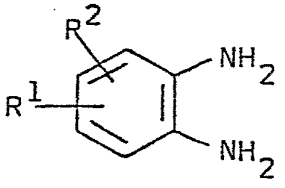
wherein R^1, and R^2 have the same meanings as given above and Z^1 is SH or a reactive esterified hydroxy group, with a compound of the formula VIII



(VIII)

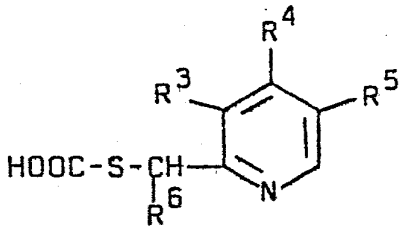
wherein R^6, R^3, R^4, and R^5 have the same meanings as given above, and Z^2 is a reactive esterified hydroxy group or SH, to the formation of an intermediate of formula IV above, which then is oxidized to give a compound of formula III;

d) reacting a compound of the formula IX



(IX)

wherein R^1 and R^2 have the same meanings as given above with a compound of the formula X



(X)

wherein R^6, R^3, R^4, and R^5 have the same meanings as given above, to the formation of an intermediate of formula IV above, which then is oxidized to give a compound of formula III, which compound may be converted to its therapeutically acceptable salts, if so desired.

In the reactions above, Z, Z^1, and Z^2 may be a reactive, esterified hydroxy group which is a hydroxy group esterified with strong, inorganic or organic acid, preferably a hydrohalogen acid, such as hydrochloric acid, hydrobromic acid, or hydroiodic acid, also sulfuric acid or a strong organic sulfonic acid as a strong aromatic acid, e.g. benzenesulfonic acid, 4-bromobenzenesulfonic acid or 4-toluenesulfonic acid.

The oxidation of the sulfur atom in the chains above to sulfinyl (S→O) takes place in the presence of an oxidizing agent selected from the group consisting of nitric acid, hydrogen peroxide, peracids, peresters, ozone, dinitrogentetraoxide, iodosobenzene, N-halosuccinimide, 1-chlorobenzotriazole, t-butylhypochlorite, diazobicyclo-[2,2,2]-octane bromine complex, sodium metaperiodate, selenium dioxide, manganese dioxide, chromic acid, cericammonium nitrate, bromine, chlorine, and sulfuryl chloride. The oxidation usually takes place in a solvent wherein the oxidizing agent is present in some excess in relation to the product to be oxidized.

Depending on the process conditions and the starting materials, the end product is obtained either as the free base or in the acid addition salt, both of which are included within the scope of the invention. Thus, basic, neutral or or mixed salts may be obtained as well as hemi,. mono, sesqui

or polyhydrates. The acid addition salts of the new compounds may in a manner known per se be transformed into free base using basic agents such as alkali or by ion exchange. On the other hand, the free bases obtained may form salts with organic or inorganic acids. In the preparation of acid addition salts preferably such acids are used which form suitable therapeutically acceptable salts. Such acids include hydrohalogen acids, sulfonic, phosphoric, nitric, and perchloric acids; aliphatic, alicyclic, aromatic, heterocyclic carboxy or sulfonic acids, such as formic, acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyruvic, phenylacetic, benzoic, p-aminobenzoic, antranilic, p-hydroxybenzoic, salicylic or p-aminosalicylic acid, embonic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogenbenzenesulfonic, toluenesulfonic, naphtylsulfonic or sulfanilic acids; methionine, tryptophane, lysine or arginine.

These or other salts of the new compounds, as e.g. picrates, may serve as purifying agents of the free bases obtained. Salts of the bases may be formed, separated from solution, and then the free base can be recovered from a new salt solution in a purer state. Because of the relationship between the new compounds in free base form and their salts, it will be understood that the corresponding salts are included within the scope of the invention.

Some of the new compounds may, depending on the choice of starting materials and process, be present as optical isomers or racemate, or if they contain at least two asymmetric carbon atoms, be present as an isomer mixture (racemate mixture).

The isomer mixtures (racemate mixtures) obtained may be separated into two stereoisomeric (diastereomeric) pure racemates by means of chromatography or fractional crystal-

lization.

The racemates obtained can be separated according to known methods, e.g. recrystallization from an optically active solvent, use of microorganisms, reactions with optically active acids forming salts which can be separated, separation based on different solubilities of the diastereomers. Suitable optically active acids are the L- and D-forms of tartaric acid, di-o-tolyl-tartaric acid, malic acid, mandelic acid, camphorsulfonic acid or quinic acid, Preferably the more active part of the two antipodes is isolated.

The starting materials are known or may, if they should be new, be obtained according to processes known per se.

In clinical use the compounds of the invention are administered orally, rectally or by injection in the form of a pharmaceutical preparation which contains an active component either as a free base or as a pharmaceutically acceptable, non-toxic acid addition salt, such as hydrochloride, lactate, acetate, sulfamate, in combination with a pharmaceutically acceptable carrier. The carrier may be in the form of a solid, semisolid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1 to 95 % by weight of the preparation, between 0.5 to 20 % by weight in preparations for injection and between 2 and 50 % by weight in preparations for oral administration.

In the preparation of pharmaceutical preparations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with a solid, pulverulent carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives or gelatin, as well as with an antifriction agent such as magnesium stearate, calcium stearate, and polyethyleneglycol waxes. The mixture is then pressed

into tablets. If coated tablets are desired, the above prepared core may be coated with a concentrated solution of sugar, which may contain gum arabic, gelatin, talc, titanium dioxide or with a lacquer dissolved in volatile organic solvent or mixture of solvents. To this coating various dyes may be added in order to distinguish among tablets with different active compounds or with different amounts of the active compound present.

Soft gelatin capsules may be prepared which capsules contain a mixture of the active compound or compounds of the invention and vegetable oil. Hard gelatin capsules may contain granules of the active compound in combination with a solid, pulverulent carrier as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance in a mixture with a neutral fat base, or they may be prepared in the form of gelatin-rectal capsules which contain the active substance in a mixture with a vegetable oil or paraffin oil.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions containing from 0.2 % to 20 % by weight of the active ingredient and the remainder consisting of sugar and a mixture of ethanol, water, glycerol and propylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharin and carboxymethylcellulose as a thickening agent.

Solutions for parenteral administration by injection may be prepared as an aqueous solution of a watersoluble pharmaceutically acceptable salt of the active compound, preferably in a concentration from 0.5 % to 10 % by weight. These solutions may also contain stabilizing agents and/or

buffering agents and may be manufactured in different dosage unit ampoules.

Pharmaceutical tablets for oral use are prepared in the following manner: The solid substances are ground or sieved to a certain particle size, and the binding agent is homogenized and suspended in a suitable solvent. The therapeutically active compounds and auxiliary agents are mixed with the binding agent solution. The resulting mixture is moistened to form a uniform suspension having the consistency of wet snow. The moistening causes the particles to aggregate slightly, and the resulting mass is pressed through a stainless steel sieve having a mesh size of approximately 1 mm. The layers of the mixture are dried in carefully controlled drying cabinets for approximately ten hours to obtain the desired particle size and consistency. The granules of the dried mixture are sieved to remove any powder. To this mixture, disintegrating, antifriction and antiadhesive agents are added. Finally, the mixture is pressed into tablets using a machine with the appropriate punches and dies to obtain the desired tablet size. The pressure applied affects the size of the tablet, its strength and its ability to dissolve in water. The compression pressure used should be in the range 0.5 to 5 tons. Tablets are manufactured at the rate of 20.000 to 200.000 per hour. The tablets, especially those which are rough or bitter, may be coated with a layer of sugar or some other palatable substance. They are then packaged by machines having electronic counting devices. The different types of packages consist of glass or plastic gallipots, boxes, tubes and specific dosage adapted packages.

The typical daily dose of the active substance varies according to the individual needs and the manner of administration. In general, oral dosages range from 100 to 400 mg/day of active substance and intravenous dosages range from 5 to 20 mg/day.

The following illustrates a preferred embodiment of the invention without being limited thereto. Temperature is given in degrees Centigrade.

The starting materials in the examples found below were prepared in accordance with the following methods:
(1) a 1,2-diamino compound, such as o-phenylenediamine was reacted with potassium ethylxanthate (according to Org. Synth. Vol. 30, p. 56) to form a 2-mercaptobenzimidazole;
(2) the compound 2-chloromethylpyridine was prepared by reacting 2-hydroxymethylpyridine with thionylchloride (according to Arch. Pharm. Vol. 26, pp. 448-451 (1956));
(3) the compound 2-chloromethylbenzimidazole was prepared by condensing o-phenylenediamine with chloroacetic acid.

Example 1

28.9 g of 2-[2-(4,5-dimethyl)pyridylmethylthio]-(5-acetyl--6-methyl)-benzimidazole were dissolved in 160 ml of $CHCl_3$, 24.4 g of m-chloroperbenzoic acid were added in portions while stirring and cooling to 5°C. After 10 minutes, the precipitated m-chlorobenzoic acid was filtered off. The filtrate was diluted with CH_2Cl_2, washed with Na_2CO_3 solution, dried over Na_2SO_4 and evaporated in vacuo. The residue crystallized when diluted with CH_3CN, and 2-[2-(4,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole was recrystallized from CH_3CN. Yield 22.3 g; m.p. 158°C.

Examples 2-30

The preparation of compounds of formula III labelled 2-26 was carried out in accordance with Example 1 above. The compounds prepared are listed in Table 1 which identifies the substituents for these compounds.

Example 31 (method c)

0.1 moles of 4-6-dimethyl-2-mercaptobenzimidazole were dissolved in 20 ml of water and 200 ml of ethanol containing 0.2 moles of sodium hydroxide. 0.1 moles of 2-chloromethyl-(3,5-dimethyl)pyridine hydrochloride were added and the mixture was refluxed for two hours. The sodium chloride formed was filtered off and the solution was evaporated in vacuo. The residue was dissolved in acetone and was treated with active carbon. An equivalent amount of concentrated hydrochloric acid was added, whereupon the mono-hydrochloride of 2-[2-(3,5-dimethyl)pyridylmethylthio]-(4,6-dimethyl)benzimidazole was isolated. Yield 0.05 moles.

This compound was then oxidized in accordance with Example 1 above to give the corresponding sulfinyl compound, melting point 50-55°C.

Example 32 (method b)

0.1 moles of 2-[Li-methylsulfinyl](5-acetyl-6-methyl)-benzimidazole were dissolved in 150 mls of benzene. 0.1 moles 2-chloro-(3,5-dimethyl)pyridine were added and the mixture was refluxed for two hours. The lithiumchloride formed was filtered off, and the solution was evaporated in vacuo. The residue was crystallized from CH_3CN, and recrystallized from the same solvent. Yield 0.82 moles of 2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole melting at 171°C.

Example 33 (method d)

23.4 g of 2-[2-(3,4,5-trimethyl)pyridylmethylthio] formic acid and 16.6 g of o-(5-acetyl-6-methyl)phenylenediamine were boiled for 40 minutes in 100 ml of 4N HCl. The mixture was cooled and neutralized with ammonia. The neutral solution was then extracted with ethyl acetate. The organic phase was

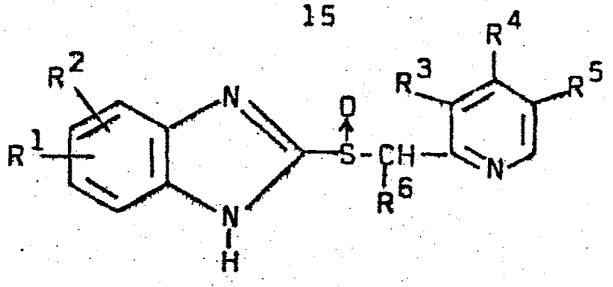
treated with active carbon and evaporated in vacuo. The residue was dissolved in acetone whereupon an equivalent of concentrated HCl was added. The precipitated hydrochloride was filtered off after cooling and the salt was recrystallized from absolute ethanol and some ether. Yield of 2-[2-(3,4,5-trimethylpyridyl)methylthio]-(5-acetyl-6-methyl)benzimidazole was 6.5 g.

This compound was then oxidized in accordance with Example 1 above, to give the corresponding sulfinyl derivative. M.p. 190°C.

Example 34 (method c)

22.0 g of 2-mercapto-(5-acetyl-6-methyl)benzimidazole and 19.5 g of chloromethyl(4,5-dimethyl)pyridine hydrochloride were dissolved in 200 ml of 95 % ethanol. 8 g of sodium hydroxide in 20 ml of water were added, whereupon the solution was refluxed for two hours. The sodium chloride formed was filtered off and the solution was evaporated in vacuo. The residue, 2-[2-(4,5-dimethyl)pyridylmethylthio]-(5-acetyl-6-methyl)benzimidazole, was recrystallized from 70 % ethanol. Yield 10.6 g.

This compound was then oxidized in accordance with Example 1 above, to give the corresponding sulfinyl derivative. M.p. 158°C.



Ex.	R^1	R^2	R^6	R^3	R^4	R^5	M.p. °C
1	5-$COCH_3$	6-CH_3	H	H	CH_3	CH_3	158
2	5-$COOCH_3$	6-CH_3	H	H	CH_3	CH_3	163
3	5-$COOCH_3$	H	H	H	CH_3	CH_3	141
4	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	H	160
5	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	H	163
6	4-CH_3	6-CH_3	H	CH_3	H	CH_3	50-55
7	5-$COCH_3$	6-CH_3	H	CH_3	H	CH_3	171
8	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	190
9	5-$COCH_3$	6-CH_3	H	H	OCH_3	H	165
10	4-CH_3	6-CH_3	H	H	OCH_3	H	122
11	5-$COCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	156
12	5-$COOCH_3$	6-CH_3	H	CH_3	H	CH_3	144
13	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	185
14	5-$COOCH_3$	6-CH_3	H	H	OCH_3	H	169
15	5-$COOCH_3$	6-CH_3	H	H	OC_2H_5	H	148
16	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	H	175
17	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	155
18	5-$COOCH_3$	6-CH_3	H	H	OCH_3	CH_3	158
19	5-$COOCH_3$	H	H	CH_3	H	CH_3	141
20	5-$COOCH_3$	H	H	CH_3	OCH_3	CH_3	142
21	5-$COCH_3$	H	H	CH_3	OCH_3	CH_3	162
22	5-OCH_3	H	H	H	OCH_3	CH_3	178
23	5-OCH_3	H	H	CH_3	OCH_3	CH_3	156
24	5-CH_3	H	H	CH_3	OCH_3	CH_3	181
25	H	H	H	CH_3	OCH_3	CH_3	165
26	5-Cl	H	H	CH_3	OCH_3	CH_3	185
27	5-CH_3	H	H	H	$OC_2H_4OCH_3$	H	119
28	5-$COOC_2H_5$	H	H	CH_3	OCH_3	CH_3	150-5
29	5-$COOCH_3$	H	CH_3	CH_3	H	CH_3	130
30	5-CH_3	H	CH_3	CH_3	H	CH_3	152

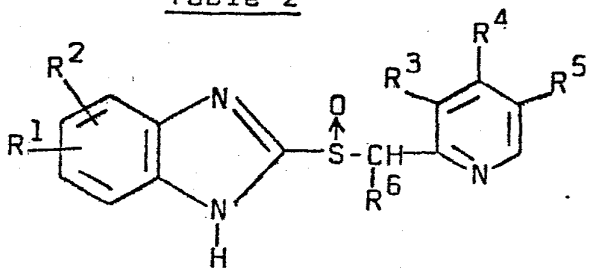
Biological effect

The compounds of the invention possess worthwhile therapeutic properties as gastric acid secretion inhibitors as demonstrated by the following tests. To determine the gastric acid secretion inhibitory properties, experiments have been performed on conscious dogs provided with gastric fistulas of conventional type and duodenal fistulas, the latter ones used for direct intraduodenal administration of the test compounds. After 18 hours starvation and deprivation of water the dogs were given a subcutaneous infusion of pentagastrin (1-4 nmol/kg, h) lasting for 6-7 hours. Gastric juice was collected in consecutive 30 minutes samples. An aliquot of each sample was titrated with 0.1 N NaOH to pH 7.0 for titrable acid concentration using an automatic titrator and pH-meter (Radiometer, Copenhagen, Denmark). Acid output was calculated as mmol H^+/60 minutes. The percent inhibition compared to control experiments was calculated for each compound and the peak inhibitory effect is given in Table 2 below. The test compounds, suspended in 0.5 % Methocel® (methyl cellulose), were given intraduodenally in doses from 4-20 µmol/kg when the secretory response to pentagastrin has reached a steady level.

In the test prior known compounds were compared with the compounds of the present invention as will be evident from the Table 2 below.

The following gastric acid inhibiting effect data were obtained for a number of compounds tested according to the method described.

Table 2



Ex.	R^1	R^2	R^6	R^3	R^4	R^5	Dose µmol/kg	Effect % inhibition
1	5-$COCH_3$	6-CH_3	H	H	CH_3	CH_3	2	90
4	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	H	1	60
7	5-$COCH_3$	6-CH_3	H	CH_3	H	CH_3	2	100
8	5-$COCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	4	100
9	5-$COCH_3$	6-CH_3	H	H	OCH_3	H	2	95
11	5-$COCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	0.5	70
×	5-$COCH_3$	6-CH_3	H	H	CH_3	H	20	30
×	5-$COCH_3$	6-CH_3	H	H	H	CH_3	8	80
2	5-$COOCH_3$	6-CH_3	H	H	CH_3	CH_3	2	60
5	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	H	2	90
12	5-$COOCH_3$	6-CH_3	H	CH_3	H	CH_3	2	70
13	5-$COOCH_3$	6-CH_3	H	CH_3	CH_3	CH_3	4	80
14	5-$COOCH_3$	6-CH_3	H	H	OCH_3	H	2	100
15	5-$COOCH_3$	6-CH_3	H	H	OC_2H_5	H	4	75
16	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	H	0.5	65
17	5-$COOCH_3$	6-CH_3	H	CH_3	OCH_3	CH_3	0.5	90
18	5-$COOCH_3$	6-CH_3	H	H	OCH_3	CH_3		
×	5-$COOCH_3$	6-CH_3	H	H	H	CH_3	4	50
×	5-$COOCH_3$	6-CH_3	H	Br	H	H	4	0
6	4-CH_3	6-CH_3	H	CH_3	H	CH_3	4	40
10	4-CH_3	6-CH_3	H	H	OCH_3	H	2	40
×	4-CH_3	6-CH_3	H	H	H	H	4	30
×	4-CH_3	6-CH_3	H	H	H	CH_3	12	50

cont.

Ex	R^1	R^2	R^6	R^3	R^4	R^5	Dose µmol/kg	Effect % inhibition
3	5-$COOCH_3$	H	H	H	CH_3	CH_3	4	100
19	5-$COOCH_3$	H	H	CH_3	H	CH_3	2	60
20	5-$COOCH_3$	H	H	CH_3	OCH_3	CH_3	0.5	65
x	5-$COOCH_3$	H	H	H	H	CH_3	20	90
x	5-$COOCH_3$	H	H	H	H	H	20	50
21	5-$COCH_3$	H	H	CH_3	OCH_3	CH_3	0.5	60
x	5-$COCH_3$	H	H	H	H	C_2H_5	20	40
22	5-OCH_3	H	H	H	OCH_3	CH_3		
23	5-OCH_3	H	H	CH_3	OCH_3	CH_3	0.5	65
x	5-OCH_3	H	H	H	CH_3	H	20	10
24	5-CH_3	H	H	CH_3	OCH_3	CH_3	0.5	50
x	5-CH_3	H	H	H	H	CH_3	4	50
25	H	H	H	CH_3	OCH_3	CH_3	0.5	60
x	H	H	H	H	H	H	4	50
28	5-$COOC_2H_5$	H	H	CH_3	OCH_3	CH_3	0.5	50
26	5-Cl	H	H	CH_3	OCH_3	CH_3	0.5	25
27	5-CH_3	H	H	H	$OC_2H_4OCH_3$	H	0.5	30
29	5-$COOCH_3$	H	CH_3	CH_3	H	CH_3	0.5	40

x denotes a previously known compound

Example 35

A syrup containing 2 % (weight per volume) of active substance was prepared from the following ingredients:

2-[2-(4,5-dimethyl)pyridylmethylsulfinyl]- -(5-acetyl-6-methyl)benzimidazole · HCl	2.0 g
Saccharin	0.6 g
Sugar	30.0 g
Glycerin	5.0 g
Flavouring agent	0.1 g
Ethanol 96 %	10.0 ml
Distilled water (sufficient to obtain a final volume of 100 ml)	

Sugar, saccharin and the acid addition salt were dissolved in 60 g of warm water. After cooling, glycerin and a solution of flavouring agents dissolved in ethanol were added. To the mixture water was added to obtain a final volume of 100 ml.

The above given active substance may be replaced with other pharmaceutically acceptable acid addition salts.

Example 36

2-[2-(3,4-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6--methyl)benzimidazole · HCl (250 g) was mixed with lactose (175.8 g), potato starch (169.7 g) and colloidal silicic acid (32 g). The mixture was moistened with 10 % solution of gelatin and was ground through a 12-mesh sieve. After drying, potato starch (160 g), talc (50 g) and magnesium stearate (5 g) were added and the mixture thus obtained was pressed into tablets (10.000), with each tablet containing 25 mg of active substance. Tablets can be prepared that contain any desired amount of the active ingredient.

Example 37

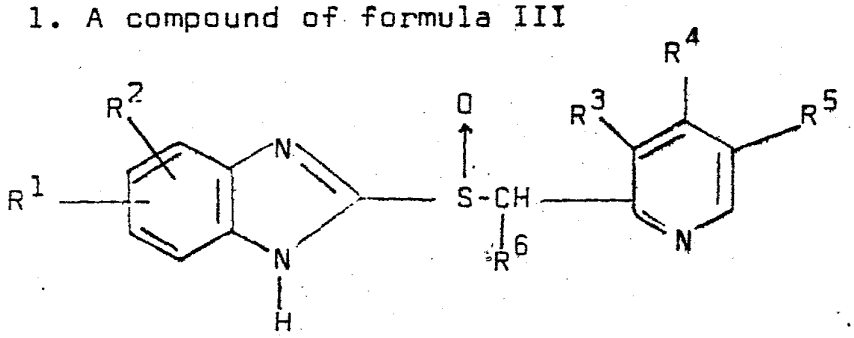
Granules were prepared from 2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6-methyl)benzimidazole-p-hydroxybenzoate (250 g), lactose (175.9 g) and an alcoholic solution of polyvinylpyrrolidone (25 g). After drying, the granules were mixed with talc (25 g), potato starch (40 g), and magnesium stearate (2.50 g) and were pressed into 10.000 tablets. These tablets are first coated with a 10 % alcoholic solution of shellac and thereupon with an aqueous solution containing saccharose (45 %), gum arabic (5 %), gelatin (4 %), and dyestuff (0.2 %). Talc and powdered sugar were used for powdering after the first five coatings. The coating was then covered with a 66 % sugar syrup and polished with a solution of 10 % carnauba wax in carbon tetrachloride.

Example 38

2-[2-(3,5-dimethyl)pyridylmethylsulfinyl]-(5-acetyl-6--methyl)benzimidazole hydrochloride (1 g), sodium chloride (0.6 g) and ascorbic acid (0.1 g) were dissolved in sufficient amount of distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance for each ml, was used in filling ampoules, which were sterilized by heating at 120°C for 20 minutes.

Claims

1. A compound of formula III



(III)

or a therapeutically acceptable salt thereof in which R^1 and R^2 are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl in any position, R^6 is selected from the group consisting of hydrogen, methyl and ethyl, R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxy-ethoxy and ethoxy-ethoxy whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4, and R^5 is not methyl.

2. A compound according to claim 1, wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, alkoxy, and alkanoyl in any position, whereby R^1 and R^2 are not both hydrogen, R^6 is hydrogen, and R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, and ethoxy, whereby R^3, R^4, and R^5 are not all hydrogen and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4, and R^5 are not methyl.

3. A compound according to claim 1, wherein R^1, R^2, and R^6 have the meanings given and R^3 and R^5 are methyl and R^4 is methoxy.

4. A compound according to claim 1, wherein R^1, R^2, and R^6 have the meanings given, R^4 is methoxy, and R^3 is hydrogen and R^5 is methyl, or R^5 is hydrogen and R^3 is methyl.

5. A compound according to claim 1 or a therapeutically acceptable salt thereof in which R^1, R^2, and R^6 have the meanings given, R^3 and R^5 are hydrogen, and R^4 is methoxy, ethoxy, methoxyethoxy or ethoxy-ethoxy.

6. A compound according to claim 1 or a therapeutically acceptable salt thereof in which R^1, R^2, and R^6 have the meanings given, and R^3, and R^5 are methyl and R^4 is hydrogen.

7. A compound according to claim 1 and selected from the group consisting of

2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6--methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(4,6-dimethyl)--benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)--benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6--methyl)-benzimidazole,

2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy--6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6--methyl)-benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)--benzimidazole

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(4,6-dimetnyl)-benzimidazole

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy--6-methyl)-benzimidazole,

2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy--6-methyl)-benzimidazole,

2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-ethoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3-methyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)--benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl)-benzimidazole,

2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-methoxy)--benzimidazole,

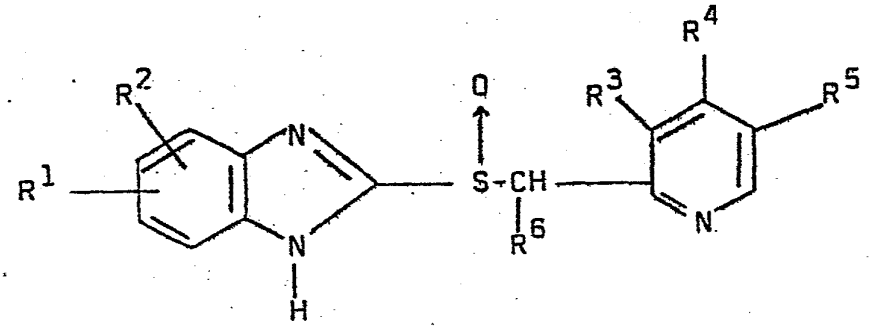
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5--methoxy)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methyl)-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-benzimidazole,

2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-chloro)-benzimidazole

8. A pharmaceutical preparation for inhibiting gastric acid secretion, characterized in that it contains as active agent a compound of formula III



(III)

or a pharmaceutically acceptable non-toxic acid addition salt thereof in a therapeutically effective amount in which R^1 and R^2 are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl in any position, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxy-ethoxy, and ethoxy-ethoxy whereby R^3, R^4, and R^5 are not all hydrogen, and whereby when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4, and R^5 is not methyl.

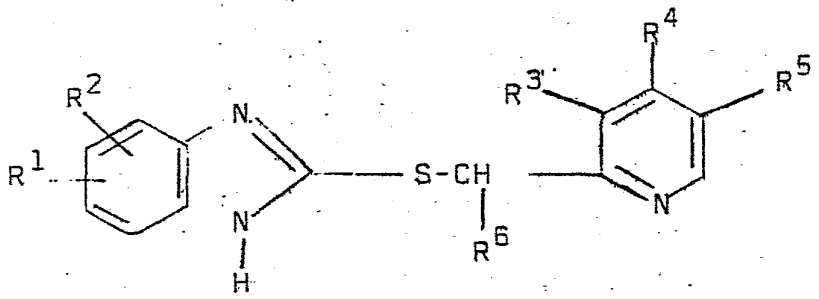
9. A pharmaceutical preparation according to claim 8 wherein the active ingredient is selected from the group consisting of

2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6--methyl)-benzimidazole,
2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(4,6-dimethyl)--benzimidazole,
2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)--benzimidazole,
2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6--methyl)-benzimidazole,
2-[2-(4,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
2-[2-(3,4-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy--6-methyl)-benzimidazole,
2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-acetyl-6--methyl)-benzimidazole,
2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)--benzimidazole,
2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(4,6-dimethyl)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl-6-methyl)-benzimidazole,
2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy--6-methyl)-benzimidazole,
2-[2-(3,4,5-trimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy--6-methyl)-benzimidazole,
2-[2-(4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6--methyl)-benzimidazole,
2-[2-(4-ethoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6--methyl)-benzimidazole,
2-[2-(3-methyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,
2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole,

2-[2-(3,5-dimethyl)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-carbomethoxy)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-acetyl)-benzimidazole,
2-[2-(4-methoxy-5-methyl)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methoxy)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-methyl)-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-benzimidazole,
2-[2-(3,5-dimethyl-4-methoxy)-pyridylmethylsulfinyl]-(5-chloro)-benzimidazole,

or a pharmaceutically acceptable non-toxic addition salt thereof.

10. Intermediates of the formula



wherein R^1 and R^2, preferably in 3 to 5 position, are the same or different and are selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, and R^3, R^4, and R^5 are the same or different and are selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxy-ethoxy, and ethoxy-ethoxy whereby R^3, R^4, and R^5

are not all hydrogen when two of R^3, R^4, and R^5 are hydrogen, the third of R^3, R^4, and R^5 is not methyl.

European Patent Office

EUROPEAN SEARCH REPORT

0005129
Application number

EP 79 85 0022

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
A	DE - A - 2 548 340 (AB HÄSSLE) * pages 1 to 12 *	1, 24

CLASSIFICATION OF THE APPLICATION (Int. Cl.²)

C 07 D 403/12
A 61 K 31/44

TECHNICAL FIELDS SEARCHED (Int.Cl.²)

C 07 D 403/12
A 61 K 31/44

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: Intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	18-07-1979	DE BUYSER

EPO Form 1503.1 06.78

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 124 495**
A2

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: **84850066.6**

(22) Date of filing: **28.02.84**

(51) Int. Cl.³: **C 07 D 401/12**, A 61 K 31/44

(30) Priority: **04.03.83 SE 8301182**

(43) Date of publication of application: **07.11.84**
Bulletin 84/45

(84) Designated Contracting States: **AT BE CH DE FR GB IT LI LU NL SE**

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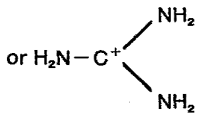
(54) **Omeprazole salts.**

(57) Novel salts of omeprazole with Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ti^{4+}, $N^+(R^1)_4$



as cation; processes for their preparation thereof, pharmaceutical compositions containing such salts and their use in medicine.

EP 0 124 495 A2

TITLE MODIFIED
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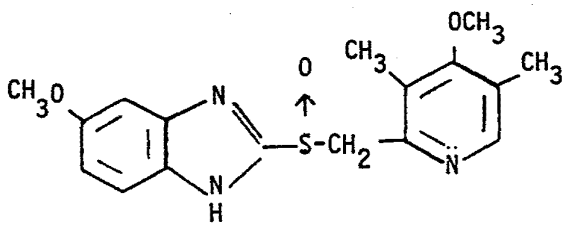
Novel compounds

Field of the invention

The invention relates to novel salts of the known compound omeprazole.

Background of the invention

The compound known under the generic name omeprazole, having the structural formula



(i)

which is described i.a. in European patent specification 0005129, is being extensively investigated clinically as a gastric acid secretion inhibiting agent.

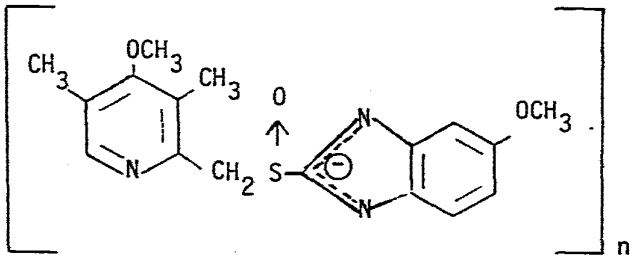
Omeprazol is useful for inhibiting gastric acid secretion as well as for providing gastrointestinal cytoprotective effects in mammals and man. In a more general sense, omeprazole may be used for prevention and treatment of gastrointestinal inflammatory diseases in mammals and man, including e.g. gastritis, gastric ulcer, and duodenal ulcer. Furthermore, omeprazole may be used for prevention and treatment of other gastrointestinal disorders where cytoprotective and/or gastric antisecretory effect is desirable, e.g. in patients with gastrinomas, in patients with acute upper gastrointestinal bleeding, and in patients with a history of chronic and excessive alcohol consumption.

The term "omeprazole" as used in this specification designates the neutral form of the compound of the formula (i), that is the form as given in the formula (i) without salt forming components present.

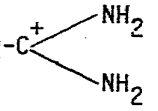
A problem with omeprazole is its stability characteristics. Upon storage without any special precautions being taken, it is degraded at a rate which is higher than desired. At storage during accelerated conditions, that is at +37°C and at a relative humidity of 80% for a period of 6 months, about 6% of the substance is converted to degradation products. While the rate of decomposition of omeprazole at normal storage conditions is lower, it is nevertheless desirable to obtain physical forms of omeprazole which exhibit improved stability. This need for more stable forms of omeprazole is apparent when considering the often considerable time periods involved from the synthesis of the active substance through its incorporation in pharmaceutical preparations, distribution of the finished product to pharmacies etc. up to the consumption of the preparation by the patient. The present invention provides such new forms of omeprazole which exhibit improved storage stability.

The invention

It has been found that the novel alkaline salts of omeprazole with the structural formula



A^{n+} I

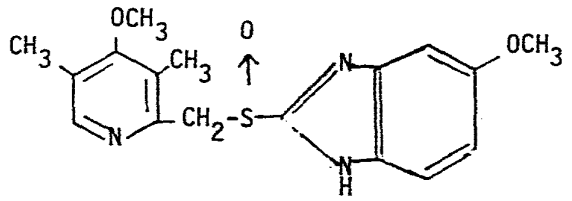
wherein n is 1, 2, or 4; A^{n+} is Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ti^{4+}, $N^+(R^1)_4$ or  , wherein R^1 is an alkyl group containing 1-4 carbon atoms are more stable during storage than the corresponding neutral form of omeprazole. The salts of the formula I are also easier to handle than the neutral form in the manufacture of pharmaceutical dosage units.

A preferred group of omeprazole salts of the formula I are those wherein A^{n+} is Na^+, K^+, Mg^{2+} and Ca^{2+}.

Further preferred salts are those wherein A^{n+} is Na^+, Mg^{2+} and Ca^{2+}. The Na^+-salt is especially preferred for the preparation of liquid pharmaceutical formulations, e.g. solutions for intravenous administration. The $Mg^{2+}$and Ca^{2+}salts are especially preferred for the preparation of tablets. The Mg^{2+} salt is particularly preferred.

Illustrative examples of the alkyl group R^1 are CH_3, C_2H_5, n-C_3H_7, and n-C_4H_9.

The novel salts I of the invention are prepared by reacting omeprazole of the formula

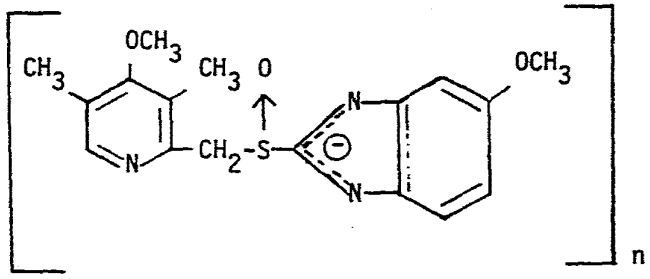


(i)

with a base capable of releasing the cation

$$A^{n+} \qquad \text{(ii)}$$

wherein A^{n+} is as defined above,
to give a salt of the formula



A^{n+} I

which salt is thereafter isolated.

Examples of bases capable of releasing the cation A^{n+}, and examples of reaction conditions are given below.

a) Salts of the formula I wherein A is Li, Na or K are prepared by treating omeprazole with LiOH, NaOH or KOH in an aqueous or nonaqueous medium or with LiOR, $LiNH_2$, $LiNR_2$, NaOR, $NaNH_2$, $NaNR_2$, KOR, KNH_2 or KNR_2, wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous medium.

b) Salts of the formula I wherein A is Mg, Ca, or Ti are prepared by treating omeprazole with $Mg(OR)_2$, $Ca(OR)_2$, CaH_2, $Ti(OR)_4$ or TiH_4, wherein R is an alkyl group containing 1-4 carbon atoms, in a nonaqueous solvent such as an alcohol (only for the alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran.