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Notice of opposition to a European patent

I. Patent opposed

Patent No.	EP1863458
Application No.	EP06737018.9
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	14 September 2016
Title of the invention	SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

II. Proprietor of the patent

first named in the patent specification	Banner Life Sciences, LLC
Opponent's or representative's reference	BD.01.17.EIN

III. Opponent

Name	DIECKHOFF Beate
Address:	Dünnwalder Grenzweg 20 51375 Leverkusen Germany
State of residence or of principal place of business	Germany
Country of nationality	Germany
Multiple opponents (see additional sheet)	☐

IV. Authorisation

1. Representative

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Multiple representatives (see additional sheet) ☐

Authorisation(s)

is/are enclosed ☐

has/have been registered under No. ☐

V. Opposition is filed against

the patent as a whole ☒

claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

- it is not new (Art. 52(1); Art. 54 EPC) ☒
- it does not involve an inventive step (Art. 52(1); Art. 56 EPC) ☒
- patentability is excluded on other grounds, namely articles ☐

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). ☒

(c) the subject-matter of the patent opposed extends beyond the content of the application/of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). ☒

VII. Facts (Rule 76(2)(c) EPC)

presented in support of the opposition are submitted herewith on an attached document ☒

VIII. Other requests:

- Oral proceedings are hereby requested auxiliarily.

IX. Evidence presented

D1	Patent document	US5,360,615 (A) , 01.11.1994 original file name: D1 - US5360615A.pdf attached as: Published-Evidence-1.pdf
D10	Non-patent literature - book	Beyer, Walter, "Lehrbuch der organischen Chemie" Stutgart: Hirzel, 1988, Ed. 21. particular relevance: page 260 original file name: D10 - Beyer Walter, Lehrbuch der organischen Chemie page 260.pdf attached as: Published-Evidence-7.pdf
D11	Non-patent literature - internet	Wikipedia , "Excerpt from the U.S. weppage pharmacopeia on PEG (lactic acid)" , [cited 13.06.2017] Available from: [http://www.pharmacopeia.cn/v29240/usp29nf24s0_m66430.html] original file name: D11 - Polyethylene Glycol USP.pdf attached as: Published-Evidence-8.pdf
D12	Non-patent literature - internet	Wikipedia, "Excerpt from the English Wikipedia weppage on citric acid" , [cited 13.06.2017] Available from: [https://en.wikipedia.org/w/index.php?title=Citric_acid&oldid=784172966] original file name: D12 - excerpt from the Wikipedia weppage on citric acid.pdf attached as: Published-Evidence-9.pdf
D13	Non-patent literature - book	Beyer, Walter, "Lehrbuch der organischen Chemie" Stuttgart: Hirzel, 1988, Ed. 21 particular relevance: page 283 original file name: D13 - Beyer Walter, Lehrbuch der organischen Chemie page 283.pdf attached as: Published-Evidence-10.pdf
D2	Patent document	WO 2016/096580 (A1) , 14.09.2006 original file name: D2 - WO2006096580A1.pdf attached as: Published-Evidence-2.pdf
D3	Patent document	US2001/0007668 (A1) , 12.07.2001 original file name: D3 - US2001007668A1.pdf attached as: Published-Evidence-3.pdf
D4	Patent document	US5,541,210 (A) , 30.07.1996 original file name: D4 - US5541210A.pdf attached as: Published-Evidence-4.pdf
D5	Other evidence	Experiments regarding the Contested Patent filed by the Patentee on September 16, 2011 during the examination procedure original file name: D5 - Experiments 2011.pdf attached as: Other-evidence-1.pdf
D6	Other evidence	Experiments regarding the Contested Patent filed by the Patentee on March 26, 2012 with the substantiation of the appeal original file name: D6 - Experiments 2012.pdf attached as: Other-evidence-2.pdf
D7	Other evidence	Technical data sheet for PEG-600

		original file name: D7 - solubility of PEG600.pdf attached as: Other-evidence-3.pdf
D8	Non-patent literature - book	Beyer, Walter, "Lehrbuch der organischen Chmie" Stuttgart: Hirzel, 1988, Ed. 21 particular relevance: page 280 original file name: D8 - Beyer Walter, Lehrbuch der organischen Chemie.pdf attached as: Published-Evidence-5.pdf
D9	Non-patent literature - internet	Wikipedia , "Excerpt from the German Wikipedia weppage on Milchsäure (lactic acid)" , [cited 13.06.2017] Available from: [https://de.wikipedia.org/w/index.php?title=Milchsäure&oldid=165775114] original file name: D9 - excerpt from the Wikipedia on Milchsäure (lactic acid).pdf attached as: Published-Evidence-6.pdf

X. Payment

Mode of payment	Debit from deposit account

The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated in the fees section below.

Currency:	EUR
Deposit account number:	28003075
Account holder:	Bernard Lohmanns

Refunds

Any refunds should be made to EPO deposit account:	28003075
Account holder:	Bernard Lohmanns

Fees

	Factor applied	Fee schedule	Amount to be paid
010 Opposition fee	1	785.00	785.00
Total:		EUR	785.00

	A Forms	Details:	System file name:
A-1	Form for notice of opposition		ep-oppo.pdf

	B Attached document files	Original file name:	System file name:
B-1	1. Facts and arguments	OPPOSITION - BD.01.17.EIN.pdf	OPPO.pdf

	C Attached evidence files	Original file name:	System file name:
C-1	1. Patent document	D1 - US5360615A.pdf	Published-Evidence-1.pdf
C-2	2. Patent document	D2 - WO2006096580A1.pdf	Published-Evidence-2.pdf
C-3	3. Patent document	D3 - US2001007668A1.pdf	Published-Evidence-3.pdf
C-4	4. Patent document	D4 - US5541210A.pdf	Published-Evidence-4.pdf
C-5	1. Non-patent literature - book	D8 - Beyer Walter, Lehrbuch der organischen Chemie.pdf	Published-Evidence-5.pdf
C-6	2. Non-patent literature - book	D10 - Beyer Walter, Lehrbuch der organischen Chemie page 260.pdf	Published-Evidence-7.pdf

C-7	3. Non-patent literature - book	D13 - Beyer Walter, Lehrbuch der organischen Chemie page 283.pdf	Published-Evidence-10.pdf
C-8	4. Non-patent literature - internet	D9 - excerpt from the Wikipedia on Milchsäure (lactic acid).pdf	Published-Evidence-6.pdf
C-9	5. Non-patent literature - internet	D11 - Polyethylene Glycol USP.pdf	Published-Evidence-8.pdf
C-10	6. Non-patent literature - internet	D12 - excerpt from the Wikipedia weppage on citric acid.pdf	Published-Evidence-9.pdf
C-11	1. Other evidence	D5 - Experiments 2011.pdf	Other-evidence-1.pdf
C-12	2. Other evidence	D6 - Experiments 2012.pdf	Other-evidence-2.pdf
C-13	3. Other evidence	D7 - solubility of PEG600.pdf	Other-evidence-3.pdf

Signature of opponent or representative

Place	**Düsseldorf**
Date:	**14 June 2017**
Signed by:	**Bernard Lohmanns 50454**
Capacity:	**(Bernard Lohmanns)**

D5

ANNEX A

Experiments to Test the Stability of Compositions of the Invention Against Formation of PEG Esters

PRODUCTION OF CAPSULES IN ACCORDANCE WITH THE INVENTION

Active Ingredients

Ingredient	Amount per Capsule
naproxen sodium	220mg

Fill Excipients

Ingredient	Amount (mg) per Capsule
Lactic Acid	44.0
Propylene Glycol	17.7
Povidone K-30	17.7
Polyethylene Glycol 600	580.6

Gelain Shell Excipients

Ingredient
Gelatin
Glycerin
Sorbital Special
Purified Water
ED&C Yellow # 6
FD&C Blue # 1

Using these ingredients capsules were produced using a method as described in the Examples of European Patent Application No. 06737018.9.

PACKAGING OF THE CAPSULES

The capsules were either packaged 15 to a bottle or 200 to a bottle or in a bulk carton. The bottles containing 15 capsules were 45 cc, round, opaque white HDPE bottles with child resistant caps.

The bottles containing 200 capsules were 400 cc, round, opaque, white, HDPE bottles with child resistant caps.

STUDY DESIGN

Bottles containing 15 capsules and bottles containing 200 capsules were stored at 25°C and a relative humidity of 60% and at 30°C and a relative humidity of 65%. A carton containing the capsules stored in bulk was stored at 25°C and 60% relative humidity.

The percentage of PEG esters in the capsules, as a percentage of the drug (naproxen sodium), was determined using HPLC, before storage and after storage for 3 months, 6 months, 9 months and 12 months.

THE RESULTS

TEST WITH BOTTLES CONTAINING 15 CAPSULES

Storage at 25°C/60% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.10%	0.17%	0.25%	0.32%
	None	0.10%	0.17%	0.25%	0.33%
	None	0.10%	0.15%	0.25%	0.32%

Storage at 30°C/65% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.15%	0.28%	0.30%	0.57%
	None	0.15%	0.29%	0.44%	0.58%
	None	0.15%	0.29%	0.44%	0.59%

TEST WITH BOTTLES CONTAINING 200 CAPSULES

Storage at 25°C/60% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.10%	0.17%	0.25%	0.31%
	None	0.11%	0.17%	0.25%	0.32%
	None	0.10%	0.17%	0.24%	0.32%

Storage at 30°C/65% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.16%	0.29%	0.41%	0.57%
	None	0.15%	0.29%	0.45%	0.59%
	None	0.15%	0.28%	0.44%	0.58%

TEST OF BULK PACK CAPSULES

Storage at 25°c/60% Relative Humidity

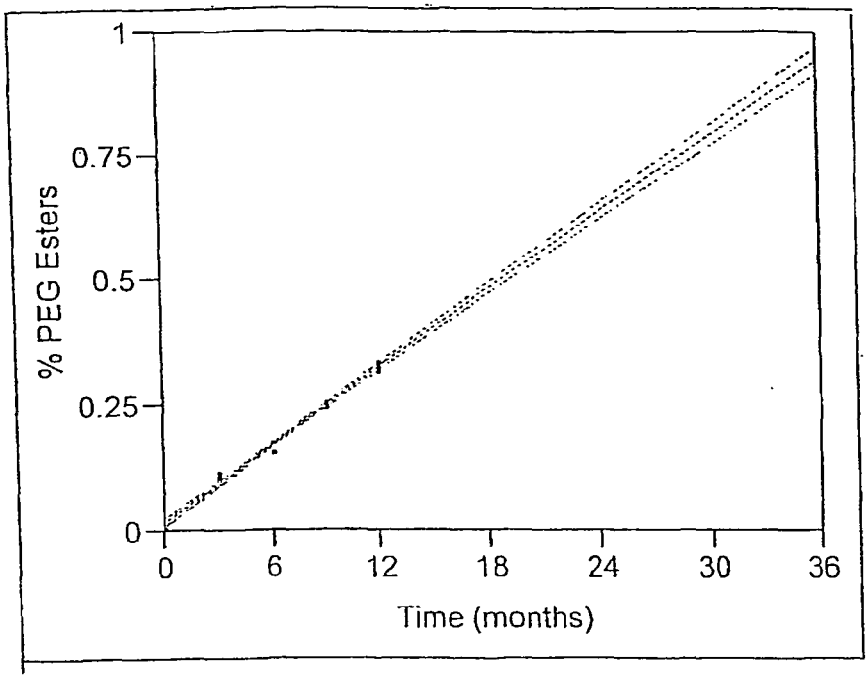
	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.10%	0.17%	0.25%	0.32%
	None	0.10%	0.16%	0.26%	0.32%
	None	0.09%	0.17%	0.22%	0.32%

These results show that initially the capsules of the invention contained no PEG esters and that even after storage for up to one year under a variety of storage conditions the capsules of the invention contained very low levels of PEG esters. In every case, significantly less than 1% of the drug had formed PEG esters even after storage for a year. Less than 1% PEG ester formation was considered to represent a low level of PEG ester formation which did not cause significant loss of activity and therefore compositions with less than 1% PEG ester were considered to be stable. All of the capsules tested passed this test.

EVALUATION OF PEG ESTER RESULTS

The percent PEG esters was plotted versus time (see graph on page 5). In addition, the 95% confidence bounds were added to the plot. Both the fitted least-squares line and the 95% upper confidence bound were extrapolated through 36 months to examine product expiration. According to the extrapolated data points for the upper 95% confidence bound, the percent PEG esters at 24 months should be 0.65 and according to the fitted least-squares line, the percent PEG esters should be 0.63. This means that even after three years the predicted values from both the upper 95% confidence and the least-squares line did not exceed the upper acceptable specification limit of not more than 1.0% PEG esters. In other words, compositions of the invention are not predicted to lose activity through PEG ester formation after 3 years and to therefore have a shelf life of at least three years.

Naproxen Sodium 220 mg SGC 25°C/60% RH
(% PEG esters vs. Time)



D6

European Patent Application No.06737018.9
Banner Pharmacaps, Inc
PC Ref: PABCX/P38814EP

ANNEX TO GROUNDS OF APPEAL

REPORT OF COMPARATIVE STUDIES CONDUCTED TO COMPARE THE PROPERTIES OF COMPOSITIONS OBTAINED IN ACCORDANCE WITH THE INVENTION AND THE COMPOSITIONS DESCRIBED IN US 5,360,615

1.0 INTRODUCTION

European patent application no. 06737018.9 is directed to a method of preparing a pharmaceutical composition. This method comprises mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid. Component (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

An advantage of the present invention is that it provides a reduction in the production of undesired degradation products such as polyethylene glycol (PEG) esters compared with the prior art.

The applicant company conducted experiments to demonstrate that preparing a pharmaceutical composition in accordance with the present invention results in reduced formation of polyethylene glycol (PEG) esters compared to producing a composition in accordance with the teaching of D1.

Accordingly, the study was designed based on the information provided in D1 and the teaching of European patent application no. 06737018.9. The compositions tested are summarized in Tables 1, 2 and 3 below.

Table 1: Study of compositions prepared in accordance with the present invention

Naproxen Form	Naproxen amount	Acid	Approximate mole equivalent level (amount of acid)		
Naproxen Sodium	285 mg	HCl	0.2	0.6	1.0
	220 mg	HCl	0.2	0.6	1.0
Naproxen Sodium	285 mg	Lactic acid	0.2	0.6	1.0
	220 mg	Lactic acid	0.2	0.6	1.0
Naproxen Sodium	285 mg	Citric acid	0.2		1.0
	220 mg	Citric acid	0.2		

285 mg of Naproxen Sodium is equivalent to 260 mg of the free acid.

220 mg of Naproxen Sodium is equivalent to 200 mg of the free acid.

Table 2: Study based on the teaching of D1

Naproxen Form	Naproxen amount	Base	Approximate mole equivalent level (amount of base)		
Naproxen free acid	260 mg	KOH	0.2	0.6	1.0
	200 mg	KOH	0.2	0.6	1.0

All the experiments were performed using PEG 600. This is a representative example of a PEG that can be used in the present invention and was used in some of the Examples of the application as filed and was also used in Example IV of D1.

Table 3: Study based of compositions containing water

Naproxen Form	Naproxen Amount	Acid/Base	Water	Approximate mole equivalent level (amount of acid/base)		
Naproxen Sodium	285 mg	Lactic acid	8.5%	0.2	0.6	1.0
	220 mg	Lactic acid	8.5%	0.2	0.6	1.0
Naproxen free acid	260 mg	KOH	8.5%	0.2	0.6	1.0
	200 mg	KOH	8.5%	0.2	0.6	1.0

2.0 MATERIALS

Material	Lot #	Supplier
6N Hydrochloric Acid	E05P01	J.T. Baker
PEG-600	100009129	Banner
Lactic Acid	20010740	Banner
Citric Acid	08-0091	Banner
Potassium Hydroxide	E17K52	J.T. Baker
Naproxen Sodium	SO60103	RoChemical International
Naproxen	081M1091V	Sigma-Aldrich

3.0 PROCEDURE

Naproxen sodium or free acid was added to PEG 600 followed by addition of molar equivalent of the appropriate acid or based in accordance with the method of the present invention and the teaching of D1, respectively.

The compositions produced in this manner were subjected to an accelerated stability study. In this study the compositions were heated to 60°C for 1 week and analyzed for the amount of PEG esters initially and at the end of the accelerated stability study.

The following formulations were prepared:

- Two series of formulations identical to that described in D1 and in the present application.
- Two series of modified formulations prepared using:

  (1) 220 mg Naproxen Sodium and PEG 600, PG and Povidone were replaced with PEG 600. Three mole ratios of acid or base such as 0.2, 0.6 and 1 were used as illustrative of the range specified in the claims of the present application.

(2) Formulations based on the teaching of D1 comprising Naproxen free acid in an amount equivalent to the molar amount used in the formulations representative of the invention, with the same amount of PEG 600 and with KOH.

Samples were analyzed by HPLC:

Agilent 1100 Series HPLC System

Column: DeactiSil ODS-3 5u 100A, 25cm X 4.6mm (ES Industries)

Column Oven Temperature: ambient

Flow Rate: 1.5 mL/min

Injection Volume: 25 uL

UV Detector at 272 nm

Run Time: 60 minutes

Mobile Phase A:

Phosphate Buffer:Acetonitrile (3:2 ratio)

Mobile Phase B:

Phosphate Buffer:Acetonitrile (1:3 ratio)

Limit of quantitation was approximated to be 0.00011 mg/mL

Banner's Formulations

Sample #	Name	Naproxen Na (g)	6N HCl (mL)	PEG-600 (g)
1	NS 285-0.2 HCl	7.128	0.95	16.950
2	NS 285-0.6 HCl	7.120	2.80	15.024
3	NS 285-1.0 HCl	7.152	4.70	13.514
4	NS 220-0.2 HCl	5.512	0.70	18.790
5	NS 220-0.6 HCl	5.521	2.15	17.413
6	NS 220-1.0 HCl	5.548	3.60	15.891

		Naproxen Na (g)	Lactic Acid (g)	DI H20 (g)	PEG-600 (g)
7	NS 285-0.2 lactic	7.133	0.513	0.434	16.947
8	NS 285-0.6 Lactic	7.150	1.528	1.295	15.053
9	NS 285-1.0 Lactic	7.132	2.544	2.167	13.188
10	NS 220-0.2 Lactic	5.559	0.388	0.460	18.789
11	NS 220-0.6 Lactic	5.518	1.186	1.030	17.339
12	NS 220-1.0 Lactic	5.523	1.972	1.660	15.899

		Naproxen Na (g)	Citric Acid (g)	DI H20 (g)	PEG-600 (g)
13	NS 285-0.2 Citric	7.129	1.020	0.439	16.364
14	NS 285-1.0 Citric	7.128	5.436	2.519	10.350
15	NS 220-0.2 Citric	5.012	0.865	0.364	18.355

Yu's Formulations

	Naproxen API	Naproxen (g)	50% KOH (9)	PEG-GOO (g)
16	Yu 260-0.2 KOH	6.499	0.330	17.892
17	Yu 260-0.6 KOH	6.497	0.957	16.681
18	Yu 260-1.0 KOH	6.510	1.594	15.357
19	Yu 200-0.2 KOH	5.027	0.286	19.555
20	Yu 200-0.6 KOH	5.100	0.757	18.580
21	Yu 200-1.0 KOH	5.134	1.230	17.540

In the tables above, "Banner's formulations" refers to formulations prepared using the method of the present invention and "Yu's formulations" refers to formulations that are representative of the teaching of D1.

4.0 RESULTS

The results are summarized in the Table below.

Banner's Formulations		Room Temperature		Stress at 60C for 7-Days		Physical Observations of Formulations	
Sample #	Name	Peaks RT	% Area	Peaks RT	% Area	Room Temp	Stress at 60C 7-Days
1	NS 285-0.2 HCl	*10.78 **14.347	0.0084% 99.9916%	14.36	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
2	NS 285-0.6 HCl	10.787 14.34	0.0101% 99.9899%	10.78 14.38	0.0030% 99.9970%	Phase Separate, precipitate	Phase Separate, precipitate
3	NS 285-1.0 HCl	10.753 14.36	0.0076% 99.9924%	10.8 14.4	0.0069% 99.9931%	Phase Separate, precipitate	Phase Separate, precipitate
4	NS 220-0.2 HCl	10.773 14.347	0.0076% 99.9924%	14.4	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
5	NS 220-0.6 HCl	14.36	100.0000%	14.427	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
6	NS 220-1.0 HCl	10.773 14.36	0.0082% 99.9918%	10.793 14.413	0.0048% 99.9952%	Phase Separate, precipitate	Phase Separate, precipitate
7	NS 285-0.2 Lactic	10.78 14.293	0.0075% 99.9925%	14.36	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
8	NS 285-0.6 Lactic	10.773 14.287	0.0072% 99.9928%	14.38	100.0000%	Clear Solution, crystallize at bottom	Clear Solution
9	NS 285-1.0 Lactic	10.767 14.327	0.0073% 99.9927%	14.413	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate

10	NS 220-0.2 Lactic	10.767 14.327	0.0069% 99.9931%	14.42	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
11	NS 220-0.6 Lactic	10.773 14.347	0.0067% 99.9933%	14.407	100.0000%	Clear solution	Clear solution
12	NS 220-1.0 Lactic	10.773 14.367	0.0064% 99.9936%	14.393	100.0000%	White semi-solid crystallized	Phase Separate, precipitate
13	NS 285-0.2 Citric	10.747 14.327	0.0087% 99.9913%	10.76 14.38	0.0038% 99.9962%	White semi-solid crystallized	Phase Separate, precipitate
14	NS 285-1.0 Citric	10.78 14.32	0.0021% 30.4552%	10.78 14.373	0.0107% 99.9893%	White semi-solid paste	White semi-solid paste
15	NS 220-0.2 Citric	10.787 14.353	0.0061% 99.9939%	14.393	100.0000%	Opaque solution fill, viscuous	Phase Separate, precipitate

Yu's Formulations		Room Temperature		Stress at 60C for 7-Days		Physical Observations of Formulations	
Sample #	**Name**	**Peaks RT**	**% Area**	**Peaks RT**	**% Area**	**Room Temp**	**Stress at 60C 7-Days**
16	Yu 260-0.2 KOH	*10.773 **14.333	0.0178% 99.8580%	10.793 14.387	0.0132% 99.8658%	Phase Separate, precipitate	Clear solution
17	Yu 260-0.6 KOH	10.767 14.367	0.0154% 99.8745%	10.807 14.387	0.0133% 99.8689%	Clear solution	Clear solution
18	Yu 260-1.0 KOH	10.793 14.36	0.0160% 99.8751%	10.813 14.373	0.0140% 99.8647%	Clear solution	Clear solution
19	Yu 200-0.2 KOH	10.793 14.393	0.0144% 99.8879%	10.8 14.413	0.0093% 99.8861%	Clear solution	Clear solution
20	Yu 200-0.6 KOH	10.787 14.387	0.0146% 99.8797%	10.793 14.4	0.0128% 99.8784%	Clear solution	Clear solution
21	Yu 200-1.0 KOH	10.787 14.38	0.0148% 99.8835%	10.807 14.387	0.0135% 99.8750%	Clear solution	Clear solution

* PEG ester peak retention time.

** Naproxen peak retention time.

In general, the amount of PEG ester in the formulations prepared in accordance with the teaching of D1 when subjected to stressed conditions varied from 0.0093 to 0.014. The compositions prepared by the method of the present invention exhibited lower levels of PEG esters at room temperature and after the stress study.

5.0 CONCLUSION

The results of these experiments show that formulations prepared in accordance with the teaching of the present invention surprisingly contain lower amounts of PEG esters that formulations prepared following the teaching of D1.

Technical Data Sheet

D7

CARBOWAX™ Polyethylene Glycol (PEG) 600

Product CAS # 25322-68-3
Description CHEMICAL FAMILY – Oxyalkylene Polymer
CFTA NOMENCLATURE – PEG-12

Typical Physical Properties – CARBOWAX™ PEG 600[1]

Range of Avg. Molecular Weight	570 - 630
Range of Average Hydroxyl Number, mg KOH/g	178 - 197
Density, g/cm^3 @ 20°C	1.1258
Melting or Freezing Range, C	15 - 25
Solubility in Water at 20°C, % by wt	Complete
Viscosity at 100°C, cSt	10.8
Average Number of Repeating Oxyethylene Units	13.2
Avg. Liquid Specific Heat, cal/g/°C	0.51
Heat of Fusion, Cal/g	35
pH at 25°C, 5% Aqueous Solution	4.5 - 7.5
Flash Point, Pensky Martens Closed Cup, C	238
Flash Point, Cleveland Open Cup, °C	274
Physical Form	Liquid
Weight per gallon, lbs/gal @ 20°C	9.39

1. Typical properties, not to be construed as specifications

Typical Known Applications for Polyethylene Glycols*

- Adhesives
- Ceramic Glaze
- Chemical Intermediates
- Food Packaging
- Inks
- Lubricants
- Mold Release Agent
- Plasticizer
- Wood Treatment

*Refer to the CARBOWAX™ Polyethylene Glycols and Methoxypolyethylene Glycols brochure (Form No. 118-01789-1011) for more specific application information

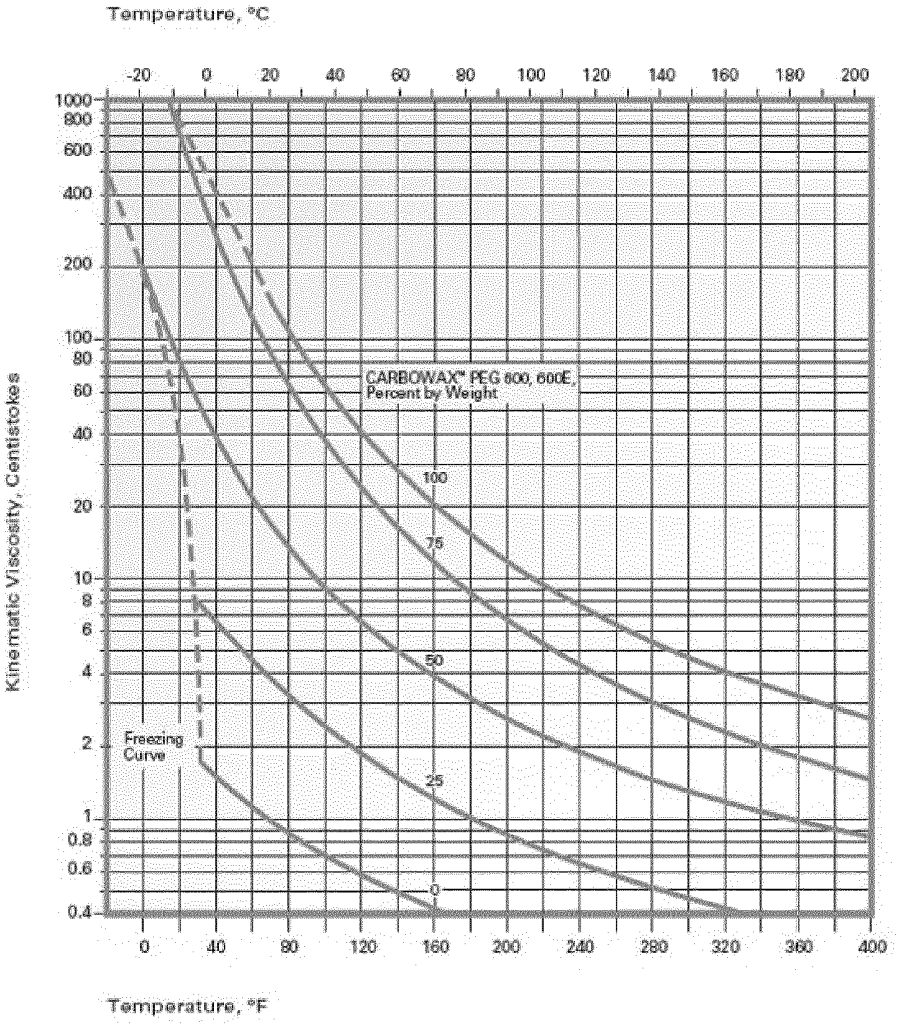
FDA Status CARBOWAX™ Polyethylene Glycols are produced to meet the requirements for use under Food Additive Regulations for indirect use as components of articles intended for use in contact with food. It is the responsibility of the user of CARBOWAX™ PEGs and MPEGs to read and understand all current applicable FDA and EPA regulations, as well as any other applicable regulations.

Product Stewardship Dow encourages its customers and potential users to review their applications from the standpoint of human health and environmental aspects. To help ensure that Dow products are not used in ways for which they are not intended or tested, Dow personnel will assist customers in dealing with environmental and product safety considerations. Dow literature, including material Safety Data Sheets, should be consulted prior to the use.

Form No. 118-01800-1211

Technical Data Sheet

Kinematic Viscosity of A ueous Solutions of CARBOWAX™ Polyethylene Glycol 600



For further information, call...

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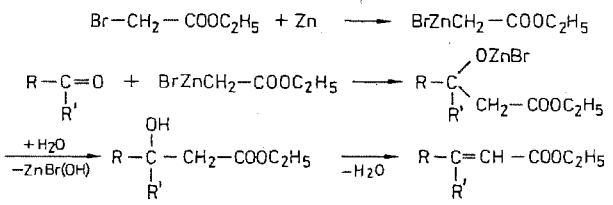
nicht mit der Estergruppe. Bei der Hydrolyse des Addukts entstehen zunächst β-Hydroxycarbonsäureester, die jedoch leicht unter Wasseraustritt in die α,β-ungesättigten Carbonsäureester übergehen, z. B.

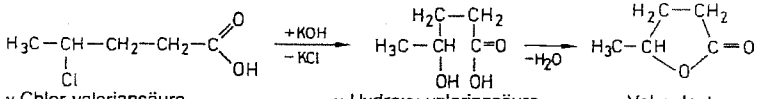


β-Hydroxycarbonsäureester

Aldehyde (R′=H) reagieren im allgemeinen leichter als Ketone. Die Reaktion wird meist durch geringe Zusätze von Iod katalysiert.

Diese metallorganische Variante der Aldoladdition kann auf breiter Basis zu Synthesen verwendet werden. Als Carbonylkomponente kommen aliphatische und aromatische Aldehyde sowie aliphatische, cyclische oder aromatische Ketone in Frage (vgl. auch *Ivanoff*-Reaktion), als „Methylenkomponente" unverzweigte und verzweigte aliphatische α, β oder γ-Bromcarbonsäureester.

2.29.4.3 γ- und δ-Hydroxysäuren erhält man *durch alkalische Hydrolyse der* γ- bzw. *δ-Halogencarbonsäuren.* Sie können jedoch nur in Form ihrer Alkalisalze isoliert werden, da sie beim Ansäuern sofort unter Wasseraustritt in γ- bzw. δ-Lactone übergehen, z. B.

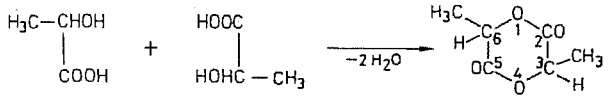


γ-Chlor-valeriansäure
4-Chlor-valeriansäure

γ-Hydroxy-valeriansäure

γ-Valerolacton

Eigenschaften. Die Hydroxysäuren sind in Wasser leichter, in Ether schwerer löslich als die zugehörigen Carbonsäuren. In Analogie zum Halogen in den Halogencarbonsäuren erhöht besonders die α-ständige Hydroxylgruppe – wenn auch in geringerem Maß – die *Acidität* der Hydroxysäuren (*−I-Effekt*). Ihr chemisches Verhalten ist durch das gleichzeitige Auftreten der alkoholischen Hydroxyl- und der Carboxylgruppe charakterisiert. Sie geben somit die für beide Funktionen spezifischen Umsetzungen.
Beim Erhitzen spalten die Hydroxysäuren Wasser ab und bilden je nach der Stellung der OH-Gruppe nachstehende Verbindungen:
Aus *α-Hydroxysäuren* entstehen unter intermolekularer Wasserabspaltung ringförmige Lactide, z. B.

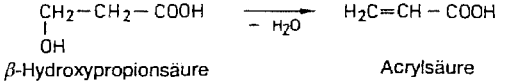


Milchsäure

3,6-Dimethyl-1,4-dioxan-2,5-dion

Der Name *Lactide* ist von der Milchsäure (*Acidum lacticum*) abgeleitet, an der diese Reaktion zuerst beobachtet wurde.

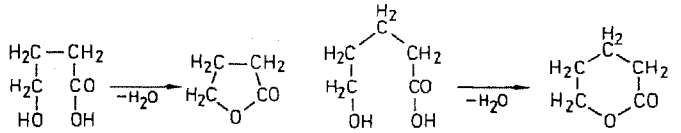
β-Hydroxysäuren spalten intramolekular Wasser ab unter Bildung α,β-ungesätt Carbonsäuren, z. B.



β-Hydroxypropionsäure

Acrylsäure

γ- bzw. *δ-Hydroxysäuren* gehen – zuweilen schon bei Raumtemperatur – unter molekularer Wasserabspaltung in γ- bzw. *δ-Lactone über, z. B.*



γ-Hydroxy-buttersäure

γ-Butyrolacton

δ-Hydroxy-valeriansäure

δ-Valerolacton

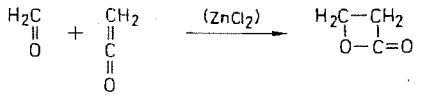
Analog cyclisieren sich γ-Thiolcarbonsäuren spontan zu *γ-Thiolactonen.*

2.29.5 Lactone

Die Lactone sind als *innere Ester* der Hydroxycarbonsäuren aufzufassen, und zwa terscheidet man α-, β-, γ-, δ- und höhergliedrige Lactone. Die aus den aliphatis Carbonsäuren entstehenden Lactone werden durch Anhängen der Endung *-olid* a Namen des *nicht hydroxylierten Kohlenwasserstoffes* mit der gleichen Zahl von Ko wasserstoffatomen benannt. Dabei wird die Positionsziffer des am Ringschluß bet ten C-Atoms vor der Endung angegeben, z. B. Propan-3-olid = β-Propiolacton, 7-H decen-16-olid = Ambrettolid, Pentadecan-15-olid = Exaltolid.
Während die α-Lactone im allgemeinen nur in Lösung nachgewiesen werden kön und die β-Lactone[2] sich nur mit Hilfe spezieller Verfahren darstellen lassen, entst die γ- und die δ-Lactone leicht aus den entsprechenden Hydroxysäuren. Die wic sten Vertreter sind *γ-Butyrolacton* sowie γ- und *δ-Valerolacton.*

Darstellung. Außer durch die allgemeinen Darstellungsverfahren gewinnt man e Lactone technisch auf folgende Weise:

2.29.5.1 *β-Propiolacton* (Hydracrylolacton) wird *durch Cycloaddition* aus Keten Formaldehyd in wasserfreiem Medium bei Gegenwart von Zinkchlorid darge (Ausbeute 90%):



Keten

β-Propiolacton
Propan-3-olid

[1] Vgl. *O. L. Chapman* et al., J. Amer. Chem. Soc. *94,* 1365 (1972); ein trifluoralkylsubstitu α-Lacton ist isoliert worden: Chem. Comm. *1982,* 362.
[2] Vgl. *H. E. Zaugg,* β-Lactones, Org. Reactions *8,* 305 (1954); *K. Kröper, Houben-Weyl,* Meth

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Milchsäure

aus Wikipedia, der freien Enzyklopädie

Milchsäure (lat. *acidum lacticum*) ist eine Hydroxycarbonsäure, also eine Alkansäure, die sowohl eine Carboxygruppe als auch eine Hydroxygruppe besitzt. Sie wird deswegen auch als **2-Hydroxypropionsäure** bezeichnet, nach den Nomenklaturempfehlungen der IUPAC ist jedoch die Bezeichnung **2-Hydroxypropansäure** zu verwenden. Die Salze und Ester der Milchsäure heißen Lactate.

Inhaltsverzeichnis

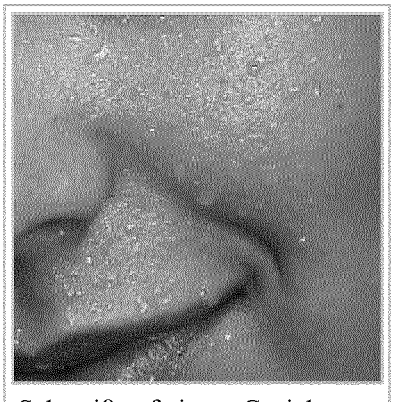
Geschichte

Milchsäure wurde historisch sowohl in Europa wie auch in Asien zur Säuerung und Konservierung von Lebensmitteln, insbesondere für Milch (Sauermilch), Gemüse (z. B. Sauerkraut) und auch zur Herstellung von Silagen als Futtermittel bereits seit Jahrhunderten oder Jahrtausenden genutzt.

Die erste Entdeckung und Isolierung der Milchsäure geht auf den schwedischen Chemiker Carl Wilhelm Scheele im Jahr 1780 zurück, der sie aus saurer Milch in Form eines braunen Sirups isolierte.[5] Die Fleischmilchsäure [L-(+)-Milchsäure] wurde von Jöns Jakob Berzelius im Jahr 1808 entdeckt und ihre Struktur 1873 von Johannes Wislicenus aufgeklärt. Henri Braconnot, ein französischer Chemiker, fand im Jahre 1813 heraus, dass Milchsäure in einem Fermentationsprozess hergestellt werden kann.[5] 1856 entdeckte Louis Pasteur die Milchsäurebakterien und entwickelte das Grundverständnis für die Milchsäuregärung. Die großtechnische Produktion von Milchsäure begann 1881 in den USA,[5] und 1895 machte auch Boehringer Ingelheim die Entdeckung, wie Milchsäure mit Hilfe von Bakterien in großen Mengen hergestellt werden konnte.

Vorkommen

L-(+)-Milchsäure kommt in Schweiß, Blut, Speichel sowie im Muskelserum, in der Niere und Galle vor. Das Racemat, eine 1:1-Mischung aus D- und L-Milchsäure, findet sich z. B. in Sauermilch- und Molkeprodukten, Tomatensaft und Bier. Bei allen Produkten, die per Milchsäuregärung haltbar gemacht werden, ist der Anteil der beiden Enantiomeren abhängig vom verwendeten Bakterienstamm und den Reaktionsbedingungen.

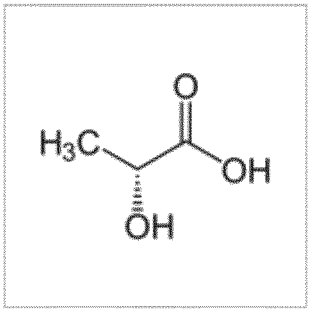


Schweiß auf einem Gesicht

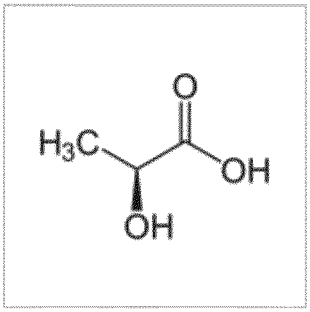
Auch Pilze erzeugen Milchsäure, z. B. Vertreter der Gattungen Rhizopodus, Allomyces und Blastocladiella.[6]

Eigenschaften

Aufgrund ihrer unterschiedlichen optischen Aktivität wird die D-(−)-Milchsäure (Syn.: (*R*)-Milchsäure) auch als *linksdrehende Milchsäure* und die L-(+)-Milchsäure (Syn.: (*S*)-Milchsäure) auch als *rechtsdrehende Milchsäure* bezeichnet. Racemische Milchsäure ist ein 1:1-Gemisch aus (*R*)- und (*S*)-Milchsäure.



D-Milchsäure

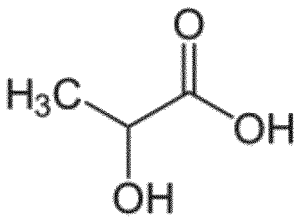


L-Milchsäure

Milchsäure ist in Form von Lactat ein wichtiges Zwischenprodukt im Stoffwechsel, zum Beispiel als Produkt beim Abbau von Zuckern durch die Milchsäuregärung. Weltweit werden jährlich etwa 250.000 Tonnen (Stand 2010) Milchsäure industriell produziert,[7] die vor allem in der Lebensmittelindustrie sowie zur Herstellung von Polylactiden (PLA; auch: *Polymilchsäuren*) genutzt werden.

Der spezifische Drehwinkel beträgt für D-Milchsäure bei 20 °C $[\alpha]_D^{20} = -2{,}6$ (H_2O) und für L-Milchsäure $[\alpha]_D^{20} = +2{,}6$ (H_2O). Bei 15 °C wird für L-Milchsäure ein Drehwinkel $[\alpha]_D^{15} = +3{,}82$ (H_2O)[2] gemessen.

Milchsäure bildet intermolekular Ester. Unter

Strukturformel	
	
Strukturformel ohne Angabe der Stereochemie	
Allgemeines	
Name	Milchsäure
Andere Namen	■ 2-Hydroxypropansäure ■ 2-Hydroxypropionsäure ■ (*R*)-Milchsäure ■ (*S*)-Milchsäure ■ (*RS*)-Milchsäure ■ DL-Milchsäure ■ (±)-Milchsäure ■ E 270
Summenformel	$C_3H_6O_3$
CAS-Nummer	■ 50-21-5 ■ 10326-41-7 (D-Milchsäure) ■ 79-33-4 (L-Milchsäure) ■ 598-82-3 (Racemat)
PubChem	612 (https://pubchem.ncbi.nlm.nih.gov/compound/612)
ATC-Code	G01AD01 (http://www.whocc.no/atc_ddd_index/?code=G01AD01)
Kurzbeschreibung	farblose, fast geruchlose, ölige Flüssigkeit (Racemat)[1]
Eigenschaften	
Molare Masse	90,08 $g \cdot mol^{-1}$
Aggregatzustand	flüssig (Racemat) fest (D-/L-Milchsäure)[1]
Dichte	1,21 $g \cdot cm^{-3}$ (Racemat)[1]
Schmelzpunkt	■ 17 °C (Racemat)[2] ■ 53 °C (D-/L-Milchsäure /Enantiomere)[2]

Abspaltung von Wasser entsteht als Dimer Lactoylmilchsäure, die beim längeren Stehen oder beim Erhitzen zu Polymilchsäure weiterverestert. Diese Makromoleküle erreichen jedoch keine relevanten Kettenlängen, um das Produkt technisch verwerten zu können.

In wässriger Milchsäurelösung liegt ein chemisches Gleichgewicht zwischen Milchsäure und ihren durch intermolekularer Wasserabspaltung entstehenden Polyester (Estoliden) vor. In 90%iger Milchsäurelösung findet man etwa 70 % als freie Säure und 20 % als ihre Estolide vor. Aus zwei Milchsäuremolekülen entstehen unter Ringschluss und Abspaltung von zwei Wassermolekülen Dilactid mit einem sechsgliedrigen Ring (Dilacton). Diese Verbindung wird in wässriger Milchsäurelösung jedoch nicht beobachtet. Aus Dilactiden lassen sich mittels Ringöffnungspolymerisation hochwertige Polyester erzeugen. Der entstehende Kunststoff ist biologisch abbaubar und zudem immunologisch neutral.

Siedepunkt	122 °C (20 hPa) (Racemat)[1]
Dampfdruck	10 Pa (25 °C)[1]
pK_s-Wert	3,90 (25 °C, Racemat)[2]
Löslichkeit	■ vollständig mischbar mit Wasser[1] ■ löslich in Ethanol[2]
Brechungsindex	1,4392 (20 °C; Racemat)[3]
Sicherheitshinweise	
Bitte die eingeschränkte Gültigkeit der Gefahrstoffkennzeichnung bei Arzneimitteln beachten	
GHS-Gefahrstoffkennzeichnung [1]  **Gefahr**	
H- und P-Sätze	H: 315-318 P: 280-305+351+338 [1]
Toxikologische Daten	3.543 mg·kg^{-1} (LD_{50}, Ratte, oral)[4]
Soweit möglich und gebräuchlich, werden SI-Einheiten verwendet. Wenn nicht anders vermerkt, gelten die angegebenen Daten bei Standardbedingungen. Brechungsindex: Na-D-Linie, 20 °C	

Herstellung

Die Herstellung von Milchsäure kann sowohl biotechnologisch über eine Fermentation von Kohlenhydraten (Zucker, Stärke) wie auch synthetisch auf der Basis petrochemischer Rohstoffe (Acetaldehyd) erfolgen.

Fermentative Herstellung

Etwa 70 bis 90 % der Weltproduktion an Milchsäure wird derzeit fermentativ hergestellt,[8] wobei beide reinen Enantiomere kommerziell durch Fermentationsverfahren mit Milchsäurebakterien in signifikanten Mengen produziert werden.[9] Biologisch entsteht bei der mikrobiellen Fermentation durch Milchsäurebakterien häufig das Racemat der Milchsäure (50:50-Gemisch) bis zu Produkten mit Anteilen von 51 bis 90 % L-Milchsäure.[10]

Industriell erfolgt die Herstellung von Sauermilchprodukten durch Vergärung von Milch oder Molke vor allem durch die *Lactobacillus*-Arten *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus delbrueckii subsp. bulgaricus* (*Lactobacillus bulgaricus*) und *Lactobacillus helveticus*, weiterhin durch *Streptococcus salivarius subsp. thermophilus* (*Streptococcus thermophilus*) und *Lactococcus lactis*.[11] Für industriell genutzte Milchsäure werden Zuckerdicksaft oder Stärkehydrolysate und *Lactobacillus delbrueckii* sowie Pentose-haltige Sulfitablaugen und *Lactobacillus pentosus* verwendet.[12] Die Bakterienstämme werden nach ihrer Eigenart eingeteilt, Glucose nur zu Lactat oder auch zu anderen Produkten zu vergären: *homofermentative* Arten, wie *Lactobacillus casei* und *Lactococcus lactis*, bilden pro Mol Glucose zwei Mol Lactat, während *heterofermentative* Arten, wie *Leuconostoc mesenteroides* und *Lactobacillus brevis*, neben einem Mol Lactat pro Mol Glucose auch Essigsäure, Kohlenstoffdioxid und Ethanol produzieren.[10]

Synthetische Herstellung

Synthetisch wird Milchsäure durch Wasseranlagerung an Cyanwasserstoff (Blausäure, HCN) hergestellt. Großtechnisch spielt dabei nur die Synthese von Milchsäure aus Acetaldehyd mit Cyanwasserstoff über Lactonitril eine gewisse Rolle. Letzteres wird über den Einsatz von Salzsäure hydrolysiert, wobei neben der Milchsäure Ammoniumchlorid entsteht. Dieser Syntheseweg wird von dem japanischen Unternehmen Musashino als letztem Großproduzenten für synthetische Milchsäure realisiert.[5]

Verwendung

Ernährung, Futter- und Genussmittel

Joghurt und andere Sauermilchprodukte basieren auf Milchsäuregärung.

Eine Reihe von Lebensmitteln werden direkt durch Milchsäuregärung hergestellt. Darunter fallen vor allem die Sauermilchprodukte wie Sauermilch, Joghurt, Kefir und Buttermilch. Diese werden durch Infektion von pasteurisierter Milch mit Starterkulturen der Milchsäurebakterien hergestellt. Weitere Produkte sind lactofermentierte Gemüse wie Sauerkraut, rote Bete in einigen Borschtsch-Varianten oder Gimchi sowie Sauerteig und entsprechend Sauerteigprodukte. Auch Silagen, durch Vergärung haltbar gemachte Frischfuttermittel, basieren auf der Milchsäuregärung.[10]

Als Lebensmittelzusatzstoff trägt Milchsäure die Bezeichnung E 270. Sie wird in der Lebens- und Genussmittelindustrie vielfältig als Säuerungsmittel eingesetzt, so etwa in Backwaren, Süßwaren und vereinzelt in Limonaden. Durch die Änderung des pH-Wertes in den Lebensmitteln auf einen pH von etwa 4 kommt es zu einer Konservierung der Lebensmittel, da eine Besiedlung mit anderen Mikroorganismen weitgehend ausgeschlossen wird.[10]

In Form der Salze Calciumlactat oder Calciumlactatgluconat kann sie zudem zur Calciumanreicherung zugesetzt werden.

Stoffliche Nutzung

Einkaufsbeutel aus PLA-Biokunststoff

Milchsäure ist das Monomer der Polylactide bzw. Polymilchsäuren (PLA), die als biologisch abbaubare Biokunststoffe vielfältige Verwendung finden.

Milchsäure wirkt antibakteriell und wird deshalb Flüssigseifen, Reinigern und Geschirrspülmitteln zugegeben. Die Desinfektionswirkung entfaltet sie optimal bei einem pH-Wert von 3 bis 4.[13] Sie wurde und wird auch als Mittel zur Schwangerschaftsverhütung eingesetzt.[14]

Milchsäure wird als Kalklöser in der Gerberei zum Entkalken von Häuten verwendet. Auch in der Textilindustrie und der Druckerei wird sie hierzu eingesetzt.

Imker nutzen Milchsäure zur Behandlung von Bienen gegen die Varroamilbe.[15] Arachnologen verwenden Milchsäure, um die präparierte Epigyne von Spinnenweibchen oder andere Chitinstrukturen aufzuhellen und um Gewebereste

aufzulösen.

Die Pharmazeutische Technologie nutzt Milchsäure, um wasserunlösliche Arzneistoffe in Salze der Milchsäure (Lactate) umzuwandeln; diese sind besser wasserlöslich (Beispiel: Ciprofloxacin).[16]

In der Kosmetik wird Milchsäure in Hautcremes und anderen Produkten zur Behandlung von Akne genutzt.

Physiologie

Bei starker Betätigung der Skelettmuskulatur kann es zum Anstieg des Blut-Lactatgehaltes von 5 mg/dl auf 100 mg/dl kommen. Die Ursache ist, dass bei anaeroben Bedingungen, wie beispielsweise bei schneller Betätigung der Skelettmuskulatur, Energie in Form von NAD^+ aus der Reduktion von Pyruvat mittels der Lactatdehydrogenase für die Fortführung der Glykolyse gewonnen werden muss. Die dabei anfallende Milchsäure (Lactat und H^+) wird über den Monocarboxylat-Transporter 1 aus den Zellen geschwemmt. Dieser Vorgang wurde früher als Ursache des Muskelkaters verstanden, jedoch wird diese Theorie heute größtenteils als falsch betrachtet.

Für den Menschen ist die rechtsdrehende L-(+)-Milchsäure die physiologische. Oral eingenommen wird sie im Organismus schneller abgebaut als die linksdrehende D-(−)-Milchsäure.[17]

Weblinks

Commons: Milchsäure (https://commons.wikimedia.org/wiki/Category:Lactic_acid?uselang=de) – Sammlung von Bildern, Videos und Audiodateien
Wiktionary: Milchsäure – Bedeutungserklärungen, Wortherkunft, Synonyme, Übersetzungen

- Kathrin Einschütz: *Wirksamkeitsprüfung verschiedener Verfahren zur Verminderung der Keimbelastung auf Handgeräten der Fleischgewinnung.* Dissertation. FU Berlin, 2004 urn:nbn:de:kobv:188-2004002043 (http://nbn-resolving.de/urn:nbn:de:kobv:188-2004002043) (Antibakterielle und konservierende Eigenschaften der Milchsäure)
- 3D-Darstellung beider Milchsäuremoleküle zum Vergleich (L- und D-Milchsäure) (http://www.cup.uni-muenchen.de/cicum/tutor/enantio/milchsre.html)

Einzelnachweise

1. Eintrag zu *Milchsäure (http://gestis.itrust.de /nxt/gateway.dll?f=id$t=default.htm$vid=gestisdeu:sdbdeu$id=013000)* in der GESTIS-Stoffdatenbank des IFA, abgerufen am 1. Februar 2016 (JavaScript erforderlich).
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15. *Gebrauchsinformation Milchsäure 15 % ad us. vet.* Serumwerk Bernburg AG, Stand: 14. Januar 2009.
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Normdaten (Sachbegriff): GND: 4114596-3 | LCCN: sh85073866 | NDL: 00568760

Abgerufen von „https://de.wikipedia.org/w/index.php?title=Milchsäure&oldid=165775114“

Kategorien: ATC-G01 | Ätzender Stoff | Reizender Stoff | Alpha-Hydroxycarbonsäure | Arzneistoff | Antioxidationsmittel | Säuerungsmittel

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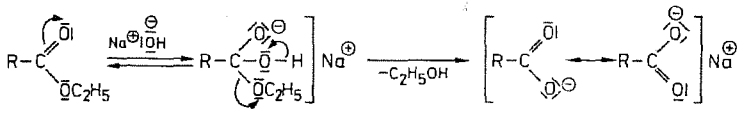
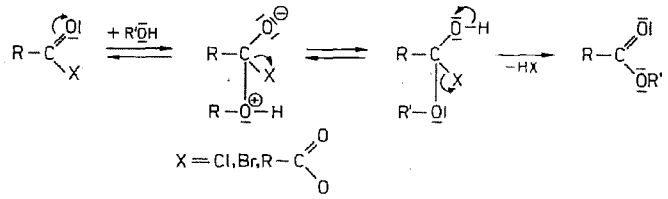
D10

Die Hydrolyse der Ester zu Carbonsäuren kann sowohl im sauren als auch im alkalischen Medium durchgeführt werden. Die *saure* Verseifung verläuft in Abhängigkeit von der Struktur des Alkylrestes in umgekehrter Richtung wie die säurekatalysierten Veresterungen (s. S. 259). Bei der *alkalischen* Verseifung der Ester greift zunächst ein *Hydroxid-Ion* das C-Atom der Alkoxycarbonylgruppe *nucleophil* an. Das entstehende Additionsprodukt stabilisiert sich dann unter Alkoholabspaltung zum Natriumsalz der Carbonsäure (*Additions-Eliminierungs-Mechanismus*):



Der Vorzug der alkalischen Esterverseifung besteht darin, daß der letzte Schritt praktisch irreversibel ist, wodurch die Hydrolyse quantitativ erfolgt. Da das Alkali bei der Reaktion verbraucht wird, ist mindestens ein Äquivalent Base erforderlich.
Die auf S. 151 beschriebene Reaktion des Methylsulfinylcarbanions mit Carbonsäureestern verläuft analog.

2.28.4.2 *Durch Umsetzung von Säurechloriden oder -anhydriden mit Alkoholen:*



Diese Reaktionen verlaufen nach dem *Additions-Eliminierungs-Mechanismus* meist quantitativ.

2.28.4.3 *Aus Silbersalzen der Carbonsäuren mit Alkylhalogeniden:*

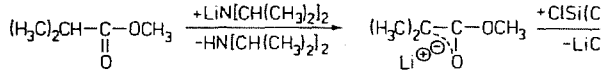
Diese Methode ist teuer und wird nur dann angewendet, wenn die direkte Veresterung versagt oder schlechte Ausbeuten liefert.

2.28.4.4 *Essigsäureethylester* wird technisch aus Acetaldehyd nach dem *Tischtschenko*-Verfahren gewonnen.

Eigenschaften. Die niederen Glieder der Carbonsäureester sind farblose Flüssigkeiten von fruchtartigem Geruch, die höheren sind geruchlos. Sie reagieren neutral, sind spezifisch leichter als Wasser und in diesem nur wenig löslich. Im Gegensatz zu den Carbonsäuren sind ihre Ester nicht assoziiert (keine H-Brücken!) und sieden daher tiefer als die entsprechenden Säuren, z. B. *Essigsäureethylester* bei 77 °C (350 K).
In Analogie zur Hydrolyse der Ester ist mit Alkoholen eine *Alkoholyse* möglich, z. B.

2.28.4.5 Derartige **Umesterungen** verlaufen unter dem katalyt
ralsäuren oder Laugen, zuweilen schon bei Raumtemperatu
gungen gelingt die Umesterung in Gegenwart von „Titanater
che funktionelle Gruppen, die mit Säuren oder Laugen reag
Art der Umesterung intakt[1].

2.28.4.6 Carbonsäureester, die am α-C-Atom mindestens ein
in Analogie zu den Ketonen *Enolate* bilden, aus denen die
Ketenacetale dargestellt werden können, z. B. aus Isobutter
thiumdiisopropylamid und Chlortrimethylsilan:



Das *Dimethylketen-methyl-trimethylsilylacetal* ist präparativ w
pen-Transfer-Polymerisation.

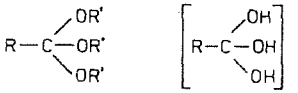
2.28.4.7 *Reduktion der Carbonsäureester zu primären Alkohole*
denen Wegen möglich, und zwar durch Reduktion mit Nat
***veault-Blanc*-Reduktion**), mit Lithiumaluminiumhydrid ode
ferchromit-Kontakt:

Mit *Grignard*-Verbindungen geben die Carbonsäureester *tertiäre* Alkol

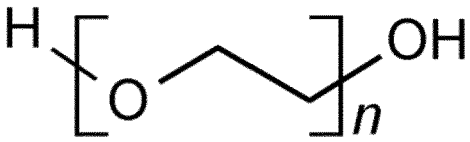
Verwendung. Die Säureester, vor allem Ethyl- und Butylacetat
tel für Nitrocellulose und Harze in der Lackindustrie sowie als
kondensationen. Einige Ester werden als künstliche Aromen
z. B. Ethylformiat (Rum, Arrak), Isobutylacetat (Banane),
Ethylbutyrat (Ananas) und Isopentylbutyrat (Birne).

2.28.5 Orthocarbonsäureester

Neben den einfachen Carbonsäureestern lassen sich unter b
auch *Orthoester* darstellen, denen folgende Konstitution zukom



Polyethylene Glycol



Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-.
Polyethylene glycol [*25322-68-3*].

» Polyethylene Glycol is an addition polymer of ethylene oxide and water, represented by the formula:

$$H(OCH_2CH_2)_nOH,$$

in which *n* represents the average number of oxyethylene groups. The average molecular weight is not less than 95.0 percent and not more than 105.0 percent of the labeled nominal value if the labeled nominal value is below 1000; it is not less than 90.0 percent and not more than 110.0 percent of the labeled nominal value if the labeled nominal value is between 1000 and 7000; it is not less than 87.5 percent and not more than 112.5 percent of the labeled nominal value if the labeled nominal value is above 7000. It may contain a suitable antioxidant.

Packaging and storage— Preserve in tight containers.

Labeling— Label it to state, as part of the official title, the average nominal molecular weight of the Polyethylene Glycol. Label it to indicate the name and quantity of any added antioxidant.

Completeness and color of solution— A solution of 5 g of Polyethylene Glycol in 50 mL of water is colorless; it is clear for liquid grades and not more than slightly hazy for solid grades.

Viscosity ⟨ 911 ⟩ — Determine its viscosity, using a capillary viscosimeter giving a flow time of not less than 200 seconds, and a liquid bath maintained at 98.9 ± 0.3° C (210° F). The viscosity is within the limits specified in the accompanying table. For a Polyethylene Glycol not listed in the table, calculate the limits by interpolation.

Nominal Average Molecular Weight	Viscosity Range, Centistokes	Nominal Average Molecular Weight	Viscosity Range, Centistokes
200	3.9 to 4.8	2200	43 to 56
300	5.4 to 6.4	2300	46 to 60
400	6.8 to 8.0	2400	49 to 65
500	8.3 to 9.6	2500	51 to 70
600	9.9 to 11.3	2600	54 to 74
700	11.5 to 13.0	2700	57 to 78
800	12.5 to 14.5	2800	60 to 83
900	15.0 to 17.0	2900	64 to 88
1000	16.0 to 19.0	3000	67 to 93
1100	18.0 to 22.0	3250	73 to 105
1200	20.0 to 24.5	3350	76 to 110
1300	22.0 to 27.5	3500	87 to 123

Nominal Average Molecular Weight	Viscosity Range, Centistokes	Nominal Average Molecular Weight	Viscosity Range, Centistokes
1400	24 to 30	3750	99 to 140
1450	25 to 32	4000	110 to 158
1500	26 to 33	4250	123 to 177
1600	28 to 36	4500	140 to 200
1700	31 to 39	4750	155 to 228
1800	33 to 42	5000	170 to 250
1900	35 to 45	5500	206 to 315
2000	38 to 49	6000	250 to 390
2100	40 to 53	6500	295 to 480
		7000	350 to 590
		7500	405 to 735
		8000	470 to 900

Average molecular weight—

Phthalic anhydride solution— Place 49.0 g of phthalic anhydride into an amber bottle, and dissolve in 300 mL of pyridine from a freshly opened bottle or that has been freshly distilled over phthalic anhydride. Shake vigorously until completely dissolved. Add 7 g of imidazole, swirl carefully to dissolve, and allow to stand for 16 hours before using.

Test preparation for liquid Polyethylene Glycols— Carefully introduce 25.0 mL of the *Phthalic anhydride solution* into a dry, heat-resistant pressure bottle. Add an accurately weighed amount of the specimen, equivalent to its expected average molecular weight divided by 160. Insert the stopper in the bottle, and wrap it securely in a cloth bag.

Test preparation for solid Polyethylene Glycols— Carefully introduce 25.0 mL of *Phthalic anhydride solution* into a dry, heat-resistant pressure bottle. Add an accurately weighed amount of the specimen, equivalent to its expected molecular weight divided by 160; however, because of limited solubility, do not use more than 25 g. Add 25 mL of pyridine, from a freshly opened bottle or that has been freshly distilled over phthalic anhydride, swirl to dissolve, insert the stopper in the bottle, and wrap it securely in a cloth bag.

Procedure— Immerse the bottle in a water bath maintained at a temperature between 96° and 100°, to the same depth as that of the mixture in the bottle. Remove the bottles from the bath after 5 minutes, and, without unwrapping, swirl for 30 seconds to homogenize. Heat in the water bath for 30 minutes (60 minutes for Polyethylene Glycols having molecular weights of 3000 or higher), then remove from the bath, and allow it to cool to room temperature. Uncap the bottle carefully to release any pressure, remove from the bag, add 10 mL of water, and swirl thoroughly. Wait 2 minutes, add 0.5 mL of a solution of phenolphthalein in pyridine (1 in 100), and titrate with 0.5 N sodium hydroxide VS to the first pink color that persists for 15 seconds, recording the volume, in mL, of 0.5 N sodium hydroxide required as *S*. Perform a blank determination on 25.0 mL of *Phthalic anhydride solution* plus any additional pyridine added to the bottle, and record the volume, in mL, of 0.5 N sodium hydroxide required as *B*. Calculate the average molecular weight by the formula:

$$[2000W]/[(B - S)(N)],$$

in which W is the weight, in g, of the Polyethylene Glycol taken for the *Test preparation; (B – S)* is the difference between the volumes of 0.5 N sodium hydroxide consumed by the blank and by the specimen, and N is the normality of the sodium hydroxide solution.

pH ⟨ 791 ⟩ **:** between 4.5 and 7.5, determined potentiometrically, in a solution prepared by dissolving 5.0 g of Polyethylene Glycol in 100 mL of carbon dioxide-free water and adding 0.30 mL of saturated potassium chloride solution.

Residue on ignition ⟨ 281 ⟩ **:** not more than 0.1%, a 25-g specimen and a tared platinum dish being used, and the residue being moistened with 2 mL of sulfuric acid.

Heavy metals ⟨ 231 ⟩ — Mix 4.0 g with 5.0 mL of 0.1 N hydrochloric acid, and dilute with water to 25 mL: the limit is 5 ppm.

Limit of free ethylene oxide and 1,4-dioxane—

Stripped polyethylene glycol 400— Into a 5000-mL 3-neck, round-bottom flask equipped with a stirrer, a gas dispersion tube, and a vacuum outlet, place 3000 g of Polyethylene Glycol 400. At room temperature, evacuate the flask carefully to a pressure of less than 1 mm of mercury, applying the vacuum slowly while observing for excessive foaming due to entrapped gases. After any foaming has subsided and while stirring continuously, sparge with nitrogen, allowing the pressure to rise to 10 mm of mercury. [NOTE—The 10-mm value is a guideline. Deviations from this value only affect the total time required to strip the Polyethylene Glycol 400.] Continue stripping for a minimum of 1 hour. [NOTE—Completeness of the stripping procedure should be verified by making a headspace injection of the stripped polyethylene glycol 400.] Shut off the vacuum pump, and bring the flask pressure back to atmospheric pressure while maintaining nitrogen sparging. Remove the gas dispersion tube with the gas still flowing, and then turn off the gas flow. Transfer the *Stripped polyethylene glycol 400* to a suitable nitrogen-filled container.

Standard preparation— [*Caution—Ethylene oxide and 1,4-dioxane are toxic and flammable. Prepare these solutions in a well-ventilated fume hood.*] Transfer 4.90 g of *Stripped polyethylene glycol 400* to a tared 22-mL pressure headspace vial that can be sealed. Add 48 µL of 1,4-dioxane, equivalent to 50 mg of 1,4-dioxane, from a syringe, seal, and cap the vial. Using the special handling described in the following, complete the preparation. Ethylene oxide is a gas at room temperature. It is usually stored in a lecture-type gas cylinder or small metal pressure bomb. Chill the cylinder in a refrigerator before use. Transfer about 5 mL of the liquid ethylene oxide to a 100-mL beaker chilled in wet ice. Using a gas-tight syringe that has been chilled in a refrigerator, transfer 57 µL of the liquid ethylene oxide, equivalent to 50 mg of ethylene oxide, to the mixture contained in the headspace vial, and mix. With the aid of a syringe, transfer about 2 mL of this solution to a 5-mL beaker. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with *Stripped polyethylene glycol 400* to volume, and mix. Transfer 10 mL of this solution to a 100-mL volumetric flask, dilute with *Stripped polyethylene glycol 400* to volume, and mix to obtain a *Standard preparation* having known concentrations of 10 µg per g for both ethylene oxide and 1,4-dioxane. Transfer 1.0 mL of the *Standard preparation* to a 22-mL pressure headspace vial, seal with a silicone septum with or without a pressure relief star spring and a pressure relief safety aluminum sealing cap, and crimp the cap closed with a cap-sealing tool.

Resolution solution— Transfer 4.90 g of *Stripped polyethylene glycol 400* to a 22-mL pressure headspace vial. Pipet 50 µL of acetaldehyde into the vial. Using the special handling described under *Standard preparation*, transfer about 50.0 µL of liquid ethylene oxide into the vial. Immediately seal the vial, and shake. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with *Stripped polyethylene glycol 400* to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with *Stripped polyethylene glycol 400* to volume, and mix. Transfer 1.0 mL of this *Resolution solution* to a 22-mL pressure headspace vial; and seal, cap, and crimp as directed for the *Standard preparation.*

Test preparation— Transfer 1.0 g of Polyethylene Glycol, to a 22-mL pressure headspace vial; and seal, cap, and crimp as directed for the *Standard preparation.*

Chromatographic system (see Chromatography ⟨ 621 ⟩)— The gas chromatograph is equipped with a balanced pressure automatic headspace sampler and a flame-ionization detector and contains a 0.32-mm × 50-m fused-silica capillary column containing bonded phase G27 in a 5-µm film thickness. The column temperature is programmed from 70° to 250° at 10° per minute, with the injection port at 85° and the detector at 250°. The carrier gas is helium at a flow rate of about 2.9 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for acetaldehyde and 1.0 for ethylene oxide; and the resolution, *R,* between the acetaldehyde peak and the ethylene oxide peak is not less than 1.3.

Procedure— Place the vials containing the *Standard preparation* and the *Test preparation* into the automated sampler, and heat the vials at a temperature of 80° for 30 minutes. Using a 2-mL gas syringe preheated in an oven at 90°, separately inject 1.0 mL of the headspace from each vial into the chromatograph, record the chromatogram, and measure the areas for the major peaks. [NOTE—A headspace apparatus that automatically transfers the measured amount of headspace may be used to perform the injection.] The relative retention times for ethylene oxide and 1,4-dioxane are about 1.0 and 3.4, respectively. The peak areas for ethylene oxide and 1,4-dioxane in the chromatogram of the *Test preparation* are not greater than those of the corresponding peaks in the chromatogram of the *Standard preparation,* corresponding to not more than 10 µg per g of ethylene oxide and not more than 10 µg per g of 1,4-dioxane.

Limit of ethylene glycol and diethylene glycol (for Polyethylene Glycol having a nominal molecular weight less than 450)—

Standard preparation— Prepare an aqueous solution containing 500 µg each of ethylene glycol and of diethylene glycol per mL.

Test preparation— Transfer about 4 g of Polyethylene Glycol, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see Chromatography ⟨ 621 ⟩)— The gas chromatograph is equipped with a flame-ionization detector and a 3-mm × 1.5-m stainless steel column packed with 12% G13 on support S1NS. The carrier gas is nitrogen or another suitable inert gas, flowing at a rate of 50 mL per minute. The column temperature is maintained at about 140°, the injection port temperature is maintained at about 250°, and the flame-ionization detector temperature is maintained at 280°.

Procedure— Inject a volume (about 2.0 µL) of the *Standard preparation* into the chromatograph, and record the chromatogram, adjusting the operational conditions to obtain peaks not less than 10 cm in height. Measure the heights of the first (ethylene glycol) and second (diethylene glycol) peaks, and record the values as P_1 and P_2, respectively. Inject a volume (about 2.0 µL) of the *Test preparation* into the chromatograph, and record the chromatogram under the same conditions as those employed for the *Standard preparation.* Measure the heights of the first (ethylene glycol) and second (diethylene glycol) peaks, and record the values as p_1 and p_2, respectively. Calculate the percentage of ethylene glycol in the portion of Polyethylene Glycol taken by the formula:

$$(C_1\, p_1)/(P_1 W),$$

in which C_1 is the concentration, in µg per mL, of ethylene glycol in the *Standard preparation;* and W is the weight, in mg, of Polyethylene Glycol taken. Calculate the percentage of diethylene glycol in the portion of Polyethylene Glycol taken by the formula:

$$(C_2\, p_2)/(P_2 W),$$

in which C_2 is the concentration, in µg per mL, of diethylene glycol in the *Standard preparation:* not more than 0.25% of the sum of ethylene glycol and diethylene glycol is found.

Limit of ethylene glycol and diethylene glycol (for Polyethylene Glycol having a nominal molecular weight 450 or above but not more than 1000)—

Ceric ammonium nitrate solution— Dissolve 6.25 g of ceric ammonium nitrate in 100 mL of 0.25 N nitric acid. Use within 3 days.

Standard preparation— Transfer 62.5 mg of diethylene glycol to a 25-mL volumetric flask, dissolve in a mixture of equal volumes of freshly distilled acetonitrile and water, dilute with the same mixture to volume, and mix.

Test preparation— Dissolve 50.0 g of Polyethylene Glycol in 75 mL of diphenyl ether, previously warmed, if necessary, just to melt the crystals, in a 250-mL distilling flask. Slowly distill at a pressure of 1 mm to 2 mm of mercury, into a receiver graduated to 100 mL in 1-mL subdivisions, until 25 mL of distillate has been collected. Add 20.0 mL of water to the distillate, shake vigorously, and allow the layers to separate. Cool in an ice bath to solidify the diphenyl ether and facilitate its removal. Filter the separated aqueous layer, wash the diphenyl ether with 5.0 mL of ice-cold water, pass the washings through the filter, and collect the filtrate and washings in a 25-mL volumetric flask. Warm to room temperature, dilute with water to volume, if necessary, and mix. Mix this solution with 25.0 mL of freshly distilled acetonitrile in a glass-stoppered, 125-mL conical flask.

Procedure— Transfer 10.0 mL each of the *Standard preparation* and the *Test preparation* to separate 50-mL flasks, each containing 15.0 mL of *Ceric ammonium nitrate solution,* and mix. Within 2 to 5 minutes, concomitantly determine the absorbances of the solutions in 1-cm cells at the wavelength of maximum absorbance at about 450 nm, with a suitable spectrophotometer, using a blank consisting of a mixture of 15.0 mL of *Ceric ammonium nitrate solution* and 10.0 mL of a mixture of equal volumes of freshly distilled acetonitrile and water: the absorbance of the solution from the *Test preparation* does not exceed that of the solution from the *Standard preparation,* corresponding to not more than 0.25% of combined ethylene glycol and diethylene glycol.

Organic volatile impurities, *Method IV* ⟨ 467 ⟩ **:** meets the requirements for chloroform, methylene chloride, and trichloroethylene.

Residual solvents ⟨ 467 ⟩ **:** meets the requirements.
(Official January 1, 2007)

Auxiliary Information— *Staff Liaison* : Hong Wang, Ph.D. , Senior Scientific Associate
Expert Committee : (EM205) Excipient Monographs 2

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Pharmacopeial Forum : Volume No. 31(3) Page 897
Phone Number : 1-301-816-8351

Citric acid

From Wikipedia, the free encyclopedia

D12

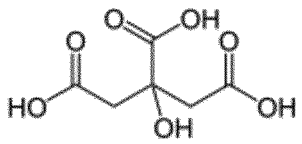
Citric acid is a weak organic tricarboxylic acid having the chemical formula $C_6H_8O_7$. It occurs naturally in citrus fruits. In biochemistry, it is an intermediate in the citric acid cycle, which occurs in the metabolism of all aerobic organisms.

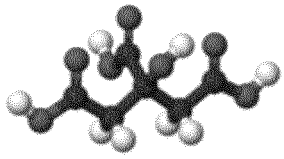
More than a million tons of citric acid are manufactured every year. It is used widely as an acidifier, as a flavoring and chelating agent.[7]

A **citrate** is a derivative of citric acid; that is, the salts, esters, and the polyatomic anion found in solution. An example of the former, a salt is trisodium citrate; an ester is triethyl citrate. When part of a salt, the formula of the citrate ion is written as $C_6H_5O_7^{3-}$ or $C_3H_5O(COO)_3^{3-}$.

Contents

Citric acid

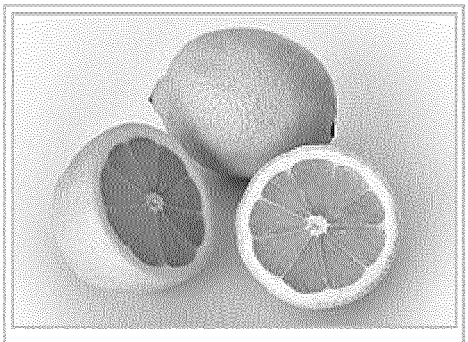




Names	
Preferred IUPAC name 2-Hydroxypropane-1,2,3-tricarboxylic acid	
Other names Citric acid	
Identifiers	
CAS Number	77-92-9 (http://www.commonchemistry.org/ChemicalDetail.aspx?ref=77-92-9) ✓
3D model (JSmol)	Interactive image (http://chemapps.stolaf.edu/jmol/jmol.php?model=OC%28%3DO%29CC%28O%29%28C%28%3DO%29O%29CC%28%3DO%29O)
ChEBI	CHEBI:30769 (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=30769) ✓
ChemSpider	305 (http://www.chemspider.com/Chemical-Structure.305.html) ✓
DrugBank	DB04272 (https://www.drugbank.ca/drugs/DB04272) ✓
ECHA InfoCard	100.000.973 (https://echa.europa.eu/substance-information/-/substanceinfo/100.000.973)
EC Number	201-069-1
E number	E330 (antioxidants, ...)
IUPHAR/BPS	2478 (http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?tab=summary&ligandId=2478)
KEGG	D00037 (http://www.kegg.jp/entry/D00037) ✓
PubChem CID	22230 (monohydrate) 311, 22230 (monohydrate) (https://pubchem.ncbi.nlm.nih.gov/compound/311,)
RTECS number	GE7350000
UNII	XF417D3PSL (https://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=XF417D3PSL) ✓

Natural occurrence and

industrial production



Lemons, oranges, limes, and other citrus fruits possess high concentrations of citric acid

Citric acid exists in greater than trace amounts in a variety of fruits and vegetables, most notably citrus fruits. Lemons and limes have particularly high concentrations of the acid; it can constitute as much as 8% of the dry weight of these fruits (about 47 g/L in the juices[8]).[a] The concentrations of citric acid in citrus fruits range from 0.005 mol/L for oranges and grapefruits to 0.30 mol/L in lemons and limes. Within species, these values vary depending on the cultivar and the circumstances in which the fruit was grown.

Industrial-scale citric acid production first began in 1890 based on the Italian citrus fruit industry, where the juice was treated with hydrated lime (calcium hydroxide) to precipitate calcium citrate, which was isolated and converted back to the acid using diluted sulfuric acid.[9] In 1893, C. Wehmer discovered *Penicillium* mold could produce citric acid from sugar. However, microbial production of citric acid did not become industrially important until World War I disrupted Italian citrus exports.

In 1917, American food chemist James Currie discovered certain strains of the mold *Aspergillus niger* could be efficient citric acid producers, and the pharmaceutical company Pfizer began industrial-level production using this technique two years later, followed by Citrique Belge in 1929. In this production

InChI	
	InChI=1S/C6H8O7/c7-3(8)1-6(13,5(11)12)2-4(9)10/h13H,1-2H2,(H,7,8)(H,9,10)(H,11,12) ✓ Key: KRKNYBCHXYNGOX-UHFFFAOYSA-N ✓
	InChI=1/C6H8O7/c7-3(8)1-6(13,5(11)12)2-4(9)10/h13H,1-2H2,(H,7,8)(H,9,10)(H,11,12) Key: KRKNYBCHXYNGOX-UHFFFAOYAM
SMILES	
	OC(=O)CC(O)(C(=O)O)CC(=O)O
Properties	
Chemical formula	$C_6H_8O_7$
Molar mass	192.12 g·mol^{-1}
Appearance	crystalline white solid
Odor	odorless
Density	1.665 g/cm^3 (anhydrous) 1.542 g/cm^3 (18 °C, monohydrate)
Melting point	156 °C (313 °F; 429 K)
Boiling point	310 °C (590 °F; 583 K) decomposes from 175 °C[1]
Solubility in water	117.43 g/100 mL (10 °C) 147.76 g/100 mL (20 °C) 180.89 g/100 mL (30 °C) 220.19 g/100 mL (40 °C) 382.48 g/100 mL (80 °C) 547.79 g/100 mL (100 °C)[2]
Solubility	soluble in alcohol, ether, ethyl acetate, DMSO insoluble in C_6H_6, $CHCl_3$, CS_2, toluene[1]
Solubility in ethanol	62 g/100 g (25 °C)[1]
Solubility in amyl acetate	4.41 g/100 g (25 °C)[1]
Solubility in diethyl ether	1.05 g/100 g (25 °C)[1]
Solubility in 1,4-Dioxane	35.9 g/100 g (25 °C)[1]
log P	−1.64
Acidity (pK_a)	pKa_1 = 3.13[3] pKa_2 = 4.76[3] pKa_3 = 6.39,[4] 6.40[5]
Refractive index (n_D)	1.493–1.509 (20 °C)[2] 1.46 (150 °C)[1]
Viscosity	6.5 cP (50% aq. sol.)[2]
Structure	
Crystal structure	Monoclinic
Thermochemistry	

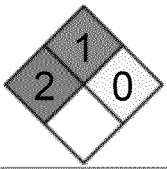
technique, which is still the major industrial route to citric acid used today, cultures of *A. niger* are fed on a sucrose or glucose-containing medium to produce citric acid. The source of sugar is corn steep liquor, molasses, hydrolyzed corn starch or other inexpensive sugary solutions.[10] After the mold is filtered out of the resulting solution, citric acid is isolated by precipitating it with calcium hydroxide to yield calcium citrate salt, from which citric acid is regenerated by treatment with sulfuric acid, as in the direct extraction from citrus fruit juice.

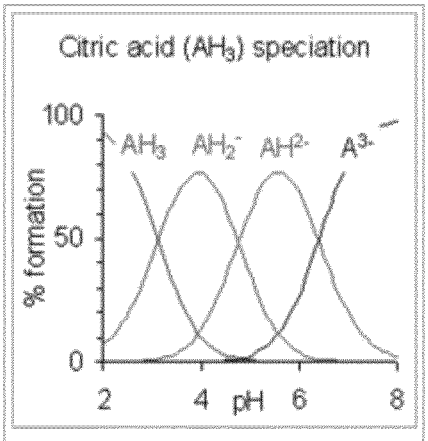
In 1977, a patent was granted to Lever Brothers for the chemical synthesis of citric acid starting either from aconitic or isocitrate/alloisocitrate calcium salts under high pressure conditions. This produced citric acid in near quantitative conversion under what appeared to be a reverse non-enzymatic Krebs cycle reaction.[11]

In 2007, worldwide annual production stood at approximately 1,600,000 tons.[12] More than 50% of this volume was produced in China. More than 50% was used as acidity regulator in beverages, some 20% in other food applications, 20% for detergent applications and 10% for related applications other than food, such as cosmetics, pharmaceutics and in the chemical industry.

Chemical characteristics

Citric acid was first isolated in 1784 by the chemist Carl Wilhelm Scheele, who crystallized it from lemon juice.[9][13] It can exist either in an anhydrous (water-free) form or as a monohydrate. The anhydrous form crystallizes from hot water, while the monohydrate forms when citric acid is crystallized from cold water. The monohydrate can be converted to the anhydrous form at about 78 °C. Citric acid also dissolves in absolute (anhydrous) ethanol (76 parts of citric acid per 100 parts of ethanol) at 15 °C. It decomposes with loss of carbon dioxide above about 175 °C.

Specific heat capacity (*C*)	226.51 J/(mol·K) (26.85 °C)[6]
Std molar entropy (S°_{298})	252.1 J/(mol·K)[6]
Std enthalpy of formation ($\Delta_f H^{\circ}_{298}$)	−1548.8 kJ/mol[2]
Std enthalpy of combustion ($\Delta_c H^{\circ}_{298}$)	−1960.6 kJ/mol[6] −1972.34 kJ/mol (monohydrate)[2]
Pharmacology	
ATC code	A09AB04 (WHO (https://www.whocc.no/atc_ddd_index/?code=A09AB04))
Hazards	
Main hazards	skin and eye irritant
Safety data sheet	HMDB (http://www.hmdb.ca/system/metabolites/msds/000/000/065/original/HMDB00094.pdf?1358893891)
GHS pictograms	 [3]
GHS signal word	Warning
GHS hazard statements	H319[3]
GHS precautionary statements	P305+351+338[3]
NFPA 704	
Flash point	155 °C (311 °F; 428 K)
Autoignition temperature	345 °C (653 °F; 618 K)
Explosive limits	8%[3]
Lethal dose or concentration (*LD*, *LC*):	
LD_{50} (median dose)	3000 mg/kg (rats, oral)
Except where otherwise noted, data are given for materials in their standard state (at 25 °C [77 °F], 100 kPa). ✘ verify (what is ✓✘ ?) Infobox references	



Speciation diagram for a 10-millimolar solution of citric acid

Citric acid is normally considered to be a tribasic acid, with pK_a values, extrapolated to zero ionic strength, of 5.21, 4.28 and 2.92 at 25 °C.[14] The pKa of the hydroxyl group has been found, by means of ^{13}C NMR spectroscopy, to be 14.4.[15] The speciation diagram shows that solutions of citric acid are buffer solutions between about pH 2 and pH 8. In biological systems around pH 7, the two species present are the citrate ion and mono-hydrogen citrate ion. The SSC 20X hybridization buffer (http://openwetware.org/wiki/SSC) is an example in common use.[16] Tables compiled for biochemical studies[17] are available.

On the other hand, the pH of a 1 mM solution of citric acid will be about 3.2. The pH of fruit juices from citrus fruits like oranges and lemons depends on the citric acid concentration, being lower for higher acid concentration and conversely.

Acid salts of citric acid can be prepared by careful adjustment of the pH before crystallizing the compound. See, for example, sodium citrate.

The citrate ion forms complexes with metallic cations. The stability constants for the formation of these complexes are quite large because of the chelate effect. Consequently, it forms complexes even with alkali metal cations. However, when a chelate complex is formed using all three carboxylate groups, the chelate rings have 7 and 8 members, which are generally less stable thermodynamically than smaller chelate rings. In consequence, the hydroxyl group can be deprotonated, forming part of a more stable 5-membered ring, as in ammonium ferric citrate, $(NH_4)_5Fe(C_6H_4O_7)_2 \cdot 2H_2O$.[18]

Esters such as triethyl citrate can be made.

Biochemistry

Citric acid cycle

Citrate is an intermediate in the TCA cycle (*aka* **Tri**C**a**rboxylic **A**cid cycle, Krebs cycle, Szent-Györgyi — Krebs cycle), a central metabolic pathway for animals, plants and bacteria. Citrate synthase catalyzes the condensation of oxaloacetate with acetyl CoA to form citrate. Citrate then acts as the substrate for aconitase and is converted into aconitic acid. The cycle ends with regeneration of oxaloacetate. This series of chemical reactions is the source of two-thirds of the food-derived energy in higher organisms. Hans Adolf Krebs received the 1953 Nobel Prize in Physiology or Medicine for the discovery.

Some bacteria, notably *E. coli*, can produce and consume citrate internally as part of their TCA cycle, but are unable to use it as food because they lack the enzymes required to import it into the cell. After tens of thousand of evolution in a minimal glucose medium that also contains citrate during Richard Lenski's Long-Term Evolution Experiment, a variant *E. coli* evolved with the ability to grow aerobically on citrate. Zachary Blount, a student of Lenski's, and colleagues studied these "Cit^+" *E. coli*[19][20] as a model for how novel traits evolve. They found evidence that in this case the innovation was immediately caused by a rare duplication mutation that was effective in causing the trait due to the accumulation of several prior "potentiating" mutations, the identity and effects of which are still under study. The evolution of the Cit^+ trait has been considered a notable example of the role of historical contingency in evolution.

Other biological roles

Citrate can be transported out of the mitochondria and into the cytoplasm, then broken down into acetyl-CoA for fatty acid synthesis and into oxaloacetate. Citrate is a positive modulator of this conversion,

and allosterically regulates the enzyme acetyl-CoA carboxylase, which is the regulating enzyme in the conversion of acetyl-CoA into malonyl-CoA (the commitment step in fatty acid synthesis). In short, citrate is transported to the cytoplasm, converted to acetyl CoA, which is converted into malonyl CoA by the acetyl CoA carboxylase, which is allosterically modulated by citrate.

High concentrations of cytosolic citrate can inhibit phosphofructokinase, the catalyst of one of the rate-limiting steps of glycolysis. This effect is advantageous: high concentrations of citrate indicate that there is a large supply of biosynthetic precursor molecules, so there is no need for phosphofructokinase to continue to send molecules of its substrate, fructose 6-phosphate, into glycolysis. Citrate acts by augmenting the inhibitory effect of high concentrations of ATP, another sign that there is no need to carry out glycolysis.[21]

Citrate is a vital component of bone, helping to regulate the size of apatite crystals.[22]

Applications

Food and drink

Because it is one of the stronger edible acids, the dominant use of citric acid is used as a flavoring and preservative in food and beverages, especially soft drinks.[9] Within the European Union it is denoted by E number **E330**. Citrate salts of various metals are used to deliver those minerals in a biologically available form in many dietary supplements. The buffering properties of citrates are used to control pH in household cleaners and pharmaceuticals. In the United States the purity requirements for citric acid as a food additive are defined by the Food Chemicals Codex, which is published by the United States Pharmacopoeia (USP).

Powdered citric acid being used to prepare lemon pepper seasoning

Citric acid can be added to ice cream as an emulsifying agent to keep fats from separating, to caramel to prevent sucrose crystallization, or in recipes in place of fresh lemon juice. Citric acid is used with sodium bicarbonate in a wide range of effervescent formulae, both for ingestion (e.g., powders and tablets) and for personal care (*e.g.*, bath salts, bath bombs, and cleaning of grease). Citric acid sold in a dry powdered form is commonly sold in markets and groceries as "sour salt", due to its physical resemblance to table salt. It has use in culinary applications, as an alternative to vinegar or lemon juice, where a pure acid is needed.

Citric acid can be used in food coloring to balance the pH level of a normally basic dye.

Cleaning and chelating agent

Citric acid is an excellent chelating agent, binding metals by making them soluble. It is used to remove and discourage the buildup of limescale from boilers and evaporators.[9] It can be used to treat water, which makes it useful in improving the effectiveness of soaps and laundry detergents. By chelating the metals in hard water, it lets these cleaners produce foam and work better without need for water softening. Citric acid is the active ingredient in some bathroom and kitchen cleaning solutions. A solution with a six percent concentration of citric acid will remove hard water stains from glass without scrubbing. In industry, it is used to dissolve rust from steel. Citric acid can be used in shampoo to wash out wax and coloring from the hair.

Illustrative of its chelating abilities, citric acid was the first successful eluant used for total ion-exchange separation of the lanthanides, during the Manhattan Project in the 1940s. In the 1950s, it was replaced by the far more efficient EDTA.

Cosmetics, pharmaceuticals, dietary supplements, and foods

Citric acid is widely used as an acidulent in creams, gels, and liquids of all kinds. In its use in foods and dietary supplements, it may be classified as a processing aid if the purpose it was added was for a technical or functional effect (e.g. acidulent, chelator, viscosifier, etc...) for a process. If it is still present in insignificant amounts, and the technical or functional effect is no longer present, it may be exempted from labeling <21 CFR §101.100(c)>.

Citric acid is an alpha hydroxy acid and used as an active ingredient in chemical peels.

Citric acid is commonly used as a buffer to increase the solubility of brown heroin. Single-use citric acid sachets have been used as an inducement to get heroin users to exchange their dirty needles for clean needles in an attempt to decrease the spread of HIV and hepatitis.[23] Other acidifiers used for brown heroin are ascorbic acid, acetic acid, and lactic acid; in their absence, a drug user will often substitute lemon juice or vinegar.

Citric acid is used as one of the active ingredients in the production of antiviral tissues.[24]

Other uses

Citric acid is used as an odorless alternative to white vinegar for home dyeing with acid dyes.

Sodium citrate is a component of Benedict's reagent, used for identification both qualitatively and quantitatively, of reducing sugars.

Citric acid can be used as an alternative to nitric acid in passivation of stainless steel.[25]

Citric acid can be used as a lower-odor stop bath as part of the process for developing photographic film. Photographic developers are alkaline, so a mild acid is used to neutralize and stop their action quickly, but commonly used acetic acid leaves a strong vinegar odor in the darkroom.[26]

Citric acid/potassium-sodium citrate can be used as a blood acid regulator.

Synthesize solid materials from small molecules

In materials science, the Citrate-gel method is a process similar to the sol-gel method, which is a method for producing solid materials from small molecules. During the synthetic process, metal salts or alkoxides are introduced into a citric acid solution. The formation of citric complexes is believed to balance the difference in individual behaviour of ions in solution, which results in a better distribution of ions and prevents the separation of components at later process stages. The polycondensation of ethylene glycol and citric acid starts above 100°C, resulting in polymer citrate gel formation.

Safety

Although a weak acid, exposure to pure citric acid can cause adverse effects. Inhalation may cause cough, shortness of breath, or sore throat. Over-ingestion may cause abdominal pain and sore throat. Exposure of concentrated solutions to skin and eyes can cause redness and pain.[27] Long-term or repeated consumption may cause erosion of tooth enamel.[27][28][29]

Compendial status

- British Pharmacopoeia[30]
- Japanese Pharmacopoeia[31]

See also

- The closely related acids isocitric acid, aconitic acid, and propane-1,2,3-tricarboxylic acid (tricarballylic acid, carballylic acid)
- Acids in wine

Wikimedia Commons has media related to ***Citric acid***.

Wikisource has the text of the 1911 *Encyclopædia Britannica* article ***Citric Acid***.

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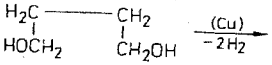
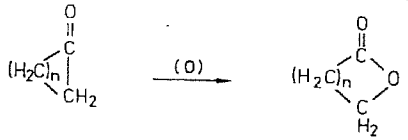
a. This still does not make the lemon particularly strongly acidic. This is because, as a weak acid, most of the acid molecules are not dissociated so not contributing to acidity inside the lemon or its juice.

γ-*Butyrolacton* entsteht durch Dehydrierung von 1,4-Butandiol am Kupfer- t bei 200. °C (475 K) (*Reppe*):

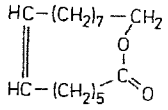


1,4-Butandiol

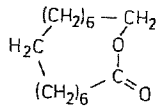
Höhergliedrige Lactone sind durch Oxid Per- vefelsäure (*Caro*sche Säure), H_2SO_5, zugänglich (*Ruzicka*):



haften. Die Lactone sieden niedriger als die zugehörigen Hydroxysäuren. Sie einen starken, meist angenehmen Geruch auf, vor allem die höhergliedrigen 17 Ringgliedern, zu denen z. B. *Ambrettolid*, der Duftstoff z. B. des Moschus- s, sowie das Lacton des Angelicawurzelöls, das unter dem Namen *Exaltolid* ch hergestellt wird, zählen:



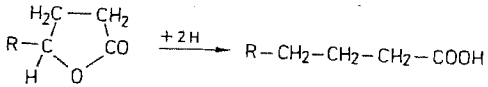
Ambrettolid



Exaltolid

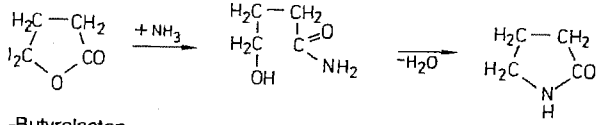
, die bis zu 7 Glieder haben, liegt die Lactongruppe in der (*E*)-Konfiguration vor; bei 0 Ringgliedern bevorzugt sie die (*Z*)-Konfiguration (vgl. S. 69).

ctivität der Lactone ist vornehmlich auf die *Lactongruppierung* beschränkt. Bei duktion mit Natriumamalgam in saurem Medium entstehen die betreffenden- iuren:



ührt die gleiche Reaktion bei Polyhydroxylactonen in schwach saurer Lösung zu den

spaltung der Lactonbindung unter Bildung der entsprechend substituierten uren tritt mit konzentrierten Halogenwasserstoffsäuren, Alkalicyanid oder ydrogensulfit ein; mit Ammoniak entstehen Hydroxycarbonsäureamide, die sserabspaltung leicht in *Lactame* übergehen, z. B.

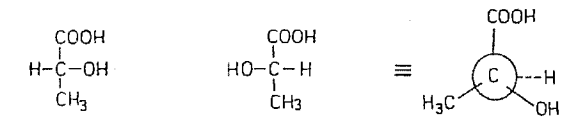


-Butyrolacton

2-Pyrrolidon, 4-Butanlactam

2.29.6.1 Glykolsäure (Hydroxy-essigsäure), $HOCH_2-COOH$, Schmp. 79 °C (352 K), kommt im Pflanzenreich vor, z. B. in unreifen Weintrauben und im Zuckerrohr.

2.29.6.2 DL-Milchsäure (α-Hydroxypropionsäure, engl. Lactic acid: Lac), $H_3C-CH(OH)-COOH$, wurde von *Scheele* (1780) in der sauren Milch entdeckt, und zwar entsteht sie durch Vergärung der Lactose (Milchzucker) mittels *Streptococcus lactis* bzw. *Lactobacillus lactis*. Außerdem tritt sie im Magensaft und in sauren Gurken auf.
Die *optisch aktiven* Milchsäuren besitzen folgende Konfigurationen:



D(−)-Milchsäure L(+)-Milchsäure (*S*)-Form

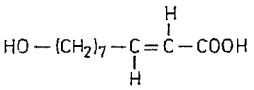
L(+)-Milchsäure findet sich in verschiedenen tierischen Organen sowie im Muskelsaft und wird daher auch *Fleischmilchsäure* (*Berzelius*, 1808) genannt. Sie weist die gleiche sterische Anordnung wie die α-Aminosäuren im Eiweiß auf. Diese ist im *CIP*-System die (*S*)-Form.
Reine DL-Milchsäure ist eine sirupöse Flüssigkeit, die bei 18 °C (291 K) erstarrt; die D- und L-Milchsäure schmelzen bei 25 °C (298 K) ($pK_a = 3{,}86$). Ihre Salze heißen *Lactate*.

2.29.6.3 Milchsäuregärung. Technisch gewinnt man Milchsäure *durch enzymatische Verzuckerung von Kohlenhydraten* (meist Kartoffel- oder Getreidestärke) mittels *Diastase* zu Maltose, die bei 35 bis 45 °C (310 − 320 K) in Gegenwart von *Lactobacillus delbrueckii* über Glucose zu Milchsäure vergoren wird:

$$C_6H_{12}O_6 \rightarrow 2\,H_3C-CH(OH)-COOH$$

Da die Vergärung der Zucker an einen bestimmten pH-Bereich gebunden ist, fängt man die entstehende Milchsäure durch Zugabe von Calciumcarbonat als *Calciumlactat* ab. Aus diesem läßt sie sich mit Schwefelsäure in Freiheit setzen. Zum *Mechanismus* der Milchsäuregärung s. S. 901.
Meist erhält man die DL-Milchsäure (Gärungsmilchsäure), jedoch mit spezifisch wirkenden Bakterien auch überwiegend D(−)- bzw. L(+)-Milchsäure. Wirtschaftliche Bedeutung kommt diesem Gärprozeß bei der *Futtersilierung* (Rübenblätter, Grünfutter) zu.

Verwendung. Die Milchsäure wird zum Entkalken von Fellen in der Gerberei, als Reduktionsmittel in der Chrombeizenfärberei und wegen ihrer leichten Verdaulichkeit als Zusatz für alkoholfreie Getränke verwendet.
Zur Aufzucht einer Bienenkönigin dient ein als Gelée royale (Weiselfuttersaft) bezeichnetes Substanzgemisch aus Proteinen, Kohlenhydraten und Lipiden, das eine Anzahl von C_{10} Carbonsäuren enthält, hauptsächlich (*E*)-10-Hydroxy-2-decensäure:



D1

US005360615A

United States Patent [19]

Yu et al.

[11] Patent Number: 5,360,615

[45] Date of Patent: * Nov. 1, 1994

[54] **SOLVENT SYSTEM ENHANCING THE SOLUBILITY OF PHARMACEUTICALS FOR ENCAPSULATION**

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[*] Notice: The portion of the term of this patent subsequent to Dec. 10, 2008 has been disclaimed.

[21] Appl. No.: **890,285**

[22] Filed: **May 26, 1992**

Related U.S. Application Data

[63] Continuation of Ser. No. 642,187, Jan. 16, 1991, abandoned, which is a continuation of Ser. No. 104,911, Oct. 9, 1987, Pat. No. 5,071,643, which is a continuation-in-part of Ser. No. 920,577, Oct. 17, 1986, abandoned.

[51] **Int. Cl.**[5] **A61K 9/08**; A61K 9/48; A61K 9/20; A61K 47/34

[52] **U.S. Cl.** **424/455**; 424/456; 424/465; 514/772.7

[58] **Field of Search** 424/80, 78, 455, 456; 514/772.7

[56] **References Cited**

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Primary Examiner—Edward J. Webman
Attorney, Agent, or Firm—Allegretti & Witcoff, Ltd.

[57] **ABSTRACT**

This invention relates to a solvent system for enhancing the solubility of an acidic, basic, or amphoteric pharmaceutical agent to produce a highly concentrated solution suitable for softgel filling or two piece encapsulation. The solvent system comprises polyethylene glycol containing 0.2–1.0 mole equivalents of an ionizing agent per mole equivalent pharmaceutical agent and 1–20% water. Glycerin or polyvinylpyrrolidone may be added to further enhance the solubility of certain drugs. The disclosed solvent system is capable of enhancing solubilities of pharmaceutical agents 40–400%.

The ionizing agent functions by causing partial ionization (neutralization) of the free pharmaceutical agent. When the pharmaceutical agent is acidic, the ionizing agent is preferably a hydroxide ion species, whereas when the pharmaceutical agent is basic, the ionizing agent is preferably a hydrogen ion species. For amphoteric pharmaceutical agents, either hydroxide ion or hydrogen ion sources may be utilized to effect partial ionization.

The disclosed solvent system is useful because it not only provides for the enhancement or improvement of bioavailability of acidic, basic and amphoteric pharmaceutical agents by delivering them already in solution, but it also provides for a highly concentrated solution capable of encapsulation in a small enough vessel to permit easy swallowing.

The highly concentrated solid solutions of the present invention are also useful for conversion into tablets and as veterinary spot and pour on preparations.

19 Claims, No Drawings

SOLVENT SYSTEM ENHANCING THE SOLUBILITY OF PHARMACEUTICALS FOR ENCAPSULATION

This application is a continuation of application Ser. No. 07/642,187, filed Jan. 16, 1991, abandoned, which is a continuation of application Ser. No. 07/104,911, filed Oct. 9, 1987, now U.S. Pat. No. 5,071,643, which is a continuation-in-part of application Ser. No. 06/920,577, filed Oct. 17, 1986, abandoned.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to a novel solvent system for enhancing the solubility of pharmaceutical agents by partial ionization to produce highly concentrated primarily non-aqueous water miscible solutions of those agents; which as liquids are suitable for encapsulation in both softgels (previously known as soft elastic gelatin capsules) and in two piece hard gelatin shells, which can be sealed to retain liquid; which as semi-solids are suitable for encapsulation in two-piece hardshell capsules; and which as solid solutions are suitable for conversion into tablets. The solvent system of the present invention is useful in that it provides for the encapsulation of a pharmaceutical agent in a volume of solution that is small enough to permit easy swallowing. It further provides for the preparation of highly concentrated solutions of a pharmaceutical agent having utility for pour on and spot on preparations in veterinary medicine.

Filled one-piece softgels have been widely known and used for many years and for a variety of purposes. Because softgels have properties which are quite different from telescoping two-piece hardshell capsules, the softgels are capable of retaining a liquid fill material. The fill material may vary from industrial adhesives to bath oils. More commonly, the softgels are used to enclose or contain consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier.

Generally, not all liquids are suitable as vehicles or carriers for enclosing softgels. For example, water, propylene glycol, glycerin and low molecular alcohols, ketones, acids, amines and esters cannot be filled in softgels by themselves and can only be present in small amounts. In particular, concentrations of water greater than 20% will dissolve the gelatin shell. Liquids that are suitable for filling softgels vary from water immiscible liquids such as vegetable oils, aromatic oils, aromatic and aliphatic hydrocarbons, chlorinated hydrocarbons, ethers and esters, to water miscible nonvolatile liquids, such as polyethylene glycols and nonionic surfactants.

There are specified limitations to the use of certain liquids as fill vehicles for softgels. For example, the pH of the fill liquid should not be below 2.5 or above 7.5. At pH's below 2.5, the gelatin is hydrolyzed causing leaking, whereas at pH's greater than 7.5, the gelatin is tanned resulting in decreased solubility of the gelatin shell. Moreover, emulsions of oil/water or water/oil are not suitable for softgel encapsulation because they eventually break up releasing water which dissolves the gelatin shell.

Vitamins and pharmaceuticals that naturally occur as liquids are ideally suited for softgels. These naturally occurring liquids are simply mixed with a miscible liquid carrier which is also suited as a softgel fill.

Vitamins and pharmaceuticals that naturally occur as solids may be filled into softgels in liquid form under primarily one of two approaches—either as a suspension of the solid in a liquid carrier or as a solution of the pharmaceutical agent in the appropriate solvent. Each approach has its attendant problems. For example, in the suspension, the solids must have a particle size no greater than 80 mesh. Coarser materials prevent the softgel filling equipment from functioning properly. They also prevent the achievement of a good "content uniformity" throughout the batch.

By contrast, a solution provides the best liquid form to obtain optimal "content uniformity" in a batch. In addition, a solution provides a faster and more uniform absorption of a pharmaceutical agent than does a suspension. Because of these distinct technical advantages, the solution is preferred over the suspension.

However, a problem in the art is that an appropriate solution of the pharmaceutical agent cannot always be achieved. One constraint is size. Often, it is not possible to dissolve the pharmaceutical agent in a volume of solvent small enough to produce a softgel that is appropriate from the standpoint of economics and patient acceptance. Another constraint, is the solvent itself. The solvent must have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a highly concentrated solution, and yet not hydrolyze, dissolve, or tan the softgel.

It is a primary object of the present invention to provide a solvent system which is capable of producing highly concentrated solutions of pharmaceutical agents and that these highly concentrated solutions be suitable for filling into softgels.

Like the one-piece softgels, the two-piece telescoping hardshell capsules have also been used for many years and for a variety of purposes. Unlike the one-piece softgels, the two piece capsules are not a sealed system and hence are generally not suited for handling liquids. However, a two-piece capsule can handle a liquid without leaking provided that it is properly sealed or that the liquid is converted into a solution which is either solid or semi-solid at room temperature. If the solid or semi-solid solution contained within the two-piece capsule is a highly concentrated solution of a pharmaceutical agent, then the advantages possessed by a solution over a suspension are made available to both the user and the manufacturer. Specifically, the advantage of a faster and more uniform absorption of the pharmaceutical agent is available to the user of the two-piece capsule, while the advantage of uniformity of the batch is available to the capsule manufacturer.

It is a further object of the present invention to provide a solvent system that is capable of producing highly concentrated solutions of pharmaceutical agents that are solid or semi-solid solutions at room temperature and that these solutions also be suitable for two-piece hardshell encapsulation. The highly concentrated solutions that are solid at room temperature have the additional utility of being suitable for conversion into tablets.

Because most pharmaceutical agents are acidic, basic, or amphoteric in nature, it is a further object of this invention to provide a solvent system (pharmaceutical carrier system) which with minor modification could be equally useful for a pharmaceutical agent regardless of its basic, acidic, or amphoteric nature.

Producing a highly concentrated solution of any acidic amphoteric or basic pharmaceutical agent is use-

ful because it permits the encapsulation of a unit dose of the pharmaceutical agent in a softgel or two-piece capsule that is small enough to permit easy swallowing. Filling of a unit dose in a small softgel or 2-piece capsule to permit easy swallowing is useful because it increases patient acceptance of the medication. Patient acceptance is especially important in the case of prescription medications, because patient acceptance of the medication is a substantial step towards solving one of the major problems of prescription drug therapy—patient noncompliance with the prescribed regimen. A further utility of the disclosed solvent system is enhancement of bioavailability of the dissolved pharmaceutical agent. Enhanced bioavailability occurs as a result of delivering the pharmaceutical agent already in solution at the site of absorption, permitting a faster and more uniform absorption to occur.

2. Description of Related Art

Weber and Molenaar U.S. Pat. No. 3,557,280, teaches the preparation of aqueous solutions of oxytetracycline suitable for intramuscular and intravenous injection or for administration as a syrup in pediatric cases. The Weber and Molenaar (Weber) invention consists of dissolving oxytetracycline in water, in which a given quantity of polyvinylpyrrolidone has been dissolved, to which has been added a suitable quantity of magnesium salt, the pH of which has been adjusted to between 8.0–9.5 using a base such as sodium hydroxide, ammonia, etc.

Although Weber uses polyvinylpyrrolidone to enhance the solubility of oxytetracycline in an aqueous system, Weber neither teaches nor suggests that polyvinylpyrrolidone would also be useful for enhancing solubility of other pharmaceutical agents in non-aqueous systems. Moreover, the aqueous solutions taught by Weber are totally unsuited for either softgel or two-piece encapsulation, since such aqueous solutions would dissolve the gelatin shells.

The present invention differs from Weber in a number of other respects as well. Whereas Weber teaches the formation of relatively dilute solutions (1–20%), the present invention teaches the preparation of more highly concentrated solutions (30–80%) requiring more skill than that disclosed in Weber.

Whereas Weber teaches at column 3, line 25 that a salt suitable for chelating, such as magnesium, is "essential" to enhance the solubility of oxytetracycline, the present invention teaches the preparation of highly concentrated non-aqueous solutions of pharmaceutical agents without resorting to chelate formation to enhance solubility.

Although both Weber and the present invention use the base, sodium hydroxide, in the preparation of their pharmaceutical formulations, the role played by the sodium hydroxide in each invention differs. Whereas Weber uses the sodium hydroxide to adjust the pH to between 8.0–9.5 as to increase the shelf life of the oxytetracycline solution (see Merck Index, 9th edition at p. 904), the present invention uses the sodium hydroxide to enhance the solubility of an acidic pharmaceutical agent by forming as much of the ionized form of the acidic agent as is capable of being solvated by the system.

Gardella et al, U.S. Pat. No. 4,002,718, teaches at column 3, line 47, the use of small amounts of polyvinylpyrrolidone or glycerin to hasten dissolution of micronized digoxin in a liquid vehicle, polyethylene glycol, to form a solution suitable for softgels. Unlike Gardella, which only teaches the use of polyvinylpyrrolidone or glycerin as a formulatory agent to hasten or speed up dissolution, the present invention teaches the use of glycerin or polyvinylpyrrolidone to enhance or increase the amount of the pharmaceutical agent that is soluble in a given volume of liquid.

In further contrast, Gardella only teaches the production of very dilute solutions (0.1%) for encapsulation, whereas the present invention teaches the production of highly concentrated solutions (30–80%). Because the solutions of the present invention are 300–800 times more concentrated than that taught by Gardella, the teachings of Gardella are not applicable to the present invention. Moreover, Gardella does not even suggest that glycerin, propylene glycol, or polyvinylpyrrolidone would be useful for enhancing solubilities of pharmaceutical agents as to produce 30–80% solutions of those agents.

Wagner, U.S. Pat. No. 4,562,192, suggests the use of polyvinylpyrrolidone as a formulatory agent (adjuvant) for pharmaceutical preparations. However, Wagner neither teaches nor suggests that polyvinylpyrrolidone is useful for enhancing the solubility of a pharmaceutical agent in a given volume of liquid.

SUMMARY OF THE INVENTION

The present invention generally relates to a pharmaceutical carrier system ("solvent system") for enhancing the solubility of any acidic, basic, or amphoteric pharmaceutical agent by partial ionization to produce a highly concentrated primarily non-aqueous solution suitable for filling softgels or for two piece encapsulation or for tablet formation, the solvent system comprising in its simplest form 10–80% by weight polyethylene glycol, a solubility enhancing amount of either hydroxide or hydrogen ion and 1–20% by weight of water.

In particular, the present invention relates to a solvent system for enhancing the solubility of an acidic pharmaceutical agent to produce a highly concentrated solution suitable for softgel filling comprising 10–80% polyethylene glycol, a solubility enhancing amount of hydroxide ion, preferably 0.2–1.0 mole equivalents of hydroxide ion per mole equivalent of acid in an acidic pharmaceutical agent, and 1–20% by weight of water.

In addition, the present invention also relates to a simple modification of the disclosed solvent system wherein hydrogen ion is substituted for hydroxide ion, thereby enhancing the solubility of any basic pharmaceutical agent in polyethylene glycol so as to produce a highly concentrated solution of the basic pharmaceutical agent which is also suited for softgel filling, encapsulation or tablet formation.

The polyethylene glycol used herein has an average molecular weight of between about 200–100,000 daltons (hereinafter, all molecular weights are expressed in daltons). Moreover, the weight of polyethylene glycol selected affects the type of solution produced. Polyethylene glycol having an average molecular weight from about 200–800, preferably from about 400–700, and most preferably about 600, produces a softgel fill solution that is a liquid. Polyethylene glycol having an average molecular weight from about 800–10,000, preferably from about 2,000–8,000, produces a softgel fill solution that is semi-solid, and polyethylene glycol having an average molecular weight between about 10,000–100,000, preferably about 15,000–60,000, produces a softgel fill solution that is solid.

Contemplated equivalents of polyethylene glycol include analogs, such as the polyethylene glycol ethers

of various alcohols including but not limited to tetraglycol—the polyethylene glycol ether of tetrahydrofurfuryl alcohol, and copolymers of polyethylene glycol.

Further enhancement of the solubility of the pharmaceutical agent in polyethylene glycol is accomplished by the addition of 4–12% by weight of glycerin or propylene glycol and/or by the further addition of 1–20% by weight of polyvinylpyrrolidone, said polyvinylpyrrolidone preferably having an average molecular weight between about 10,000–100,000.

For the acidic pharmaceutical agents, it is preferred that the concentration of liquids with hydroxyl ions, such as glycerin, ethanol, propylene glycol be kept as low as possible. In contrast, the concentration of water in the solvent system should be as high as possible.

The present invention further relates to highly concentrated solutions of the acidic pharmaceutical agents ibuprofen, naproxen, indomethacin, and acetaminophen suitable for filling softgels or two piece capsules, or for tablet formation;

said solution of ibuprofen comprising 40–80% by weight ibuprofen, 0.1–1.5 moles of hydroxide ion per mole of ibuprofen, 1–20% by weight water, and 4–12% by weight glycerin or propylene glycol in polyethylene glycol, wherein said hydroxide ion is more preferredly in the range of 0.2–0.5 moles of hydroxide ion per mole of ibuprofen;

said solution of naproxen comprising 20–50% by weight naproxen, 0.2–0.9 moles of hydroxide ion per mole of naproxen and 1–20% by weight water in polyethylene glycol, wherein said hydroxide ion is more preferredly in the range of 0.4–0.6 moles of hydroxide ion per mole of naproxen;

said solution of indomethacin comprising 30–60% by weight indomethacin, 0.5–1.0 moles of hydroxide ion per mole of indomethacin, and 1–20% by weight water in polyethylene glycol; and

said solution of acetaminophen comprising 25–40% by weight acetaminophen, 0.4–1.0 moles of hydroxide ion per mole of acetaminophen, and 1–20% by weight water in polyethylene glycol.

The solubility of the above mentioned acidic pharmaceutical agents in said solutions is further enhanced 2–10% by the further addition of 3–10% by weight of glycerin, or propylene glycol or 1–20% by weight of polyvinylpyrrolidone; the higher percentages (>5%) of polyvinylpyrrolidone being more suited for use in suppositories, two piece capsules, and tablet formation.

The present invention also relates to unit dose forms of ibuprofen, naproxen, indomethacin, and acetaminophen comprising either a softgel or two piece capsule or a tablet containing within a therapeutically effective amount of the appropriate highly concentrated solution of said pharmaceutical agent as disclosed above.

Exactly as was disclosed for the acidic pharmaceutical agents, selection of the polyethylene glycol solvent in the disclosed molecular weight ranges enables the production of liquid semi-solid and solid solutions of the basic pharmaceutical agents.

By way of example, said basic pharmaceutical agents include but are not limited to cimetidine, ranitidine, and nifedipine.

Finally, the present invention relates to a solvent system for enhancing the solubility of amphoteric pharmaceutical agents wherein either hydrogen or hydroxide ions can be used to enhance the solubility of the amphoteric agent by partially ionizing it in the polyethylene glycol systems just described.

This invention further relates to a modification of the disclosed system wherein the ionizable species of the pharmaceutical agent of interest is added directly to polyethylene glycol systems in the form of its pharmaceutically acceptable salt. By selecting the proper ratio of the free pharmaceutical agent and its salt, the solubility of that agent can be maximized.

DETAILED DESCRIPTION

The invention encompasses a solvent system for preparing highly concentrated solutions of pharmaceutical agents wherein the prepared solutions are particularly suitable for softgel filling. The pharmaceutical agents suitable for use with the solvent system of this invention are either acidic, basic or amphoteric compounds, i.e., compounds that are readily ionizable.

Specific examples employing the disclosed solvent system are given for four acidic pharmaceutical agents, indomethacin, ibuprofen, naproxen and acetaminophen. By varying the acidic pharmaceutical agent and by employing the solvent system taught in this invention, one of ordinary skill in the art could produce a highly concentrated solution of any acidic pharmaceutical agent and said concentrated solution would be suitable for filling into softgels.

The present solvent system uses polyethylene glycol (PEG) as its base, preferably having an average molecular weight between about 200–100,000, and most preferably having an average molecular weight between about 400–600 for liquid fills, between about 800–10,000 for semi-solid fills, and between 10,000–100,000 for solid fills. Non-ionized acidic pharmaceutical agents have some solubility in polyethylene glycol, utilizing the solvents hydrophobic binding sites. However, this solubility alone is insufficient to produce a highly concentrated solution which would permit encapsulation of a unit dose in a softgel that would be small enough to permit easy swallowing. For example, Table 1 lists solubilities of the acidic pharmaceutical agents, ibuprofen, naproxen, indomethacin and acetaminophen in polyethylene glycol and the corresponding minimum softgel capsule size required to encapsulate a unit dose as a clear solution. Table 1 further lists the enhanced solubilites of the same pharmaceutical agents in the disclosed solvent system and the corresponding reduced softgel size. In the disclosed solvent system, the enhancement in solubility is presumably due in part to the further ability of the solvent, polyethylene glycol, to utilize separate hydrophilic binding sites to solvate the ionized (hydrophilic) species of the pharmaceutical agent.

TABLE 1

SOLUBILITIES AND CAPSULE SIZE FOR UNIT DOSES OF SOME ACIDIC PHARMACEUTICAL AGENTS IN POLYETHYLENE GLYCOL AND IN THE DISCLOSED SOLVENT SYSTEM

		Using Polyethylene Glycol 600		Using the Disclosed Solvent System	
Agent	Unit Dosage (mg)	Solubility (%)	Minimum Capsule Size*	Solubility (%)	Minimum Capsule Size
Ibuprofen	200	23	14 oblong	67	5 oblong
Naproxen	250	15	20 oblong	40	7 oblong
Indomethacin	25	25	1 round	35	1 round
Acetaminophen	500	25	30 oval	35	20 oval

*minimum capsule size for a clear fill as a solution and not as a suspension.

Thus, the present solvent system enhances the solubility of acidic pharmaceutical agents in polyethylene glycol by increasing the number of species of the acidic agent (ionized and unionized) that are available to go into solution and by providing adequate solvation for each species. The present solvent system accomplishes this increase in solubility by utilizing both the hydrophobic and hydrophilic binding sites in polyethylene glycol; and by further employing a combination of adjunctive devices which act complementary to one another producing an overall solubility that is greater than could be produced by the addition of any one alone. The adjunctive devices employed in the present invention include hydroxide ion, water, glycerin, and/or polyvinylpyrrolidone.

In the present solvent system in its simplest form comprising polyethylene glycol, sodium hydroxide, and water, the polyethylene glycol acts to dissolve the free form of the acidic agent in monomer, dimer, trimer, etc. form; the sodium hydroxide is present in sufficient quantity to only partially form the sodium salt of the acidic pharmaceutical agent; and the small amount of water present acts to form a solvation sphere around the acid salt permitting it to go into solution in the polyethylene glycol.

Table 2 shows the cumulative effect of the addition of several of the adjunctive devices on the solubility of ibuprofen in PEG 600—polyethylene glycol having an average molecular weight of 600. As Table 2 suggests, the combination of hydroxide ion and water in PEG 600 produces a 67% solution of ibuprofen versus a 23% solution for PEG 600 without adjuncts. This is a 44% overall enhancement in solubility produced by the present solvent system.

A similar result is found for the other three acidic pharmaceutical agents tested in this experiment and there is no reason to believe that the combination of hydroxide ion and water would not produce an analogous enhancement of solubility in PEG for other acidic pharmaceutical agents not tested in this invention.

TABLE 2

EFFECT OF ADJUNCTIVE DEVICES ON THE SOLUBILITY OF IBUPROFEN IN PEG 600

Ibuprofen (mg)	PEG 600 (mg)	Glycerin (wt %)	Water (wt %)	M/E OH*	Ibuprofen Solubility
200	870	0	0	0	23%
200	100	0	4.5	0.3	61%
402	100	3.3	6.4	0.3	67%

*M/E = moles of hydroxide ion for each mole of acidic drug.

The addition of sodium hydroxide and water to ibuprofen (Table 3), or to naproxen, indomethacin, or acetaminophen in polyethylene glycol (PEG) increases the solubility of that pharmaceutical agent up to a certain point. The further addition of sodium hydroxide beyond this point has the reverse effect and causes the pharmaceutical agent to precipitate out of solution as the sodium salt. The optimal amount of sodium hydroxide—the amount of sodium hydroxide producing maximum solubility of the acidic pharmaceutical agent in polyethylene glycol—was in all cases tested less than 1 mole of sodium hydroxide for each mole of acid in the acidic drug, i.e., the NaOH concentration was always less than 1 mole equivalent. In the specific case of ibuprofen in PEG 400 (Table 3), the solubility was maximal (47%) when the sodium hydroxide was present at a mole equivalent of about 0.3 (0.3 moles of sodium hydroxide/mole of the monoacid compound ibuprofen).

TABLE 3

EFFECT OF SODIUM HYDROXIDE ON THE SOLUBILITY OF IBUPROFEN IN PEG 400

Ibuprofen (mg)	Polyethylene Glycol 400 (mg)	Sodium Hydroxide (M/E)	Water (wt %)	Appearance (Room temp)
200	200	0.1	1.5	Insoluble (slight ppt)
200	200	0.2	2.8	Soluble
200	200	0.3	4.1	Soluble
200	200	0.4	5.2	Soluble
200	200	0.5	6.6	Insoluble (solid admixture)

An unexpected result was obtained when potassium hydroxide was substituted for sodium hydroxide in the preceding discussion. At equimolar concentrations of hydroxide ion, the solubility of ibuprofen, naproxen, indomethacin and acetaminophen was greater in the presence of potassium hydroxide than in the presence of sodium hydroxide. Moreover, much greater concentrations of potassium hydroxide than sodium hydroxide could be utilized to prepare the highly concentrated solutions of the acidic pharmaceutical agents in polyethylene glycol without precipitation occurring. For example, in the case of ibuprofen in PEG 400, precipitation occurs in the presence of 0.5 or more mole equivalents of sodium hydroxide, whereas no precipitation occurs in the presence of 1.0 mole equivalents of potassium hydroxide even at 4° C. (Table 4). Accordingly, potassium hydroxide is the preferred form of hydroxide ion not only because it enhances the solubility of an acidic pharmaceutical agent to a greater extent than sodium hydroxide but also because it is less likely to result in precipitation over a wide variety of concentration ranges even at low temperatures (4° C.) as may occur during shipping.

The above result is very likely explainable based upon the relative sizes of the sodium and potassium ions. The potassium ion is larger than the sodium ion. Hence, the charge on the potassium ion is dispensed over a larger area causing it to require less solvation thereby permitting more solvation for other species. Accordingly, any hydroxide species, with a pharmaceutically acceptable cation as large or larger than potassium, such as ammonium and the like, should be equally or more suited to producing a highly concentrated solution of an acidic pharmaceutical agent.

If one wishes to further enhance solubility an additional 2–10% beyond that produced by the polyethylene glycol, hydroxide ion, and water system, it is necessary to either add glycerin and propylene glycol or polyvinylpyrrolidone or both to the disclosed system. Glycerin is especially effective in enhancing the solubility of ibuprofen when present in a preferred concentration range of 3–12% by weight. The concentration range most preferred being 4–8% by weight.

Polyvinylpyrrolidone enhances the solubility of acidic pharmaceutical agents when present in the disclosed system in a concentration range of 1–20%. The preferred average molecular weight for the polyvinylpyrrolidone is 10,000–100,000. The addition of polyvinylpyrrolidone to the present system can serve a dual function. Not only does the polyvinylpyrrolidone enhance solubility as to enable production of a highly concentrated solution suitable for filling softgels, but it

is also useful for enabling production of a highly viscous as well as a highly concentrated solution suitable for filling a softgel where use is intended as a vaginal or rectal suppository. Although solubility is enhanced by polyvinylpyrrolidone over the entire molecular weight range as disclosed, the polyvinylpyrrolidones at the high molecular weight end of the range are preferred for use in the preparation of suppositories.

The use of either the higher molecular weight polyvinylpyrrolidones or the higher molecular weight polyethylene glycols at a concentration of 5–10% by weight permits the production of a highly concentrated solution of an acidic pharmaceutical agent that is a semisolid or solid solution at room temperature and thereby is suitable for two-piece encapsulation without leaking. The solid solutions have an additional utility in that they can even be converted into tablets by processes known to those skilled in the art.

Using the disclosed solvent system, it is possible to prepare a unit dose of any acidic pharmaceutical agent by enclosing a highly concentrated solution of the acidic pharmaceutical agent in a softgel or two piece capsule, wherein the fill solution (liquid or solid) contains a therapeutically effective amount of acidic pharmaceutical agent dissolved within. The dosages administered will vary depending upon the acidic pharmaceutical agent employed, the mode of administration, the treatment desired, the size, age, and weight of the patient being treated and the like.

Aside from the solubility enhancing adjuvants already disclosed, the highly concentrated solutions of this invention may also contain suitable preserving, stabilizing, or wetting agents, and coloring substances. Pharmaceutically acceptable preservatives include for example benzyl alcohol and the like.

By substituting hydrogen ion for hydroxide ion, the disclosed solvent system is modified to enhance the solubility of basic pharmaceutical agents in polyethylene glycol so as to provide highly concentrated solutions of the basic pharmaceutical agents which are suited for filling softgels, encapsulation, or tablet formation. As an example, the basic drug, thioridazine was insoluble in PEG 400 at temperatures slightly below room temperature, whereas thioridazine in the presence of hydrogen ion was soluble in PEG 400 even when the temperature was dropped to −5° C. (Table 4).

TABLE 4

SOLUBILITY OF THE BASIC DRUG THIORIDAZINE IN PEG 400 IN THE PRESENCE AND ABSENCE OF HYDROGEN ION

INGREDIENTS	FORMULA I (mg)	FORMULA II (mg)
Thioridazine	25.0	25.0
Hydrochloric Acid	0.0	2.4
Water	8.0	8.0
Polyethylene Glycol 400	150.0	150.0
Propylene Glycol	12.0	12.0
Alcohol, (USP)	8.0	8.0
Povidone (polyvinylpyrrolidone)	5.0	5.0
RESULT at 5° C.	INSOLUBLE	SOLUBLE

By way of further example, basic pharmaceutical agents suited for forming the highly concentrated solutions of this invention include but are not limited to cimetidine, ranitidine, and nifedipine. Pharmaceutically acceptable sources of hydrogen ion include the mineral acids such as hydrochloric, hydrobromic, and sulfuric, and the organic acids such as fumaric, maleic, tartaric, (methane-, ethane-, and benzene) sulfonates, citric, and malic.

The contribution to enhanced solubility made by each component of the disclosed solvent system is apparent from Table 5, where the maximal solubility of the basic pharmaceutical agent, cimetidine, is reported in stepwise fashion from polyethylene glycol through the disclosed systems.

TABLE 5

CONTRIBUTIONS TO ENHANCED SOLUBILITY OF CIMETIDINE MADE BY COMPONENTS OF THE DISCLOSED SOLVENT SYSTEM

Solvent System	Solvent Proportions (%)	Maximal Solubility of Cimetidine (wt %)
Polyethylene Glycol 600	100	8.6%
Polyethylene Glycol 600/Glycerin/Water	85:5:10	11.7%
Polyethylene Glycol 600/Glycerin/Water/ 0.25 mole equivalents of Hydrochloric Acid	82:5:12:1	21.3%
Polyethylene Glycol 600/Glycerin/Water/ 0.26–0.50 mole equivalents of Hydrochloric Acid	79:5:14:2	>21.3%
Tetraglycol*/ Glycerin/Water/ 1 Mole equivalent of Hydrochloric Acid	36:20:29:15	~50%

*Tetraglycol is the polyethylene glycol ether of tetrahydrofurfuryl alcohol and one of the equivalents of polyethylene glycol.

The concepts disclosed herein for producing highly concentrated solutions of acidic and basic pharmaceutical agents are equally applicable to amphoteric compounds—compounds possessing the properties of an acid and a base. Examples of an amphoteric pharmaceutical agent suitable for use with this invention are the amino acid, methyldopa and enalapril.

It is also within the scope of this invention to directly add in the appropriate ratio to PEG and water, both the ionizable species (salt) of the pharmaceutical agent and its non-ionized species (free pharmaceutical agent) to produce a highly concentrated solution of the pharmaceutical agent suitable for soft-gel encapsulation. In this way, the use of ionizing agents such as hydroxide or hydrogen ion to produce the desired ratio of ionization (neutralization) of the pharmaceutical is avoided or minimized.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

The following examples are given by way of illustration only and in no way should be construed as limiting the invention in spirit or in scope, as many modifications in materials and methods will be apparent from this disclosure to those skilled in the art.

EXAMPLE I

Preparation of Highly Concentrated Solutions of Acidic Pharmaceutical Agents

Mixtures were prepared in 10 g quantities by dispersing the acidic pharmaceutical agent in polyethylene glycol or polyethylene glycol and glycerin or polyethylene glycol and polyvinylpyrrolidone or polyethylene glycol, glycerin, and polyvinylpyrrolidone. Aqueous solutions of hydroxide were then added. To facilitate mixing, the mixtures were warmed to 60° C. The mix-

tures were then permitted to cool to the required temperature, (room temperature or 4° C.), and were occasionally mixed for the next 2–7 days. The resulting mixture was then visually inspected to determine whether the solubility of the acidic pharmaceutical agent in the formulation had been exceeded.

EXAMPLE II

Saturation Solubilities of Acidic Pharmaceutical Agents

Mixtures were prepared as described in Example I except that an excess of the acidic pharmaceutical agent was present and the mixture was continuously agitated for at least 7 days. The mixture was then filtered through a Durapore 0.45M filter and the filtrate analyzed.

Once the saturation solubility of a particular acidic pharmaceutical agent has been determined, one can prepare highly concentrated solutions of that particular agent at or near the saturation point utilizing the protocol described in Example I. The highly concentrated solutions so prepared are then suitable for softgels, or for two piece encapsulation, or for conversion into tablets.

EXAMPLE III

Formulation for a Highly Concentrated Solution of Ibuprofen

The following formulation produces a highly concentrated solution of ibuprofen (67%) and is suitable as a softgel fill:

Ibuprofen	402 mg	
Potassium Hydroxide	38.4 mg	(0.3 mole equivalents)
Polyethylene Glycol 600	100 mg	
Water	38.4 mg	(6.4% by wt)
Glycerin/or Propylene Glycol	19.8 mg	(3.3% by wt)
Total	598.6 mg	

EXAMPLE IV

Formulation for a Highly Concentrated Solution of Naproxen

The following general formulation produces a highly concentrated solution of naproxen (35.9%) and is suitable as a softgel fill:

Naproxen	1 equivalent (35.9% by wt)
Potassium Hydroxide	0.50 mole equivalents as a 50% aqueous solution
Polyethylene Glycol 600	balance

EXAMPLE V

Formulation for a Highly Concentrated Solution of Indomethacin

The following general formulation produces a highly concentrated solution (34.5%) of indomethacin suitable as a softgel fill:

Indomethacin	1 equivalent (34.5% by wt)
Potassium Hydroxide	1.08 mole equivalents
Polyethylene Glycol 600	balance

EXAMPLE VI

Formulation for a Highly Concentrated Solution of Acetaminophen

The following general formulation produces a highly concentrated solution (35.0%) of acetaminophen suitable as a softgel fill:

Acetaminophen	1 equivalent (35% by wt)
Potassium Hydroxide	1 equivalent
Polyethylene Glycol 600	balance

EXAMPLE VII

Formulation for a Highly Concentrated Solution of Cimetidine

The following formulation produces a highly concentrated solution (50% by weight) of cimetidine suitable as a softgel fill:

Cimetidine	50% by weight
Hydrochloric Acid	7.5% by weight
Tetraglycol*	18% by weight
Glycerin	10% by weight
Water	14.5% by weight

*Tetraglycol is the polyethylene glycol ether of tetrahydrofurfuryl alcohol.

EXAMPLE VIII

Formulation for a Highly Concentrated Solution of Diclofenac Sodium

The following formulation produces a highly concentrated (20% by weight) solution of diclofenac sodium suitable as a softgel fill and having a water content of 8.0% w/w.

Diclofenac Sodium	100.0 mg	
Polyethylene Glycol 600	357.7 mg	
Hydrochloric Acid (36.5% w/w solution)	6.5 mg	(0.2 mole equivalent)
Water	35.8 mg	
Total	500.0 mg	

EXAMPLE IX

Formulation for a Highly Concentrated Semi-Solid Solution of Ibuprofen

The following formulation produces a highly concentrated (34% by weight) semi-solid solution of ibuprofen which is suitable for encapsulation in a hard gelatin capsule.

Ibuprofen	206.3 mg	
Polyethylene Glycol 4000	336.3 mg	
Polyethylene Glycol 400	37.4 mg	
Potassium Hydroxide	20.0 mg	(0.35 mole equivalent
Total	600.0 mg	

The polyethylene glycol 400 and 4000 were warmed to 60° C. until a clear solution was obtained. The drug and powered potassium hydroxide were dispersed in the melt and stirred for about thirty minutes. This solution was then clarified and filled, at 60° C., into hard-shell capsules.

EXAMPLE X

Formulation for a Highly Concentrated Semi-Solid Solution of Naproxen

The following formulation produces a highly concentrated (43% by weight) semi-solid solution of naproxen which is suitable for encapsulation in a hard gelatin capsule.

Naproxen	260.4 mg	
Polyethylene Glycol 4000	285.4 mg	
Polyethylene Glycol 400	31.7 mg	
Potassium Hydroxide	22.5 mg	(0.35 mole equivalent
Total	600.0 mg	

The capsules were prepared in a similar manner to the method disclosed in Example XI.

EXAMPLE XI

Formulation for a Highly Concentrated Solid Solution of Naproxen

The following formulation produces a highly concentrated (40% by weight) solid solution of naproxen suitable for producing tablets.

Naproxen	250.0 mg	
Polyethylene Glycol 20,000	338.5 mg	
Potassium Hydroxide	18.25 mg	(0.3 mole equivalent
Water	18.25 mg	
Total	625.0 mg	

The polyethylene glycol 20,000 was heated to 80° C. to produce a clear solution. The drug was then added and with gentle stirring, dispersed. The potassium hydroxide was added in aqueous solution and the mixture stirred until a clear solution was produced. The molten solution was then poured into 16 mm round PVC blisters and allowed to cool to form tablets.

EXAMPLE XII

Formulation for a Highly Concentrated Solution of Ibuprofen

The following formulation produces a highly concentrated (40% by weight) solution of ibuprofen, without using strongly alkaline solutions, which is suitable as a softgel fill.

Ibuprofen	120.0 mg	
Ibuprofen Sodium	92.6 mg	(0.4 mole equivalent
Polyethylene Glycol 600	263.6 mg	
Water	23.8 mg	
Total	500.0 mg	

EXAMPLE XIII

Dissolution Profiles of Semi-Solid Formulations

The dissolution profiles of the formulation described in Example X which had been filled into size 1 hard gelatin capsules was determined using the USP dissolution test (apparatus 1). The basket speed was set at 100 rpm and the dissolution medium used as pH 7 buffer. Release of drug was determined by UV-spectroscopy at the wavelength of maximum absorption. The times for 25, 50 and 70% release of drug are given in the table below.

Time for % Release	Example IX Ibuprofen
25%	15.9 min.
50%	23.3 min.
70%	29.0 min.

EXAMPLE XIV

Dissolution Profile of Solid Formulation

The dissolution profile of a tablet of the formulation described in Example XI was compared to a tablet made from the same formulation, but omitting the potassium hydroxide. The USP dissolution test (apparatus 2) was used with the paddle speed set at 100 rpm and a dissolution medium of pH 7 buffer. The tablets were fixed to allow only the top surface to be in contact with the dissolution medium to allow intrinsic dissolution measurements. UV-spectroscopy at the wavelength of maximum absorption was used to quantify drug release. The intrinsic dissolution rate constants were calculated from the slope of the release curve over the initial thirty minutes and are given in the table below.

Formulation	Dissolution Rate
Example XII	0.74 mg/min/cm^2
Example XII without Potassium Hydroxide	0.41 mg/min/cm^2

What is claimed is:

1. A pharmaceutically acceptable solution of an acidic pharmaceutical agent suitable for filling softgels and having a pH of 2.5 to 7.5 for subsequent oral administration, comprising the acidic pharmaceutical agent and a solvent system, the solvent system comprising 10% to 80% polyethylene glycol by weight of the solvent system, 1% to 20% water by weight of the solvent system and a hydroxide species, the hydroxide species being capable of dissociating in the solvent system into pharmaceutically acceptable cations and hydroxide ions, the hydroxide species being present in an amount such that between 0.1 and less than one mole of hydroxide ions per mole of acidic groups in the acidic pharmaceutical agent is present in the solution, the hydroxide species partially ionizing the acidic pharmaceutical agent such that the acidic pharmaceutical agent is present in a dissolved state in the solution as both a free acid and a cationic salt, the acidic pharmaceutical agent being present in a dissolved state in the solution in a solubility enhanced amount greater than the maximum amount of the acidic pharmaceutical agent capable of dissolving in the solvent system in the absence of the hydroxide species and less than or equal to 80% by weight of the solution.

2. The solution according to claim 1 further containing 4–12% glycerin by weight of the solvent system.

3. The solution according to claim 2 wherein said polyethylene glycol has an average molecular weight of between about 200–100,000.

4. The solution according to claim 1 wherein the hydroxide species is selected from the group consisting of sodium hydroxide, ammonium hydroxide and potassium hydroxide.

5. The solution according to claim 1 wherein said polyethylene glycol has an average molecular weight of between about 200–100,000.

6. The solution according to claim 5 further containing 1–20% polyvinylpyrrolidone by weight of the solvent system; said polyvinylpyrrolidone having an average molecular weight between about 10,000–100,000.

7. The solution according to claim 1 further containing 1–20% polyvinylpyrrolidone by weight of the solvent system.

8. The solution of claim 1 wherein the acidic pharmaceutical agent is selected from the group consisting of ibuprofen, naproxen, indomethacin, acetaminophen and diclofenac sodium.

9. A pharmaceutically acceptable solution of a basic pharmaceutical agent suitable for filling softgels and having a pH of 2.5 to 7.5 for subsequent oral administration, comprising the basic pharmaceutical agent and a solvent system, the solvent system comprising 10% to 80% polyethylene glycol by weight of the solvent system, 1% to 20% water by weight of the solvent system and a hydrogen ion species, the hydrogen ion species being capable of dissociating in the solvent system into hydrogen ions and pharmaceutically acceptable anions, the hydrogen ion species being present in an amount such that between 0.1 and less than one mole of hydrogen ions per mole of basic groups in the basic pharmaceutical agent is present in the solution, the hydrogen ion species partially ionizing the basic pharmaceutical agent such that the basic pharmaceutical agent is present in a dissolved state in the solution as both a free base and an anionic salt, the basic pharmaceutical agent being present in a dissolved state in the solution in a solubility enhanced amount greater than the maximum amount of the basic pharmaceutical agent capable of dissolving in the solvent system in the absence of the hydrogen ion species and less than or equal to 80% by weight of the solution.

10. The solution according to claim 9 wherein said polyethylene glycol has an average molecular weight of between about 200–800.

11. The solution according to claim 9 wherein 50–95% of the polyethylene glycol has an average molecular weight between about 800 to about 10,000.

12. The solution according to claim 9 wherein the polyethylene glycol has an average molecular weight between about 10,000 to about 100,000.

13. The solution according to claim 9 further containing 1–20% polyvinylpyrrolidone by weight of the solvent system; said polyvinylpyrrolidone having an average molecular weight between about 10,000–100,000.

14. The solution of claim 9 wherein the basic pharmaceutical agent is selected from the group consisting of thioridazine, cimetidine and ranitidine.

15. A pharmaceutically acceptable solution of an amphoteric pharmaceutical agent suitable for filling softgels and having a pH of 2.5 to 7.5 for subsequent oral administration, comprising the amphoteric pharmaceutical agent and a solvent system, the solvent system comprising 10% to 80% polyethylene glycol by weight of the solvent system, 1% to 20% water by weight of the solvent system and an ion species selected from the group consisting of cationic hydroxide species and anionic hydrogen ion species, the ion species being capable of dissociating in the solvent system into pharmaceutically acceptable ions, the ion species being present in an amount such that between 0.1 and less than one mole of ions selected from the group consisting of hydrogen ions and hydroxide ions per mole of ionizable groups in the amphoteric pharmaceutical agent is present in the solution, the ion species partially ionizing the amphoteric pharmaceutical agent such that the amphoteric pharmaceutical agent is present in a dissolved state in the solution both in a free form and a salt form, the amphoteric pharmaceutical agent being present in a dissolved state in the solution in a solubility enhanced amount greater than the maximum amount of the amphoteric pharmaceutical agent capable of dissolving in the solvent system in the absence of the ion species and less than or equal to 80% by weight of the solution.

16. The solution of claim 15 wherein the amphoteric pharmaceutical agent is selected from the group consisting of methyldopa and enalapril.

17. A pharmaceutically acceptable solution of an acidic pharmaceutical agent suitable for two-piece encapsulation or for tablet formation for subsequent oral administration, comprising the acidic pharmaceutical agent and a solvent system, the solvent system comprising 10% to 80% polyethylene glycol by weight of the solvent system, 1% to 20% water by weight of the solvent system and a hydroxide species, the hydroxide species being capable of dissociating in the solvent system into pharmaceutically acceptable cations and hydroxide ions, the hydroxide species being present in an amount such that between 0.1 and less than one mole of hydroxide ions per mole of acidic groups in the acidic pharmaceutical agent is present in the solution, the hydroxide species partially ionizing the acidic pharmaceutical agent such that the acidic pharmaceutical agent is present in a dissolved state in the solution as both a free acid and a cationic salt, the acidic pharmaceutical agent being present in a dissolved state in the solution in a solubility enhanced amount greater than the maximum amount of the acidic pharmaceutical agent capable of dissolving in the solvent system in the absence of the hydroxide species and less than or equal to 80% by weight of the solution.

18. A pharmaceutically acceptable solution of a basic pharmaceutical agent suitable for two-piece encapsulation or for tablet formation for subsequent oral administration, comprising the basic pharmaceutical agent and a solvent system, the solvent system comprising 10% to 80% polyethylene glycol by weight of the solvent system, 1% to 20% water by weight of the solvent system and a hydrogen ion species, the hydrogen ion species being capable of dissociating in the solvent system into hydrogen ions and pharmaceutically acceptable anions, the hydrogen ion species being present in an amount such that between 0.1 and less than one mole of hydrogen ions per mole of basic groups in the basic pharmaceutical agent is present in the solution, the hydrogen ion species partially ionizing the basic pharmaceutical agent such that the basic pharmaceutical agent is present in a dissolved state in the solution as both a free base and an anionic salt, the basic pharmaceutical agent being present in a dissolved state in the solution in a solubility enhanced amount greater than the maximum amount of the basic pharmaceutical agent capable of dissolving in the solvent system in the absence of the hydrogen ion species and less than or equal to 80% by weight of the solution.

19. A pharmaceutically acceptable solution of an amphoteric pharmaceutical agent suitable for two-piece encapsulation or for tablet formation for subsequent oral administration, comprising the amphoteric pharmaceutical agent and a solvent system, the solvent system

comprising 10% to 80% polyethylene glycol by weight of the solvent system, 1% to 20% water by weight of the solvent system and an ion species selected from the group consisting of cationic hydroxide species and anionic hydrogen ion species, the ion species being capable of dissociating in the solvent system into pharmaceutically acceptable ions, the ion species being present in an amount such that between 0.1 and less than one mole of ions selected from the group consisting of hydrogen ions and hydroxide ions per mole of ionizable groups in the amphoteric pharmaceutical agent is present in the solution, the ion species partially ionizing the amphoteric pharmaceutical agent such that the amphoteric pharmaceutical agent is present in a dissolved state in the solution both in a free form and a salt form, the amphoteric pharmaceutical agent being present in a dissolved state in the solution in a solubility enhanced amount greater than the maximum amount of the amphoteric pharmaceutical agent capable of dissolving in the solvent system in the absence of the ion species and less than or equal to 80% by weight of the solution.

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(54) Title: SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

(57) Abstract: Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one ore more active agents, polyethylene glycol, 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent, and water. The pH of the composition is adjusted within the range of 2.5 - 7.5. The de-ionizing agent causes partial de- ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as lesser amounts of polyethylene glycol (PEG) esters.

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SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

This invention is in the field of fill materials encapsulated in soft gelatin capsules.

This application claims priority under 35 U.S.C. 119 to U.S.S.N. 60/659,679 filed March 8, 2005.

BACKGROUND OF THE INVENTION

Filled one-piece soft gelatin capsules ("softgels") have been widely used for years to encapsulate consumable materials such as vitamins and pharmaceuticals in a liquid vehicle or carrier. Because softgels have properties which are quite different from two-piece hardshell capsules, softgels are more capable of retaining a liquid fill material.

Not all liquids may be enclosed in a softgel capsule. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Other solvents such as propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the gelatin shell to some extent.

Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. In contrast, solutions provide the best liquid form for obtaining optimal "content uniformity" in a batch. Further, solutions typically provide a faster and more uniform absorption of an active agent than do suspensions.

Suitable softgel solutions, however, can be difficult to achieve. One constraint is size. Many pharmaceutical agents require volumes of solvent

too large to produce a softgel capsule small enough to be taken by patients. The solvent must also have sufficient solvating power to dissolve a large amount of the pharmaceutical agent to produce a concentrated solution and yet not dissolve, hydrolyze or tan the gelatin shell.

Concentrated solutions of pharmaceutical agents for use in softgel capsules have been described. Most of these systems involve ionizing the free pharmaceutical agent *in situ* to the corresponding salt. For example, U.S. Patent No. 5,360,615 to Yu *et al.* discloses a solvent system for enhancing the solubility of acidic, basic, or amphoteric pharmaceutical agents. The solvent system comprises polyethylene glycol, an ionizing agent, and water. The ionizing agent functions by causing the partial ionization of the free pharmaceutical agent. U.S. Patent No. 6,383,515, U.S. Patent Application Publication No. 2002/0187195, and U.S. Patent Application Publication No. 2001/0007668 to Sawyer *et al.* discloses pharmaceutically acceptable solutions containing a medicament suitable for filling softgel capsules comprising a polymer such as polyethylene glycol and an acid salt of a compound having three or more carbon atoms, such as sodium propionate. The salt helps to ionize the medicament without relying on the use of strong acids or bases. U.S. Patent No. 6,689,382 to Berthel *et al.* describes a pharmaceutical formulation suitable for filling softgel capsules comprising (a) a therapeutically effective amount of a non-steroidal anti-inflammatory drug (NSAID); and (b) a solvent system comprising 40% to 60% by weight a polyoxyethylene ether, 15% to 35% by weight of glycerin and 15% to 35% by weight water. In cases where the NSAID has a carboxyl or an acidic functional group, the solvent system also includes hydroxide ions. U.S. Patent No. 5,505,961 to Shelley *et al.* describes a method for increasing the solubility of acetaminophen alone or in combination with other pharmaceutically active agents to form a clear solution for encapsulation into a softgel capsule. The method comprises solubilizing acetaminophen in a mixture of propylene glycol, polyethylene glycol, water, polyvinylpyrrolidone and sodium or potassium acetate.

The previously described methods all involve the conversion of the free pharmaceutical agent to the corresponding salt. In cases where the free pharmaceutical agent is acidic, the resulting anion can react with the polyethylene glycol in the fill to produce polyethylene glycol esters, thus reducing the amount of available pharmaceutical agent.

There is a need for a solvent system containing a medicament, which can be encapsulated in a softgel capsule, wherein the formation of PEG esters is minimized.

Therefore it is an object of the invention to provide a stable solvent system for pharmaceutical agents, which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

BRIEF SUMMARY OF THE INVENTION

Liquid and semi-solid pharmaceutical compositions, which can be administered in liquid form or can be used for preparing capsules, are described herein. The composition comprises the salt of one or more active agents, and 0.2-1.0 mole equivalents of a de-ionizing agent per mole of active agent. The pH of the composition is adjusted within the range of 2.5 – 7.5. The de-ionizing agent causes partial de-ionization (neutralization) of the salt of the active agent resulting in enhanced bioavailability of salts of weakly acidic, basic or amphoteric active agents as well as decreased amounts of polyethylene glycol (PEG) esters.

DETAILED DESCRIPTION OF THE INVENTION

I. Composition

A. Fill Materials

1. Drugs to be Formulated

The formulation can contain any therapeutic, diagnostic, prophylactic or nutraceutical agent. Exemplary agents include, but are not limited to, analeptic agents; analgesic agents; anesthetic agents; antiasthmatic agents; antiarthritic agents; anticancer agents; anticholinergic agents; anticonvulsant agents; antidepressant agents; antidiabetic agents; antidiarrheal agents; antiemetic agents; antihelminthic agents; antihistamines; antihyperlipidemic agents; antihypertensive agents; anti-infective agents; anti-inflammatory

agents; antimigraine agents; antineoplastic agents; antiparkinson drugs; antipruritic agents; antipsychotic agents; antipyretic agents; antispasmodic agents; antitubercular agents; antiulcer agents; antiviral agents; anxiolytic agents; appetite suppressants (anorexic agents); attention deficit disorder and attention deficit hyperactivity disorder drugs; cardiovascular agents including calcium channel blockers, antianginal agents, central nervous system ("CNS") agents, beta-blockers and antiarrhythmic agents; central nervous system stimulants; diuretics; genetic materials; hormonolytics; hypnotics; hypoglycemic agents; immunosuppressive agents; muscle relaxants; narcotic antagonists; nicotine; nutritional agents; parasympatholytics; peptide drugs; psychostimulants; sedatives; sialagogues, steroids; smoking cessation agents; sympathomimetics; tranquilizers; vasodilators; beta-agonist; and tocolytic agents.

A first class of drugs is selected based on inclusion in the molecule of a weakly acidic, basic or amphoteric group that can form a salt. Any drug that bears an acidic or a basic functional group, for example, an amine, imine, imidazoyl, guanidine, piperidinyl, pyridinyl, quaternary ammonium, or other basic group, or a carboxylic, phosphoric, phenolic, sulfuric, sulfonic or other acidic group, can react with the de-ionizing agent.

Some specific drugs that bear acidic or basic functional groups and thus may be converted to the corresponding salt for use in the described formulations include, but are not limited to, Acetaminophen, Acetylsalicylic acid, Alendronic acid, Alosetron, Amantadine, Amlopidine, Anagrelide, Argatroban, Atomoxetine, Atrovastatin, Azithromycin dehydrate, Balsalazide, Bromocriptan, Bupropion, Candesartan, Carboplatin, Ceftriaxone, Clavulonic acid, Clindamycin, Cimetadine, Dehydrocholic (acid), Dexmethylphenidate, Diclofenac, Dicyclomine, Diflunisal, Diltiazem, Donepezil, Doxorubicin, Doxepin, Epirubicin, Etodolic acid, Ethacrynic acid, Fenoprofen, Fluoxetine, Flurbiprofen, Furosemide, Gemfibrozil, Hydroxyzine, Ibuprofen, Imipramine, Indomethacin, Ketoprofen, Levothyroxine, Maprolitline, Meclizine, Methadone, Methylphenidate, Minocycline, Mitoxantone, Moxifloxacin, Mycophenolic

acid, Naproxen, Niflumic acid, Ofloxacin, Ondansetron, Pantoprazole, Paroxetine, Pergolide, Pramipexole, Phenytoin, Pravastain, Probenecid, Rabeprazole, Risedronic acid, Retinoic acid, Ropinirole, Selegiline, Sulindac, Tamsulosin, Telmisertan, Terbinafine, Theophyline, Tiludronic Acid, Tinzaparin, Ticarcillin, Tometin, Valproic acid, Salicylic acid, Sevelamer, Ziprasidone, Zoledronic acid, Acetophenazine, Albuterol, Almotriptan, Amitriptyline, Amphetamine, Atracurium, Beclomethasone, Benztropine, Biperiden, Bosentan, Bromodiphenhydramine, Brompheniramine carbinoxamine, Caffeine, Capecitabine, Carbergoline, Cetirizine, Chlocylizine, Chlorpheniramine, Chlorphenoxamine, Chlorpromazine, Citalopram, Clavunate potassium, Ciprofloxacin, Clemastine, Clomiphene, Clonidine, Clopidogrel, Codeine, Cyclizine, Cyclobenzaprine, Cyproheptadine, Delavirdine, Diethylpropion, Divalproex, Desipramine, Dexmethylphenidate, Dexbrompheniramine, Dexchlopheniramine, Dexchlor, Dextroamphetamine, Dexedrine, Dextromethorphan, Fiflunisal, Diphemanil methylsulphate, Diphenhydramine, Dolasetron, Doxylamine, Enoxaparin, Ergotamine, Ertepenem, Eprosartan, Escitalopram, Esomeprazole, Fenoldopam, Fentanyl, Fexofenadine, Flufenamic acid, Fluvastatin, Fluphenazine, Fluticasone, Fosinopril, Frovatriptan, Gabapentin, Galatamine, Gatifloxacin, Gemcitabine, Haloperidol, Hyalurondate, Hydrocodone, Hydroxychloroquine, Hyoscyamine, Imatinib, Imipenem, Ipatropin, Lisinopril, Leuprolide, Levopropoxyphene, Losartan, Meclofenamic acid, Mefanamic acid, Mesalamine, Mepenzolate, Meperidine, Mephentermine, Mesalimine, Mesoridazine, Metaproteranol, Metformin, Methdialazine, Methscopolamine, Methysergide, Metoprolol, Metronidazole, Mibefradil, Montelukast, Morphine, Mometasone, Naratriptan, Nelfinavir, Nortriptylene, Noscapine, Nylindrin, Omeprazole, Orphenadrine, Oseltamivir, Oxybutynin, Papaverine, Pentazocine, Phendimetrazine, Phentermine, Pioglitazone, Pilocarpine, Prochloroperazine, Pyrilamine, Quetapine, Ranitidine, Rivastigmine, Rosiglitazone, Salmetrol, Sertaline, Sotalol, Sumatriptan, Tazobactam, Tacrolimus, Tamoxifen, Ticlopidine, Topiramate, Tolterodine,

Triptorelin, Triplennamine, Triprolidine, Tramadol, Trovofloxacin, Ursodiol, Promazine, Propoxyphene, Propanolol, Pseudoephedrine, Pyrilamine, Quinidine, Oxybate sodium, Sermorelin, Tacrolimus, Tegaseroid, Teriparatide, Tolterodine, Triptorelin pamoate, Scoplolamine, Venlafaxine, Zamivir, Aminocaproic acid, Aminosalicylic acid, Hydromorphone, Isosuprine, Levorphanol, Melhalan, Nalidixic acid, and Para-aminosalicylic acid.

2. Deionizing Agent

The deionizing agent functions by causing partial deionization (neutralization) of the salt of one or more pharmaceutically active agents. When the active agent is the salt of a weak acid and a strong base, the deionizing agent is preferably a hydrogen ion species. When the active agent is the salt of a weak base and a strong acid, the deionizing agent is preferably a hydroxide ion species. The deionizing agent is preferably present in an amount between 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent.

Exemplary hydrogen ion species useful as de-ionizing agents described herein, include, but are not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, methane-, ethane-, and benzene sulfonates, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, and lactic acid.

Exemplary hydroxide ion species useful as de-ionizing agents described herein, include, but are not limited to, metal hydroxides such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, aluminum hydroxide, and magnesium hydroxide.

Additional acid or base can be added to adjust the pH of the fill composition. In a preferred embodiment, the pH of the fill composition is from about 2.5 to about 7.5.

3. Excipients

Formulations may be prepared using a pharmaceutically acceptable carrier composed of materials that are considered safe and effective and may be administered to an individual without causing undesirable biological side

effects or unwanted interactions. The carrier is all components present in the pharmaceutical formulation other than the active ingredient or ingredients. As generally used herein "carrier" includes, but is not limited to, plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents and combinations thereof.

In a preferred embodiment, a mixture of polyethylene glycol and water is used as a solvent for the salt of the active agent and the de-ionizing agent. Polyethylene glycol is present in an amount from about 10% to about 80% by weight. Water is present in an amount from about 1% to 18% by weight. The molecular weight of polyethylene glycol is between 300 and 1500. Other suitable solvents include surfactants and copolymers of polyethylene glycol. Optionally, glycerin, polyvinyl pyrrolidone (PVP) or propylene glycol (PPG) can be added to enhance the solubility of the drug agent.

B. Shell Composition

1. Gelatin

Gelatin is the product of the partial hydrolysis of collagen. Gelatin is classified as either Type A or Type B gelatin. Type A gelatin is derived from the acid hydrolysis of collagen while Type B gelatin is derived from alkaline hydrolysis of collagen. Traditionally, bovine bones and skins have been used as raw materials for manufacturing Type A and Type B gelatin while porcine skins have been used extensively for manufacturing Type A gelatin. In general acid-processed gelatins form stronger gels than lime-processed gelatins of the same average molecular weight.

2. Other Shell Additives

Other suitable shell additives include plasticizers, opacifiers, colorants, humectants, preservatives, flavorings, and buffering salts and acids.

Plasticizers are chemical agents added to gelatin to make the material softer and more flexible. Suitable plasticizers include glycerin, sorbitol

solutions which are mixtures of sorbitol and sorbitan, and other polyhydric alcohols such as propylene glycol and maltitol or combinations thereof.

Opacifiers are used to opacify the capsule shell when the encapsulated active agents are light sensitive. Suitable opacifiers include titanium dioxide, zinc oxide, calcium carbonate and combinations thereof.

Colorants can be used to for marketing and product identification/differentiation purposes. Suitable colorants include synthetic and natural dyes and combinations thereof.

Humectants can be used to suppress the water activity of the softgel. Suitable humectants include glycerin and sorbitol, which are often components of the plasticizer composition. Due to the low water activity of dried, properly stored softgels, the greatest risk from microorganisms comes from molds and yeasts. For this reason, preservatives can be incorporated into the capsule shell. Suitable preservatives include alkyl esters of p-hydroxy benzoic acid such as methyl, ethyl, propyl, butyl and heptyl (collectively known as "parabens") or combinations thereof.

Flavorings can be used to mask unpleasant odors and tastes of fill formulations. Suitable flavorings include synthetic and natural flavorings. The use of flavorings can be problematic due to the presence of aldehydes which can cross-link gelatin. As a result, buffering salts and acids can be used in conjunction with flavorings that contain aldehydes in order to inhibit cross-linking of the gelatin.

II. Method of Making

A. Fill Material

The fill material is prepared by mixing the agent (such as a salt of the drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight.

Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

B. Gel Mass

The main ingredients of the softgel capsule shell are gelatin, plasticizer, and purified water. Typical gel formulations contain (w/w) 40-50% gelatin, 20-30% plasticizer, and 30-40% purified water. Most of the water is subsequently lost during capsule drying. The ingredients are combined to form a molten gelatin mass using either a cold melt or a hot melt process. The prepared gel masses are transferred to preheated, temperature-controlled, jacketed holding tanks where the gel mass is aged at 50-60°C until used for encapsulation.

1. Cold Melt Process

The cold melt process involves mixing gelatin with plasticizer and chilled water and then transferring the mixture to a jacket-heated tank. Typically, gelatin is added to the plasticizer at ambient temperature (18-22°C). The mixture is cooked (57-95°C) under vacuum for 15-30 minutes to a homogeneous, deaerated gel mass. Additional shell additives can be added to the gel mass at any point during the gel manufacturing process or they may be incorporated into the finished gel mass using a high torque mixer.

2. Hot Melt Process

The hot melt process involves adding, under mild agitation, the gelatin to a preheated (60-80°C) mixture of plasticizer and water and stirring the blend until complete melting is achieved. While the hot melt process is faster than the cold melt process, it is less accurately controlled and more susceptible to foaming and dusting.

C. Softgel Capsule

Softgel capsules are typically produced using a rotary die encapsulation process. The gel mass is fed either by gravity or through positive displacement pumping to two heated (48-65°C) metering devices. The metering devices control the flow of gel into cooled (10-18°C), rotating casting drums. Ribbons are formed as the cast gel masses set on contact with the surface of the drums.

The ribbons are fed through a series of guide rolls and between injection wedges and the capsule-forming dies. A food-grade lubricant oil is applied onto the ribbons to reduce their tackiness and facilitate their transfer. Suitable lubricants include mineral oil, medium chain triglycerides, and soybean oil. Fill formulations are fed into the encapsulation machine by gravity. In the preferred embodiment, the softgels contain printing on the surface, optionally identifying the encapsulated agent and/or dosage.

III. Method of Use

The softgels may be used to encapsulate a wide range of pharmaceutically active agents, nutritional agents and personal care products. Softgel capsules may be administered orally to a patient to deliver a pharmaceutically active agent.

Examples

In the following examples, the fill material can be prepared by mixing the salt of one or more pharmaceutically active agents, the deionizing agent, water and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution can be encapsulated in a softgel capsule using the appropriate gel mass.

Example 1. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	62.30
Water	7.40

Example 2. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4.75
PVP	1.85
PEG 400	60.50
Water	7.40

Example 3. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4.72
PVP	1.85
PEG 400	63.52
Water	7.40

Example 4. Naproxen Sodium with Acetic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Acetic Acid	3.00
PVP	1.85
PEG 400	31.15
Water	7.40
PEG 600	31.15

Example 5. Naproxen Sodium with Citric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Citric Acid	4075
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 6. Naproxen Sodium with Hydrochloric Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.50
Hydrochloric Acid	4072
PVP	1.85
PEG 400	30.25
Water	7.40
PEG 600	30.25

Example 7. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	27.50
Lactic Acid	5.27
Propylene Glycol	2.00
PEG 400	64.64
Water	0.60

Example 8. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	0.24-0.35 M
Propylene glycol	2.00
PEG 600.	q.s.

Example 9. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	61.2
PEG 1000	6.80

Example 10. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	51.00
PEG 1000	17.00

Example 11. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic Acid	5.00
Propylene glycol	2.00
PEG 600	34.00
PEG 1000	34.00

Example 12. Naproxen Sodium with Lactic Acid as the Deionizing Agent

Fill Material:

Ingredients	% (by weight)
Naproxen Sodium	25.00
Lactic acid	5.00
Propylene glycol	2.00
PEG 600	17.00
PEG 1000	51.00

It is understood that the disclosed invention is not limited to the particular methodology, protocols, and reagents described as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of skill in the art to which the disclosed invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods, devices, and materials are as described. Publications cited herein and the materials

for which they are cited are specifically incorporated by reference. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

We claim:

1. A pharmaceutical composition comprising

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

2. The composition of claim 1 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

3. The composition of claim 1 wherein the deionizing agent is present in an
amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

4. The composition of claim 1 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

5. The composition of claim 1 further comprising polyethylene glycol.

6. The composition of claim 5 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight

7. The composition of claim 5 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

8. The composition of claim 1 further comprising water.

9. The composition of claim 8 wherein water is present in an amount from about 1% to about 18% by weight.

10. The composition of claim 1 further comprising one or more excipients.

11. The composition of claim 7 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

12. The composition of claim 11 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

13. The composition of claim 12 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

14. A method of making the composition of any of claims 1-13 comprising

(a) mixing the salt of one or more pharmaceutically active agents, and the deionizing agent at an appropriate temperature; and

(b) encapsulating the mixture in a softgel capsule.

15. The method of claim 14 further comprising polyethylene glycol.

16. The method of claim 14 further comprising water.

17. The method of claim 14 wherein the appropriate temperature is from about 50°C to about 70°C.

18. A method of using the composition of any of claims 1-13 comprising
administering to a patient in need thereof the salt of one or more pharmaceutically active agents.

19. A softgel capsule comprising a fill material wherein the fill material comprises

(a) a salt of one or more pharmaceutically active agents; and

(b) a deionizing agent.

20. The capsule of claim 19 wherein the pharmaceutically active agent is selected from the group consisting of therapeutically active agents, diagnostic agents, and prophylactic agents.

21. The capsule of claim 19 wherein the deionizing agent is present in an
amount from about 0.2 to 1.0 mole equivalents per mole of the pharmaceutically active agent(s).

22. The capsule of claim 19 wherein the deionizing agent is selected from the group consisting of hydrogen ion and hydroxide ion.

23. The capsule of claim 19 further comprising polyethylene glycol.

24. The capsule of claim 23 wherein polyethylene glycol is present in an amount from about 10% to about 80% by weight

25. The capsule of claim 23 wherein polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

26. The capsule of claim 19 further comprising water.

27. The capsule of claim 26 wherein water is present in an amount from about 1% to about 18% by weight.

28. The capsule of claim 19 further comprising one or more excipients.

29. The capsule of claim 28 wherein the excipients are selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, pH-adjusting agents, dyes, preservatives, solvents, surfactants, and combinations thereof.

30. The capsule of claim 29 wherein the solubilizer is selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

31. The capsule of claim 29 wherein the solubilizer is present in amount from about 1% to about 10% by weight.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/007788

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/48

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)
A61K

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 practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 360 615 A (YU ET AL) 1 November 1994 (1994-11-01) cited in the application example 8	1-31
X	WO 95/31979 A (R.P. SCHERER INTERNATIONAL CORPORATION; SHELLEY, RICKEY, S; WEI, YOUCH) 30 November 1995 (1995-11-30) page 4, line 1 - line 10 example 8	1-31
X	US 2001/007668 A1 (SAWYER MARYJEAN ET AL) 12 July 2001 (2001-07-12) paragraph [0061]; tables 1-17	1-31
X	US 5 484 606 A (DHABHAR ET AL) 16 January 1996 (1996-01-16) examples	1-31

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* 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 document 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
28 June 2006	06/07/2006

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/007788

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 912 011 A (MAKINO ET AL) 15 June 1999 (1999-06-15) tables 2,3 ----	1-31
A	US 2004/157928 A1 (KIM JAE-HWAN ET AL) 12 August 2004 (2004-08-12) tables 5c,5d paragraph [0005] ----	1-31

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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US 20010007668A1

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(12) Patent Application Publication (10) Pub. No.: US 2001/0007668 A1

SAWYER et al. (43) Pub. Date: Jul. 12, 2001

(54) SOLVENT SYSTEM FOR ENHANCING SOLUBILITY

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(57) ABSTRACT

A pharmaceutically acceptable solution with a medicament suitable for filling a soft gelatin capsule is made from a solvent. The solvent contains a polymer, such as polyethylene glycol, and an acid salt of a compound having 3 or more carbon atoms, and a salt such as sodium propionate. The solvent may optionally contain a cosolvent, such as dimethyl isosorbide. The medicament may preferably comprise an analgesic such as aspirin or naproxen.

SOLVENT SYSTEM FOR ENHANCING SOLUBILITY

BACKGROUND OF THE INVENTION

[0001] 1. Field of the Invention

[0002] The invention relates to medicinal solutions suitable for encapsulation in soft gelatin capsules. More particularly, the invention relates to pharmaceutically acceptable solvent systems capable of producing a highly concentrated solution of a medicament, such as acetaminophen or naproxen, for use in a soft gelatin capsule.

[0003] 2. Description of Related Art

[0004] Soft gelatin capsules or "softgels" are, as their name implies, gelatin capsules that are softer than conventional caplets, capsules or tablets. They are commonly used to encapsulate liquids containing an active ingredient or ingredients. Softgels are used to contain consumables, such as vitamins or pharmaceuticals, including products in the over-the-counter market. Softgels are also used in many other industries, and have been used to encapsulate such diverse substances as industrial adhesives and bath oils.

[0005] In the pharmaceutical industry, softgels provide many benefits over conventional liquid and solid administration vehicles. They dissolve in the stomach faster than compressed tablets. Tablets must dissolve in the stomach or intestines and so generally retard the speed of onset of a medicament administered in a tablet form. Tablets are also generally unsuited for administration of liquids. Hard gelatin or starch-based capsules may be used for liquid or solid delivery systems. But, capsules are generally not appropriate for liquids because the hard gelatin or starch capsules may be either softened or entirely dissolved by a liquid medicament. In addition, some air is usually trapped in a hard gelatin capsule, where a liquid "fill" is put into the capsule. This air bubble can affect the active ingredients and detract from the appearance of the product. Softgels are better than direct liquid administration because liquids spill, and some medicaments may have unacceptable or unpleasant taste even with taste masking agents. Softgels, on the other hand, dissolve rapidly in the stomach and the body quickly absorbs the liquid interior of the softgel, so softgels offer an attractive means of administering a medicament.

[0006] Not all liquids may be enclosed in a softgel. Liquids containing more than about 20% water by weight are generally not enclosed in softgels, because the water tends to dissolve the gelatin shell. Propylene glycol, glycerin, low molecular weight alcohols, ketones, acids, amines, and esters all tend to degrade or dissolve the softgel layer gelatin to some extent. Thus, formulations that are enclosed in a softgel cannot contain significant amounts of many well-known solvents.

[0007] Softgels are also somewhat sensitive to pH, and generally require a pH in the encapsulated liquid from about 2.5 to about 7.5. Highly acidic liquids may hydrolyze the gelatin, resulting in leaks, while basic liquids may tan the gelatin, resulting in decreased solubility of the gelatin shell.

[0008] Pharmaceutical liquids are usually enclosed in softgels as either viscous solutions or suspensions. Suspensions are pharmaceutically less desirable because they can settle during manufacture, which leads to a less uniform product. If a suspension is used, the solid particles in a suspension should be smaller than about 80 mesh, otherwise the softgel filling equipment might not function optimally.

[0009] Suitable softgel solutions, however, can be difficult to achieve. The walls of a softgel are thicker than the walls of a caplet or a hard gelatin capsule. The softgel should be small enough for patient acceptance. The thickness of the walls reduces the available space for the medicament. But, the softgel must contain sufficient quantities of the medicament to be effective. One approach, of course, is simply to require the consumer to swallow more than one softgel to achieve any adequate dose of the medicament. Consumers, however, prefer taking one or two softgels, tablets or capsules and resist taking more than three.

[0010] The solution in the softgel must thus be highly concentrated. High concentration levels, though, strain the ability of conventional solvent systems to dissolve a sufficient quantity of the pharmaceutical agent. A strong solvent, on the other hand, can degrade the gelatin coating. So, a frequent problem in softgel applications is dissolving the active ingredient or ingredients in a sufficiently small amount of solvent to provide a potent dose of the medicament in the softgel. Solvent systems must be used that are tailored to the specific needs of a specific medicament or blend of medicaments. For example, U.S. Pat. No. 3,557,280 to Weber et al., issued January 1971, used a magnesium salt, polyvinylpyrrolidone and water to dissolve oxytetracycline for injection or oral liquid administration. U.S. Pat. No. 5,071,643 to Yu et al., issued Dec. 10, 1991 and U.S. Pat. No. 5,360,615 also to Yu et al., issued Nov. 1, 1994, used polyethylene glycol and an acid or a base to dissolve ibuprofen, naproxen, indomethacin or acetaminophen (among others).

[0011] Another solvent system, found in U.S. Pat. No. 5,505,961 to Shelley et al., issued Apr. 9, 1996, used polyethylene glycol and sodium or potassium acetate to enhance the solubility of acetaminophen.

[0012] Despite these efforts, there is still a strong need in the art for solvent systems that can dissolve large amounts of a medicament, especially without the addition of large amounts of an acid or base.

SUMMARY OF THE INVENTION

[0013] It is an object of the present invention to provide a solvent system capable of producing a highly concentrated solution of a pharmaceutical agent suitable for encapsulation into a softgel of suitable size without neutralizing large amounts of the agent.

[0014] It is a further object of the present invention to create such a solvent system that can be safely consumed by human beings.

[0015] It is a further object of the present invention to use such a solvent system to create a highly concentrated solution of a medicament, like acetaminophen or naproxen, suitable for use as a fill in a softgel. About a one ml softgel should encapsulate about 325 mg of acetaminophen or about 220 mg of naproxen.

[0016] It is a further object of the present invention to create a solvent system for enhancing the solubility of

medicaments, including such over-the-counter medicaments as pain relievers and cold remedies.

[0017] It is an advantage of the invention that one of the ingredients in the solvent system may itself be an antifungal agent, thereby increasing the safety of the solvent system during storage and handling.

[0018] Additional objects and advantages of the invention will be set forth in part in the description that follows, and in part will be obvious from the description.

[0019] To achieve the foregoing objects and in accordance with the purpose of the invention, as embodied and broadly described herein, the invention provides a pharmaceutically acceptable solution comprising a medicament and a solvent system. The solvent system comprises a low molecular weight polymer and a salt of an organic acid containing at least three carbon atoms.

[0020] To further achieve the foregoing objects and in accordance with the purpose of the invention, as embodied and broadly described herein, the invention provides a method for dissolving a large amount of a medicament in a small amount of solvent. The solvent comprises a low molecular weight polymer and a salt of an organic acid containing at least three carbon atoms.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0021] We will now describe the preferred embodiments of the invention.

[0022] The formulation of the invention comprises three types of systems: (a) a solvent system; (b) a solvent system and a medicament; and (c) a solvent system, at least one medicament dissolved in the solvent system, and a softgel surrounding the medicament and solvent system.

[0023] The solvent system of the invention comprises a low molecular weight polymeric material and a salt of an organic acid containing at least three carbon atoms. The system may also contain additional ingredients as set out below.

[0024] One part of the solvent system of the invention is a low molecular weight polymeric material. As used herein, "a low molecular weight" polymer is any polymer that is liquid or semi-solid at about room temperature and pressure when combined in a solvent system or any polymer that can dissolve in a limited amount of water to form a solvent system. The particular identity of the polymeric entity selected as the solvent will guide one skilled in the art to the appropriate molecular weight for the polymer. Since the polymer will be ingested into the human body, it must be safe and nontoxic (at least when used in the amounts contemplated herein). While the polymer need not be organoleptically pleasing, the polymer preferably does not cause any adverse side reactions or other detrimental effect on humans upon ingestion.

[0025] Linear or branched polymers, of course, generally do not have a single molecular weight. Rather, each strand in a polymer sample will have a different length and the "molecular weight" of a polymer sample will be the average molecular weight of the strands.

[0026] Acceptable polymers that may be used in the invention include polyalkylene glycols and polyvinyl pyrollidones and analogs thereof, including various copolymers, polymer blends and modified polymers thereof. The polymers of the invention may also include polymeric materials that are not ordinarily thought of as polymers, such as glycerin and propylene glycol. The preferred polymers of the invention are polyols, such as glycerin, propylene glycol and polyalkylene glycols. More preferred are polyethylene glycols and polypropylene glycols. More preferably, the polyethylene glycols of the invention have a molecular weight of less than about 1500, since polyethylene glycol 1500 is reported to be solid at room temperature. (Molecular weights of about 1500 or above are not excluded from the invention to the extent that the polymer may be semi-solid, liquid or soluble in limited amounts of water.) Most preferably, the molecular weight of the polyethylene oxide is from about 400 to about 600 daltons, and the most preferred embodiment of the invention uses polyethylene glycol having a molecular weight of about 600. The solvent may comprise mixtures of materials as well. For example, a polyethylene glycol having a molecular weight of about 600 may be obtained by using PEG 600 or about a 50/50 mixture of PEG 400 and PEG 800.

[0027] The polymeric material preferably comprises from about 10% by weight to about 70% by weight of the solution of the invention. More preferably, the polymeric material comprises from about 15% by weight to about 65% by weight of the solution and even more preferably, the polymeric material comprises from about 20% by weight to about 55% by weight of the solution. Most preferably, the polymeric material comprises from about 30% by weight to about 50% by weight of the solution of the invention. When blends of the polymers are used as a solvent, it is preferable, but not critical, that one species of polymer predominates. Thus, in one preferred embodiment of the invention, the solvent system comprises from about 15% to about 65% by weight polyethylene glycol 600 and from 0% to about 5% by weight of (and more preferably from 0% to about 2% by weight) propylene glycol.

[0028] In addition to the polymeric material, the invention also comprises a salt of an organic acid containing at least three carbon atoms. The salt helps to ionize the medicament, especially where the medicament is capable of forming a zwitterion, without relying on strong acids or bases.

[0029] Preferred cations for the salt are monovalent and divalent cations that are nontoxic and acceptable for human consumption. These cations include, but are not limited to, sodium, potassium, and calcium ions. Alkali cations are preferred, and sodium is the most preferred cation.

[0030] The anion of the salt is an organic acid anion containing at least three carbon atoms. Acceptable acid anions include those capable of forming a nontoxic salt with any of the cations of the invention. Although the preferred acid anions are from saturated aliphatic acids having from three to six carbon atoms, other acids are not excluded from the scope of the invention. Aromatic acids, saturated acids having more than six carbon atoms, and unsaturated acids having more than three carbon atoms may be used, so long as the acid forms a nontoxic salt. More preferred acids include mono, di- and tri-carboxylic acids having three to six carbon atoms, including propionic acid, pyruvic acid, citric acid, and butanoic acid. Propionic acid is the most preferred because it has antifungal properties.

[0031] In a highly preferred embodiment of the invention, the salt is a sodium propionate salt that is added to the solution of the invention as a salt/water solution. Preferred concentrations of the salt solution are from about 40% by weight to a saturated solution of the salt in water.

[0032] The pH of this propionate solution may be adjusted by the addition of small amounts of propionic acid, usually no more than about 1-2% by weight of the propionate solution. So, the numbers in the examples may be slightly incorrect.

[0033] The salt may comprise from about 2% by weight to about 40% by weight of the solution of the invention. More preferably, the salt comprises from about 4% to about 35% by weight of the solution of the invention, and even more preferably, from about 4% by weight to about 25% by weight of the solution of the invention. Preferably the pH is adjusted in the salt/water solution to provide acceptable pH limits in the softgel.

[0034] The solvent system of the invention may also contain additional ingredients such as cosolvents, including dimethyl isosorbide, oils, including soybean oil, and water. The cosolvent may comprise from 0% by weight to about 30% by weight of the solution of the invention, and more preferably from about 5% by weight to about 20% by weight of the solution of the invention. Most preferably, the cosolvent is dimethyl isosorbide and comprises from about 5% by weight to about 10% by weight of the solution of the invention. Water may comprise from 0% by weight to about 25% by weight of the solution of the invention. Oils may comprise from 0% to about 20% by weight of the solution of the invention, and more preferably from 0% to about 15% by weight of the solution of the invention. In the examples that follow, water is added as part of a sodium propionate solution that is added to the solvent system. In some of these examples, the reported amounts in grams were calculated from the density and volume of the propionate solution added.

[0035] The medicament of the invention may be any medicament, but the softgels of the invention are of primary benefit in human consumption, so the medicaments of the invention are preferably those intended for use by humans. Preferred medicaments are those used in over-the-counter treatments of coughs, colds and other common ailments. Thus, highly preferred medicaments include pain relievers, such as aspirin, acetaminophen, naproxen, ibuprofen and other nonsteroidal anti-inflammatory drugs, as well as the so-called "Cox-2" inhibitors. Other highly preferred medicaments include, but are not limited to, cough suppressants, such as dextromethorphan, decongestants, such as pseudoephedrine, and antihistamines, such as chlorpheniramine and doxylamine compounds. Medicaments that form zwitterions when dissolved with the salts of the invention are most highly preferred.

[0036] The total amount of medicaments of the invention may comprise from about 25% by weight of the solution up to the amount that will form a fully saturated solution, usually up to about 70% by weight of the solution. Preferably, however, the medicaments comprise from about 30% by weight to about 55% by weight of the solution of the invention. Of course, dosage levels will be adjusted to reflect the needs of the patient, not the needs of the solvent.

[0037] Consumer preference suggests that clear or at least translucent solutions should be used in softgels. The solvent system of the present invention may be adjusted to provide such a clear solution acceptable to consumers. In the examples that follow, many of the solutions have a color. The color may be significantly reduced by carrying out the solution process in the absence of oxygen. While the examples used a nitrogen blanket, the solution was exposed to air while various materials were added, which affected the final color of the solution.

[0038] The medicament should remain in solution to achieve the benefits of the invention, and the solution should remain stable over time and under conditions normally encountered in consumer applications. The solution disclosed in the present invention has been found stable and robust in a number of tests. For instance, the solution has been placed "on the shelf" at room temperature for extended periods of time, and has remained clear and stable, without precipitation of the medicament. Moreover, the solution has been subjected to alternating refrigeration and room temperature conditions, and the medicament has not crystallized, and has remained stable and clear.

[0039] The solution has been placed in softgels successfully, at least on an experimental level. The gelatin in a softgel may be any known on the art. Suitable results have been achieved with Type A gelatin, bloom strength 150. Hydrophilic softgels are preferred.

[0040] The selection of ingredients to be used in the solvent system will, of course, depend on the medicament to be administered. Different medicaments, such as naproxen, aspirin and acetaminophen, have different chemical structures and different affinities for various solvent combinations. Highly concentrated solutions of medicaments, such as aspirin and naproxen, require a solvent system tailored to the specific needs of the medicament.

[0041] The solution of the invention may be prepared through mixing of the ingredients. This mixing takes place preferably at an elevated temperature and with applied shear. While the applied shear does not necessarily allow for greater solubility of any ingredient, it appears to provide better stability of the solution during handling and storage. Preferably, the solvent is prepared first and the medicament is then added to the solvent. The salt is then also added slowly to help dissolve the medicament. It appears that if the salt is added too quickly, ionization of the medicament does not take place and the material does not form a successful solution. The process may be carried out in whole or in part in a nitrogen atmosphere if the presence of oxygen might discolor or otherwise damage any ingredient in the solution.

[0042] Preferred embodiments of the invention have been prepared as described in the examples below. A solution of polyethylene glycol 600 and, optionally, dimethyl isosorbide is prepared in a glass flask, and is stirred at about 250 rpm, and heated to about 50° C. (An acceptable solution may be prepared without dimethyl isosorbide.) The flask may then be deaerated with nitrogen. Acetaminophen or another medicament is added and a stopper is used to cover the flask. Next, the sodium propionate solution is added dropwise, using a metered flow control device. The formulation is again blanketed with nitrogen and then stirred at about 300 rpm with heat until clear, which usually requires from about 30 to about 120 minutes. Another preferred embodiment incorporates shear to help the materials to blend more quickly and thoroughly.

EXAMPLES

[0043] The following examples are intended to demonstrate some embodiments of the invention without limiting the scope or spirit of the invention. Due to rounding, total percentages for some of the formulations described below do not equal 100%. In some examples the amount of added propionate solution was recorded in mls. of solution added. This recorded number was converted to grams using an approximate density of 1.17 to 1.18

Example 1

[0044] A solution was prepared having the formulation set forth in Table 1 as follows. The polyethylene glycol, dimethyl isosorbide and soybean oil were combined in a 250 ml flask. This mixture was heated to about 45° C. and stirred at about 250 rpm. The flask was blanketed with nitrogen gas, and acetaminophen was added as quickly as possible to reduce discoloration of the solution. A solution containing the water and the sodium propionate was slowly added to the mixture. A clear, brown colored solution was obtained. Due to rounding, the percentages do not add up to 100%.

TABLE 1

Formulation of Example 1

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	25 g	25%
Dimethyl isosorbide	15 g	15%
Water	5 g	5%
Soybean oil	16 g	16%
Sodium propionate	5.5 g	5.5%
Acetaminophen	33 g	33%
Chlorpheniramine	0 g	0%
Pseudoephedrine	0 g	0%
Dextromethorphan	0 g	0%
Doxylamine succinate	0 g	0%
Propylene glycol	0 g	0%

Example 2

[0045] A formulation was prepared with the ingredients set forth in Table 2. The polyethylene glycol and dimethyl isosorbide were mixed, and a slurry of the sodium propionate and water was added to the mixture. This mixture was heated to 45° C. and stirred to dissolve the slurry. The acetaminophen was added in 5-gram portions, and complete solubility was obtained, providing a clear, light pink colored solution. Although some crystallization was observed upon cooling, only minimal precipitation had been observed after storage for ten days at room temperature.

TABLE 2

Formulation of Example 2

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	35 g	43%
Dimethyl isosorbide	5 g	6%
Water	4 g	5%
Soybean oil	0 g	0%
Sodium propionate	5 g	6%
Acetaminophen	32.5 g	40%
Chlorpheniramine	0 g	0%
Pseudoephedrine	0 g	0%

TABLE 2-continued

Formulation of Example 2

Ingredient	Amount	Weight Percent (%)
Dextromethorphan	0 g	0%
Doxylamine succinate	0 g	0%
Propylene glycol	0 g	0%

Example 3

[0046] A formulation was prepared with the ingredients set forth in Table 3. Polyethylene glycol 600 and dimethyl isosorbide were combined, heated to 45° C., and stirred. The sodium propionate was mixed with the water to form a solution and added to the solvents. Acetaminophen was added, and a clear, pink colored solution was obtained.

TABLE 3

Formulation of Example 3

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	21 g	20%
Dimethyl isosorbide	6 g	6%
Water	15 g	14%
Soybean oil	0 g	0%
Sodium propionate	12 g	11%
Acetaminophen	51 g	49%
Chlorpheniramine	0 g	0%
Pseudoephedrine	0 g	0%
Dextromethorphan	0 g	0%
Doxylamine succinate	0 g	0%
Propylene glycol	0 g	0%

Example 4

[0047] A formulation was prepared with the ingredients set forth in Table 4. A solution of the sodium propionate in the water was prepared by mixing at room temperature until dissolved. The polyethylene glycol and the dimethyl isosorbide were put into a 125-ml glass-stoppered Erlenmeyer flask. The mixture was stirred and heated and blanketed with nitrogen. The acetaminophen was then added, and the sodium propionate solution was then added. A clear, pink colored solution was obtained. After placing the solution in a freezer for four hours the solution was removed and allowed to return to room temperature. No crystallization was observed.

TABLE 4

Formulation of Example 4

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	39.6 g	40%
Dimethyl isosorbide	6.2 g	6%
Water	10 g	10%
Soybean oil	0 g	0%
Sodium propionate	7.9 g	8%
Acetaminophen	33 g	34%
Chlorpheniramine	0 g	0%
Pseudoephedrine	0 g	0%
Dextromethorphan	0 g	0%
Doxylamine succinate	0 g	0%
Propylene glycol	1.8 g	2%

Example 5

[0048] A formulation was prepared with the ingredients set forth in Table 5. A sodium propionate solution was prepared by dissolving 40 grams of sodium propionate in 50 mls of water. Polyethylene glycol and dimethyl isosorbide were then placed in a 250-ml distillation flask, stirred and heated. The acetaminophen was then added and nitrogen was blown into the stopper of the flask to keep oxygen away from the solution. 20-21 ml of the propionate solution were then added to the flask and stirring continued until a clear, pink colored solution was obtained. This solution was blanketed with nitrogen, stoppered and frozen for 16 hours. The solution then returned to room temperature, and slight crystal formation was observed on the surface of the solution.

TABLE 5

Formulation of Example 5

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	42.4 g	39%
Dimethyl isosorbide	9.94 g	9%
Water	13.7 g	12%
Soybean oil	0 g	0%
Sodium propionate	11 g	10%
Acetaminophen	32.7 g	30%
Chlorpheniramine	0 g	0%
Pseudoephedrine	0 g	0%
Dextromethorphan	0 g	0%
Doxylamine succinate	0 g	0%
Propylene glycol	0 g	0%

Example 6

[0049] A formulation was prepared with the ingredients set forth in Table 6. A sodium propionate solution was prepared by dissolving 40 grams of sodium propionate in 50 mls of water. Polyethylene glycol and dimethyl isosorbide were then placed in a 250-ml distillation flask, stirred and heated. The acetaminophen was then added and nitrogen was blown into the stopper of the flask to keep oxygen away from the solution. 20-21 ml of the propionate solution were then added to the flask and stirring continued until a clear, pink colored solution was obtained. This solution was blanketed with nitrogen, stoppered and frozen for 16 hours. The solution was then returned to room temperature, and slight crystal formation was observed on the bottom of the solution.

TABLE 6

Formulation of Example 6

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	29.5 g	27%
Dimethyl isosorbide	19.9 g	19%
Water	13.7 g	13%
Soybean oil	0 g	0%
Sodium propionate	11 g	10%
Acetaminophen	33.2 g	31%
Chlorpheniramine	0 g	0%
Pseudoephedrine	0 g	0%
Dextromethorphan	0 g	0%
Doxylamine succinate	0 g	0%

TABLE 6-continued

Formulation of Example 6

Ingredient	Amount	Weight Percent (%)
Propylene glycol	0 g	0%

Example 7

[0050] A formulation was prepared with the ingredients set forth in Table 7. A sodium propionate solution was prepared by dissolving 40 grams of sodium propionate in 50 mls of water. Polyethylene glycol and dimethyl isosorbide were then placed in a 250-ml distillation flask, stirred and heated. The acetaminophen was then added and nitrogen was blown into the stopper of the flask to keep oxygen away from the solution. 20-21 ml of the propionate solution were then added to the flask and stirring continued until a clear, pink colored solution was obtained. This solution was blanketed with nitrogen, stoppered and frozen for 16 hours. The solution was then allowed to return to room temperature, and no crystal formation was observed.

TABLE 7

Formulation of Example 7

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	27.2 g	24%
Dimethyl isosorbide	28.8 g	25%
Water	13.7 g	12%
Soybean oil	0 g	0%
Sodium propionate	11 g	10%
Acetaminophen	33 g	29%
Chlorpheniramine	0 g	0%
Pseudoephedrine	0 g	0%
Dextromethorphan	0 g	0%
Doxylamine succinate	0 g	0%
Propylene glycol	0 g	0%

Example 8

[0051] A formulation was prepared with the ingredients set forth in Table 8. The polyethylene glycol and the dimethyl isosorbide were placed into a 250-ml distillation flask, heated to 50° C. and stirred. The chlorpheniramine was added and stirring continued until it was completely dissolved. The acetaminophen was then added and the flask was blanketed with nitrogen. 20 ml of a sodium propionate solution (600 g sodium propionate in 800 ml water) was added to the flask and the nitrogen blanket was reapplied. Stirring continued for about two hours. Pseudoephedrine was then added and stirring continued overnight. A cloudy, light yellow solution was obtained. An additional 5 ml of the sodium propionate solution was added, the solution was reheated and stirring continued until a clear, light orange colored solution was obtained.

TABLE 8

Formulation of Example 8

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	38.2 g	34%
Dimethyl isosorbide	12.9 g	11%
Water	15.1 g	12%
Soybean oil	0 g	0%
Sodium propionate	10.5 g	9%
Acetaminophen	37.6 g	31%
Chlorpheniramine	0.24 g	0.2%
Pseudoephedrine	3.2 g	2.8%
Dextromethorphan	0 g	0%
Doxylamine succinate	0 g	0%
Propylene glycol	0 g	0%

Example 9

[0052] A formulation was prepared with the ingredients set forth in Table 9. The polyethylene glycol was charged into a 250-ml distillation flask and heated to 50° C. and stirred. The acetaeminophen was added to the flask, and the flask was blanketed with nitrogen while stirring and heating continued. 30 mls of the sodium propionate solution were added, the nitrogen blanket was reapplied and stirring continued for two hours until a light pink solution was obtained. After the solution was kept in the freezer overnight and then placed in warm water some crystals appeared, so an additional 5 ml of the sodium propionate solution was added under heat and stirring to redissolve the crystals.

TABLE 9

Formulation of Example 9

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	50.1 g	40%
Dimethyl isosorbide	0 g	0%
Water	22.9 g	18%
Soybean oil	0 g	0%
Sodium propionate	18.4 g	15%
Acetaminophen	33.5 g	27%
Chlorpheniramine	0 g	0%
Pseudoephedrine	0 g	0%
Dextromethorphan	0 g	0%
Doxylamine succinate	0 g	0%
Propylene glycol	0 g	0%

Example 10

[0053] A formulation was prepared using the ingredients set forth in Table 10. The PEG-600 was added to a tared, 250-ml glass-stoppered flask and blanketed with nitrogen. The PEG-600 was heated to about 60° C. with stirring. The acetaminophen was then added slowly and the mixture was blanketed with nitrogen. Sodium propionate: solution was prepared by dissolving 500 grams of sodium propionate into 500 mls water. This solution was then added dropwise to the flask until a clear, yellow colored solution was obtained. The percentages do not add up to 100% due to rounding errors.

TABLE 10

Formulation of Example 10

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	54.8 g	54%
Dimethyl isosorbide	0	0%
Water	7.1 g	7%
Soybean oil	0	0%
Sodium propionate	7.1 g	7%
Acetaminophen	33.4 g	33%
Chlorpheniramine	0	0%
Pseudoephedrine	0	0%
Dextromethorphan	0	0%
Doxylamine succinate	0	0%
Propylene glycol	0	0%

Example 11

[0054] A formulation was prepared with the ingredients set forth in Table 11. A flask was charged with PEG-600 and heated to about 55° C. The PEG was blanketed with nitrogen and stirred with an impeller blade at about 200 rpm. Acetaminophen was slowly added over a 25-minute period to form a fully wetted white slurry. A 1:1 by weight sodium propionate solution (in water) was added to the mix dropwise at about 4 to 5 drops per minute while the slurry was maintained under nitrogen and while stirring continued at about 200 rpm. The temperature of the PEG was maintained at about 48° to about 55° C. A clear, pink colored solution was obtained. The pH of the sodium propionate solution was adjusted from 9.1 to 7.1 by the addition of a small amount of undiluted propionic acid. The percentages do not add up to 100% due to rounding errors.

TABLE 11

Formulation of Example 11

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	262 g	51%
Dimethyl isosorbide	0 g	0%
Water	38.4 g	7.5%
Soybean oil	0 g	0%
Sodium propionate solution	38.4 g	7.5%
Acetaminophen	170.5 g	33%
Chlorpheniramine	0 g	0%
Pseudoephedrine	0 g	0%
Dextromethorphan	0 g	0%
Doxylamine succinate	0 g	0%
Propylene glycol	0 g	0%

Example 12

[0055] A formulation was prepared with the ingredients set forth in Table 12. The PEG-600 was added to 250-ml glass-stoppered distillation flask. A stir bar was added to the flask, and the PEG was heated to about 60° C. with stirring. The pseudoephedrine was mixed with 1.5 ml water and dissolved in the PEG. The acetaminophen was then added slowly, and the temperature was lowered to 50-55° C. The flask was blanketed with nitrogen. A 1:1 by weight solution of sodium propionate in water was prepared. About 16 ml of the sodium propionate solution was added slowly to the flask over two hours. A clear, pink/orange colored solution was obtained. An additional 5 ml of the sodium propionate

solution was added after 24 hours to redissolve some crystals that had settled out overnight. The pH of the sodium propionate solution had been adjusted to 6.8 by the addition of undiluted propionic acid. Due to rounding errors, the percentages do not add up to 100%/

TABLE 12

Formulation of Example 12

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	51 g	45%
Dimethyl isosorbide	0 g	0%
Water	0 g	11%
Soybean oil	0 g	0%
Sodium propionate	12.4 g	11%
Acetaminophen	35 g	31%
Chlorpheniramine	0 g	0%
Pseudoephedrine	3 g	3%
Dextromethorphan	0 g	0%
Doxylamine succinate	0 g	0%
Propylene glycol	0 g	0%

Example 13

[0056] A formulation was prepared with the ingredients set forth in Table 13. The PEG-600 was added to 250-ml glass-stoppered distillation flask. A stir bar was added to the flask, and the PEG was heated to about 60° C. with stirring. The pseudoephedrine was mixed with 1.5 ml water and dissolved in the PEG. The acetaminophen was then added slowly, and the temperature was lowered to 50-55° C. The flask was blanketed with nitrogen. The 1:1 by weight sodium propionate solution was added slowly over two hours. A clear, pink colored solution was obtained. The pH of the sodium propionate solution was adjusted to 6.8 by the addition of undiluted propionic acid. The percentages do not add up to 100% due to rounding errors.

TABLE 13

Formulation of Example 13

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	50 g	48%
Dimethyl isosorbide	0 g	0%
Water	9.2 g	9%
Soybean oil	0 g	0%
Sodium propionate	7.7 g	7%
Acetaminophen	34 g	33%
Chlorpheniramine	0.25 g	0.2%
Pseudoephedrine	3 g	3%
Dextromethorphan	0 g	0%
Doxylamine succinate	0 g	0%
Propylene glycol	0 g	0%

Example 14

[0057] A formulation was prepared with the ingredients set forth in Table 14. The PEG-600 was added to 250-ml glass-stoppered distillation flask. A stir bar was added to the flask, and the PEG was heated to about 60° C. with stirring. The pseudoephedrine was mixed with 1.5 ml water and dissolved in the PEG. The acetaminophen was then added slowly, and the temperature was lowered to 50-55° C. The flask was blanketed with nitrogen. The 1:1 by weight sodium propionate solution was added slowly over about one hour. A clear, pink colored solution was obtained. The pH of the sodium propionate solution was adjusted to 6.8 by the addition of undiluted propionic acid. The percentages do not add up to 100% due to rounding errors.

TABLE 14

Formulation of Example 14

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	57 g	42.9%
Dimethyl isosorbide	0 g	0%
Water	12.7 g	10.6%
Soybean oil	0 g	0%
Sodium propionate solution	11.2 g	9.4%
Acetaminophen	35 g	29.4%
Chlorpheniramine	0 g	0%
Pseudoephedrine	3 g	2.5%
Dextromethorphan	0.15 g	0.1%
Doxylamine succinate	0 g	0%
Propylene glycol	0 g	0%

Example 15

[0058] A formulation was prepared with the ingredients set forth in Table 15. The PEG-600 was added to 250-ml glass-stoppered distillation flask. A stir bar was added to the flask, and the PEG was heated to about 60° C. with stirring. The pseudoephedrine was mixed with 1.5 ml water and dissolved in the PEG. The acetaminophen was then added slowly, and the temperature was lowered to 50-55° C. The flask was blanketed with nitrogen. The 1:1 by weight sodium propionate solution was added slowly over two hours. A clear, pink colored solution was obtained. The pH of the sodium propionate solution was adjusted to 6.8 by the addition of undiluted propionic acid. After 24 hours, some fine crystals appeared at the bottom of the flask. The percentages do not add up to 100% due to rounding errors.

TABLE 15

Formulation of Example 15

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	51 g	42.8%
Dimethyl isosorbide	0 g	0%
Water	15.1 g	12.7%
Soybean oil	0 g	0%
Sodium propionate	13.6 g	11.4%
Acetaminophen	36 g	30.2%
Chlorpheniramine	0.25 g	0.2%
Pseudoephedrine	3 g	2.5%
Dextromethorphan	0.16 g	0.1%
Doxylamine succinate	0 g	0%
Propylene glycol	0 g	0%

Example 16

[0059] A formulation was prepared with the ingredients set forth in Table 16. The PEG-600 was added to 250-ml glass-stoppered distillation flask. A stir bar was added to the flask, and the PEG was heated to about 60° C. with stirring. The pseudoephedrine was mixed with 1.5 ml water and dissolved in the PEG. The acetaminophen was then added slowly, and the temperature was lowered to 50-55° C. The flask was blanketed with nitrogen. 23 ml of a 1:1 by weight sodium propionate solution was added slowly over two hours. A clear, light orange colored solution was obtained.

The pH of the sodium propionate solution was adjusted to 6.8 by the addition of undiluted propionic acid. After 24 hours, some crystal had appeared on the bottom of the flask. The solution we reheated to 55° C. with stirring and an additional 4 ml of the sodium propionate solution were added. The percentages do not add up to 100% due to rounding errors.

TABLE 16

Formulation of Example 16

Ingredient	Amount	Weight Percent (%)
Polyethylene glycol 600	50 g	40.6%
Dimethyl isosorbide	0 g	0%
Water	017.4 g	14.1%
Soybean oil	0 g	0%
Sodium propionate	15.9 g	12.9%
Acetaminophen	36 g	29.2%
Chlorpheniramine	0 g	0%
Pseudoephedrine	3 g	2.4%
Dextromethorphan	0.16 g	0.1%
Doxylamine succinate	0.72 g	0.6%
Propylene glycol	0 g	0%

Example 17

[0060] A formulation was prepared with the ingredients set forth in Table 17. The ingredients were mixed and the sample was heated in a steam bath and swirled until dissolved. The potassium hydroxide was added as a solution of 6.8 g KOH in 100 mls of water. The sodium propionate was added as a solution of 500 g sodium propionate in 700 mls of water. A clear solution was obtained.

TABLE 17

Formulation of Example 17

Ingredient	Amount	Weight Percent (%)
Naproxen sodium	3.0033 g	21.67
Polyethylene Glycol 300	10.0332 g	72.40
Potassium hydroxide	6.66 mg	0.05
Sodium propionate	0.8153 g	5.88

[0061] In each of the above examples, the solutions obtained were stable, and the acetaminophen did not precipitate. Also, in each of the above examples, we observed no evidence of acetaminophen degradation. Assay values showed greater than 98% recovery after ten weeks stored at room temperature under nitrogen.

[0062] Several of the solutions of the examples have been successfully incorporated into soft gelatin capsules using techniques well known in the art.

[0063] The purpose of the above description is to illustrate some embodiments of the invention without implying a limitation. It will be apparent to those skilled in the art that various modifications and variations may be made in the apparatus or procedure of the invention without departing from the scope or spirit of the invention.

We claim:

1. A pharmaceutically acceptable solution comprising a medicament and a solvent system, wherein said solvent system comprises a low molecular weight polymeric material and a salt of an organic acid containing at least three carbon atoms.

2. The solution of claim 1, wherein said medicament is capable of forming a zwitterion.

3. The solution of claim 2, wherein said medicament is acetaminophen.

4. The solution of claim 1, wherein said medicament comprises at least about 25% by weight of said solution.

5. The solution of claim 1, wherein said polymeric material is selected from the group consisting of polymers of alkylene glycols, copolymers thereof, polymers of vinyl pyrollidones, copolymers thereof, glycerin, propylene glycol and mixtures and analogs thereof.

6. The solution of claim 1, wherein said polymeric material is selected from the group consisting of polymers and copolymers of ethylene glycol.

7. The solution of claim 6, wherein said polymeric material has an average molecular weight of less than about 1,500 daltons.

8. The solution of claim 1, wherein said polymeric material comprises from about 10% to about 70% by weight of the solution.

9. The solution of claim 1, wherein said salt is an alkali propionate.

10. The solution of claim 1, wherein said salt comprises from about 2% by weight to about 40% by weight of the solution.

11. The solution of claim 1, further comprising a cosolvent.

12. A gelcap for administering a medicament comprising an outer shell comprising gelatin fully or partially enclosing a solution comprising a medicament and a solvent system, wherein said solvent system comprises a low molecular weight polymeric material and a salt of an organic acid containing at least three carbon atoms.

13. The gelcap of claim 12, wherein said medicament is an analgesic.

14. The gelcap of claim 13, wherein said medicament is acetaminophen.

15. The gelcap of claim 12, wherein said medicament comprises at least about 25% by weight of said solution.

16. The gelcap of claim 12, wherein said polymeric material is selected from the group consisting of polymers of alkylene glycols, copolymers thereof, polymers of vinyl pyrollidones, copolymers thereof, glycerin, propylene glycol and mixtures and analogs thereof.

17. The gelcap of claim 12, wherein said polymeric material is selected from the group consisting of polymers and copolymers of ethylene glycol.

18. The gelcap of claim 17, wherein said polymeric material has a molecular weight of less than about 1,500 daltons.

19. The gelcap of claim 12, wherein said polymeric material comprises from about 10% to about 70% by weight of the solution.

20. The gelcap of claim 12, wherein said salt is an alkali propionate.

21. The gelcap of claim 12, wherein said salt comprises from about 2% by weight to about 40% by weight of the solution.

22. The gelcap of claim 12, further comprising a cosolvent.

23. A method of making a solution comprising the steps of: (a) preparing a solvent comprising a low molecular weight polymeric material; (b) adding a medicament to said solvent system to form a solution; and (c) blending a salt of an organic acid containing at least three carbon atoms with said polymeric material to form a solvent system.

24. The method of claim 23, further comprising the step of heating at least one of said solvent, said solvent system or said solution.

* * * * *

D4

US005541210A

United States Patent [19]

Cupps et al.

[11] Patent Number: 5,541,210

[45] Date of Patent: Jul. 30, 1996

[54] **5-(2-IMIDAZOLINYLAMINO) BENZIMIDAZOLE COMPOUNDS USEFUL AS ALPHA-2 ANDRENOCEPTOR AGONISTS**

[75] Inventors: **Thomas L. Cupps**, Oxford; **Sophie E. Bogdan**, Maineville, both of Ohio

[73] Assignee: **The Procter & Gamble Company**, Cincinnati, Ohio

[21] Appl. No.: **496,706**

[22] Filed: **Jun. 29, 1995**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 349,558, Dec. 8, 1994, Pat. No. 5,478,858, which is a continuation-in-part of Ser. No. 169,868, Dec. 17, 1993, abandoned.

[51] **Int. Cl.**[6] **A61K 31/415**

[52] **U.S. Cl.** **514/394**

[58] **Field of Search** 514/394

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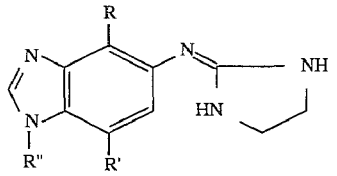
Primary Examiner—Kimberly Jordan

Attorney, Agent, or Firm—Richard A. Hake; Karen F. Clark; Milton B. Graff, IV

[57] **ABSTRACT**

The subject invention involves compounds having the following structure:



wherein:

(a) R is unsubstituted C_1–C_3 alkanyl or alkenyl;

(b) R' is selected from hydrogen; unsubstituted C_1–C_3 alkanyl or alkenyl; unsubstituted C_1–C_3 alkylthio or alkoxy; hydroxy; thiol; cyano; and halo; and

(c) R' is selected from hydrogen, methyl, ethyl and i-propyl.

The subject invention also involves pharmaceutical compositions containing such novel compounds, compositions thereof and the use of such compounds for preventing or treating respiratory, ocular and/or gastrointestinal disorders.

15 Claims, No Drawings

5-(2-IMIDAZOLINYLAMINO)BENZIMIDAZOLE COMPOUNDS USEFUL AS ALPHA-2 ANDRENOCEPTOR AGONISTS

This is a continuation-in-part of application Ser. No. 08/349,558, filed on Dec. 8, 1994, now U.S. Pat. No. 5,478,858 which is a continuation-in-part of Ser. No. 08/169,868, filed on Dec. 17, 1993, now abandoned.

TECHNICAL FIELD

The subject invention relates to certain substituted 5-(2-imidazolinylamino)benzimidazole compounds. The compounds have been found to be alpha adrenoceptor agonists and are useful for treatment of one or more of respiratory disorders.

BACKGROUND OF THE INVENTION

Information regarding alpha adrenergic receptors, agonists and antagonists, in general, and regarding compounds related in structure to those of the subject invention are disclosed in the following references: Timmermans, P.B.M.W.M., A. T. Chiu & M.J.M.C. Thoolen, "12.1 α-Adrenergic Receptors", *Comprehensive Medicinal Chemistry,* Vol. 3, Membranes & Receptors, P. G. Sammes & J. B. Taylor, eds., Pergamon Press (1990), pp. 133–185; Timmermans, P.B.M.W.M. & P. A. van Zwieten," α-Adrenoceptor Agonists and Antagonists", *Drugs of the Future,* Vol. 9, No. 1, (January, 1984), pp. 41–55; Megens, A.A.H.P., J. E. Leysen, F. H. L. Awouters & C. J. E. Niemegeers, "Further Validation of in vivo and in vitro Pharmacological Procedures for Assessing the α_1 and α_2-Selectivity of Test Compounds: (2) α-Adrenoceptor Agonists", *European Journal of Pharmacology,* Vol. 129 (1986), pp. 57–64; Timmermans, P.B.M.W.M., A. de Jonge, M.J.M.C. Thoolen, B. Wilfred, H. Batink & P. A. van Zwieten, "Quantitative Relationships between α-Adrenergic Activity and Binding Affinity of α-Adrenoceptor Agonists and Antagonists", *Journal of Medicinal Chemistry,* Vol. 27 (1984) pp. 495–503; van Meel, J. C. A., A. de Jonge, P.B.M.W.M. Timmermans & P. A. van Zwieten, "Selectivity of Some Alpha Adrenoceptor Agonists for Peripheral Alpha-1 and Alpha-2 Adrenoceptors in the Normotensive Rat", *The Journal of Pharmacology and Experimental Therapeutics,* Vol. 219, No. 3 (1981), pp. 760–767; Chapleo, C. B., J. C. Doxey, P. L. Myers, M. Myers, C. F. C. Smith & M. R. Stillings, "Effect of 1,4-Dioxanyl Substitution on the Adrenergic Activity of Some Standard α-Adrenoreceptor Agents", *European Journal of Medicinal Chemistry,* Vol. 24 (1989), pp. 619–622; Chapleo, C. B., R. C. M. Butler, D. C. England, P. L. Myers, A. G. Roach, C. F. C. Smith, M. R. Stillings & I. F. Tulloch, "Heteroaromatic Analogues of the α_2-Adrenoreceptor Partial Agonist Clondine", *J. Med. Chem.,* Vol. 32 (1989), pp. 1627–1630; Clare, K. A., M. C. Scrutton & N. T. Thompson, "Effects of α_2-Adrenoceptor Agonists and of Related Compounds on Aggregation of, and on Adenylate Cyclase Activity in, Human Platelets", *Br. J. Pharmac.,* Vol. 82 (1984), pp. 467–476; U.S. Pat. No. 3,890,319 issued to Danielewicz, Snarey & Thomas on Jun. 17, 1975; and U.S. Pat. No. 5,091,528 issued to Gluchowski on Feb. 25, 1992. However, many compounds related in structure to those of the subject invention do not provide the activity and specificity desirable when treating respiratory, ocular or gastrointestinal disorders.

It is particularly relevant to the subject invention that compounds found to be effective nasal decongestants are frequently found to have undesirable side effects, such as causing hypertension and insomnia, particularly when administered systemically. There is a need for new drugs which provide relief from nasal congestion without causing these undesirable side effects.

It is an object of the subject invention to provide novel compounds having substantial activity in preventing or treating nasal congestion.

It is a further object of the subject invention to provide such compounds which do not cause hypotension, drowsiness, hypertension, insomnia or other undesirable side effects, particularly when administered systemically.

It is also an object of the subject invention to provide novel compounds for treating cough, chronic obstructive pulmonary disease (COPD) and/or asthma.

It is also an object of the subject invention to provide novel compounds for treating glaucoma and/or diarrhea.

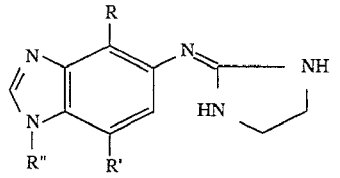
It is a still further object of the subject invention to provide such compounds which have good activity from peroral and/or topical and/or intranasal dosing.

It is an object of the subject invention to provide such novel compounds in pharmaceutically acceptable compositions.

It is an object of the subject invention to provide such novel compounds in pharmaceutically acceptable compositions in combinations with other active which provide further theraputic benefit.

SUMMARY OF THE INVENTION

The subject invention relates compounds having the following structure:



wherein:

(a) R is unsubstituted C_1–C_3 alkanyl or alkenyl;

(b) R' is selected from hydrogen; unsubstituted C_1–C_3 alkanyl or alkenyl; unsubstituted C_1–C_3 alkylthio or alkoxy; hydroxy; thiol; cyano; and halo; and

(c) R" is selected from hydrogen, methyl, ethyl and i-propyl; pharmaceutical compositions containing such novel compounds, and the use of such compounds for preventing or treating other respiratory, ocular and/or gastrointestinal disorders.

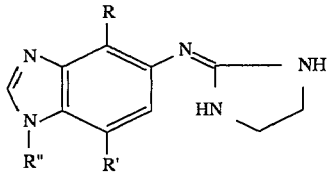
DETAILED DESCRIPTION OF THE INVENTION

As used herein, "alkanyl" means a saturated hydrocarbon substituent, straight or branched chain, unsubstituted or substituted. As used herein, "alkenyl" means a hydrocarbon substituent with one double bond, straight or branched chain, unsubstituted or substituted. As used herein, "alkylthio" means a substituent having the structure Q—S—, where Q is alkanyl or alkenyl.

As used herein, "alkoxy" means a substituent having the structure Q—O—, where Q is alkanyl or alkenyl.

Compounds

The subject invention involves compounds having the following structure:

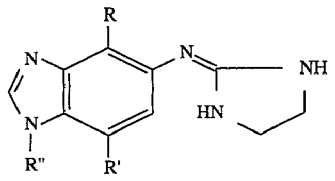


In the above structure, R is unsubstituted alkanyl or alkenyl having from 1 to about 3 carbon atoms. R is preferably alkanyl. R is most preferably methyl or ethyl.

In the above structure, R' is selected from hydrogen; unsubstituted alkanyl or alkenyl having from 1 to about 3 carbon atoms; unsubstituted alkylthio or alkoxy having from 1 to about 3 carbon atoms; hydroxy; thiol; cyano; and halo. R' is preferably hydrogen. R' is also preferably alkanyl, more preferably methyl or ethyl, most preferably methyl. R' which is alkylthio or alkoxy is preferably saturated, also preferably C_1 or C_2, more preferably methylthio or methoxy. R' which is halo is preferably chloro or bromo or fluoro, more preferably chloro or especially fluoro.

In the above structure, R" is selected from hydrogen, methyl, ethyl and i-propyl. R" is preferably hydrogen, methyl or ethyl, more preferably hydrogen or methyl, most preferably hydrogen.

Preferred compounds of the subject invention have the following structure:



where R, R' and R" are as indicated in the following table:

Compound No.	R	R'	R"
1	CH_3	H	H
2	CH_2CH_3	H	H
3	CH_3	CH_3	H
4	CH_3	H	CH_3
5	CH_3	F	H

The compounds of the subject invention are particularly useful for the treatment of nasal congestion associated with allergies, colds, and other nasal disorders with associated nasal congestion, as well as their sequelae (for example, sinusitis and otitis). At the same time, it has been found that undesired side effects, such as hypotension, drowsiness, hypertension, or insomnia can often be avoided. While not limited to a particular mechanism of action, the subject compounds are believed to provide advantages in the treatment of nasal decongestion over related compounds through their ability to interact with alpha-2 adrenoceptors. The subject compounds have been found to be alpha-2 adrenoceptor agonists which cause constriction of peripheral vascular beds in the turbinates.

Particular subject compounds have no or only weak alpha-1 agonist activity, and have little or no effect on the central nervous system, even when dosed systemically.

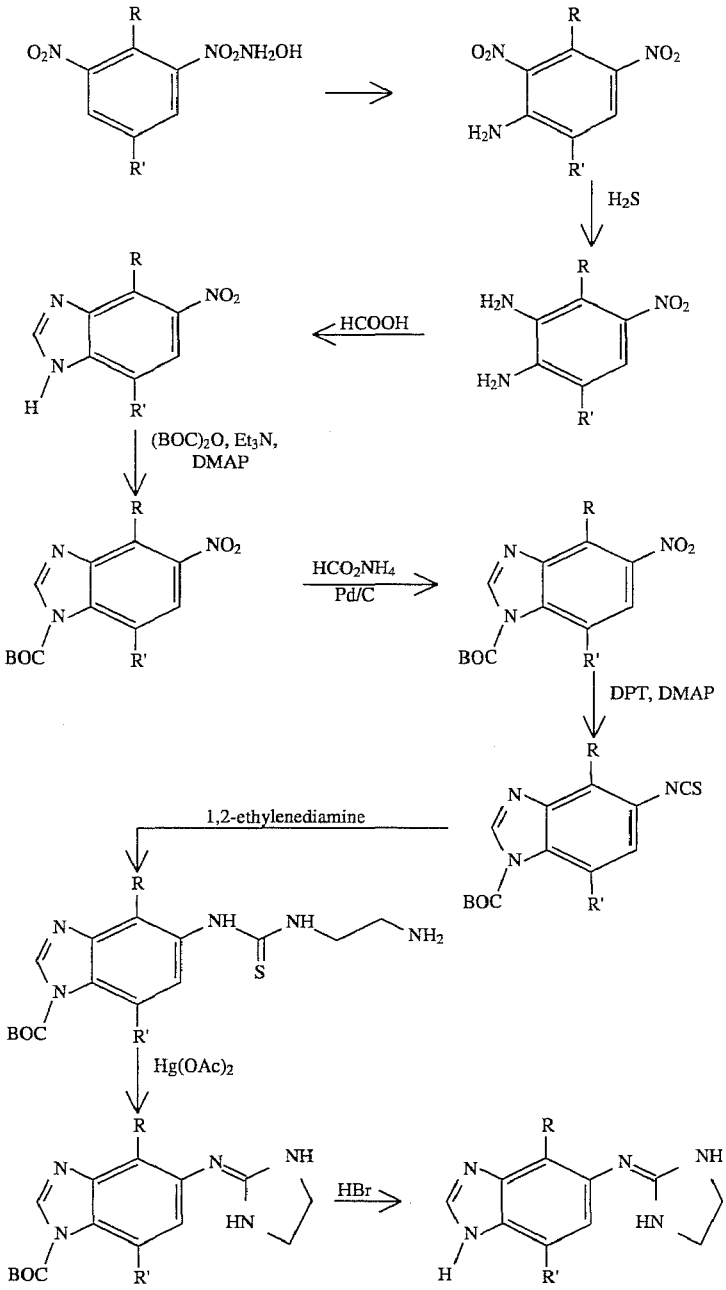
The compounds of the subject invention are also useful for the treatment of ocular disorders associated with increased intraocular pressure, such as glaucoma. The compounds are administered either perorally, or topically as drops, gels or creams directly to the surface of the mammalian eye.

The compounds of the subject invention are also useful for controlling gastrointestinal motility disorders, such as diarrhea, by antimotility and antisecretory actions on the gastrointestinal tract.

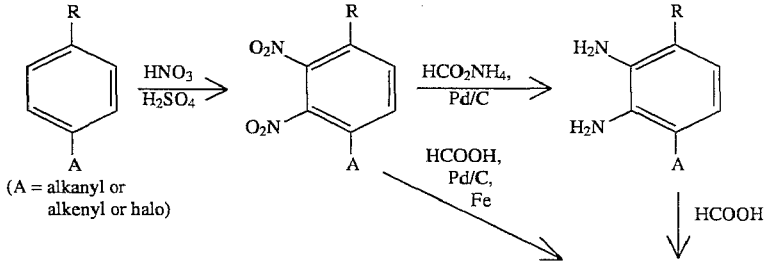
The pharmacological activity and selectivity of the subject compounds can be determined using published test procedures. The alpha-2 selectivity of the compounds is determined by measuring receptor binding affinities and in vitro functional potencies in a variety of tissues known to possess alpha-2 and/or alpha-1 receptors. (See, e.g., *The Alpha- 2 Adrenergic Receptors,* L. E. Limbird, ed., Humana Press, Clifton, N.J.) The following in vivo assays are typically conducted in rodents or other species. Central nervous system activity is determined by measuring locomotor activity as an index of sedation. (See, e.g., Spyraki, C. & H. Fibiger, "Clonidine-induced Sedation in Rats: Evidence for Mediation by Postsynaptic Alpha-2 Adrenoreceptors", *J. Neural. Trans.,* Vol. 54 (1982), pp. 153–163). Nasal decongestant activity is measured using rhinomanometry as an estimate of nasal airway resistance. (See, e.g., Salem, S. & E. Clemente, "A New Experimental Method for Evaluating Drugs in the Nasal Cavity", *Arch. Otolarynng,* Vol. 96 (1972), pp. 524–529). Antiglaucoma activity is determined by measuring intraocular pressure. (See, e.g., Potter, D., "Adrenergic Pharmacology of Aqueous Human Dynamics", *Pharmacol. Rev.,* Vol. 13 (1981), pp. 133–153). Antidiarrheal activity is determined by measuring the ability of the compounds to inhibit prostaglandin-induced diarrhea. (See, e.g., Thollander, M., P. Hellstrom & T. Svensson, "Suppression of Castor Oil-Induced Diarrhea by Alpha-2 Adrenoceptor Agonists", *Aliment. Pharmacol. Therap.,* Vol. 5 (1991), pp. 255–262). Antiasthma activity is determined by measuring the effect of the compound on bronchoconstriction associated with pulmonary challenges such as inhaled antigens. (See, e.g., Chang, J. J. Musser & J. Hind, "Effects of a Novel Leukotriene D_4 Antagonist with 5-Lipoxygenase and Cyclooxygenase Inhibitory Activity, Wy-45,911, on Leukotriene-D_4- and Antigen-Induced Bronchoconstriction in Guinea Pig", *Int. Arch. Allergy Appl. Immun.,* Vol. 86 (1988), pp. 48–54; and Delehunt, J., A. Perruchound, L. Yerger, B. Marchette, J. Stevenson & W. Abraham, "The Role of Slow-Reacting Substance of Anaphylaxis in the Late Bronchial Response After Antigen Challenge in Allergic Sheep", *Am. Rev. Respir. Dis.,* Vol. 130 (1984), pp. 748–754). Activity in cough is determined by measuring the number and latency of the cough response to respiratory challenges such as inhaled citric acid. (See, e.g., Callaway, J. & R. King, "Effects of Inhaled Alpha-2-Adrenoceptor and $GABA_B$ Receptor Agonists on Citric Acid-Induced Cough and Tidal Volume Changes in Guinea Pigs", *Eur. J. Pharmacol.,* Vol. 220 (1992), pp. 187–195).

The compounds of the subject invention are synthesized using the following general procedures:

Scheme 1



Scheme 2



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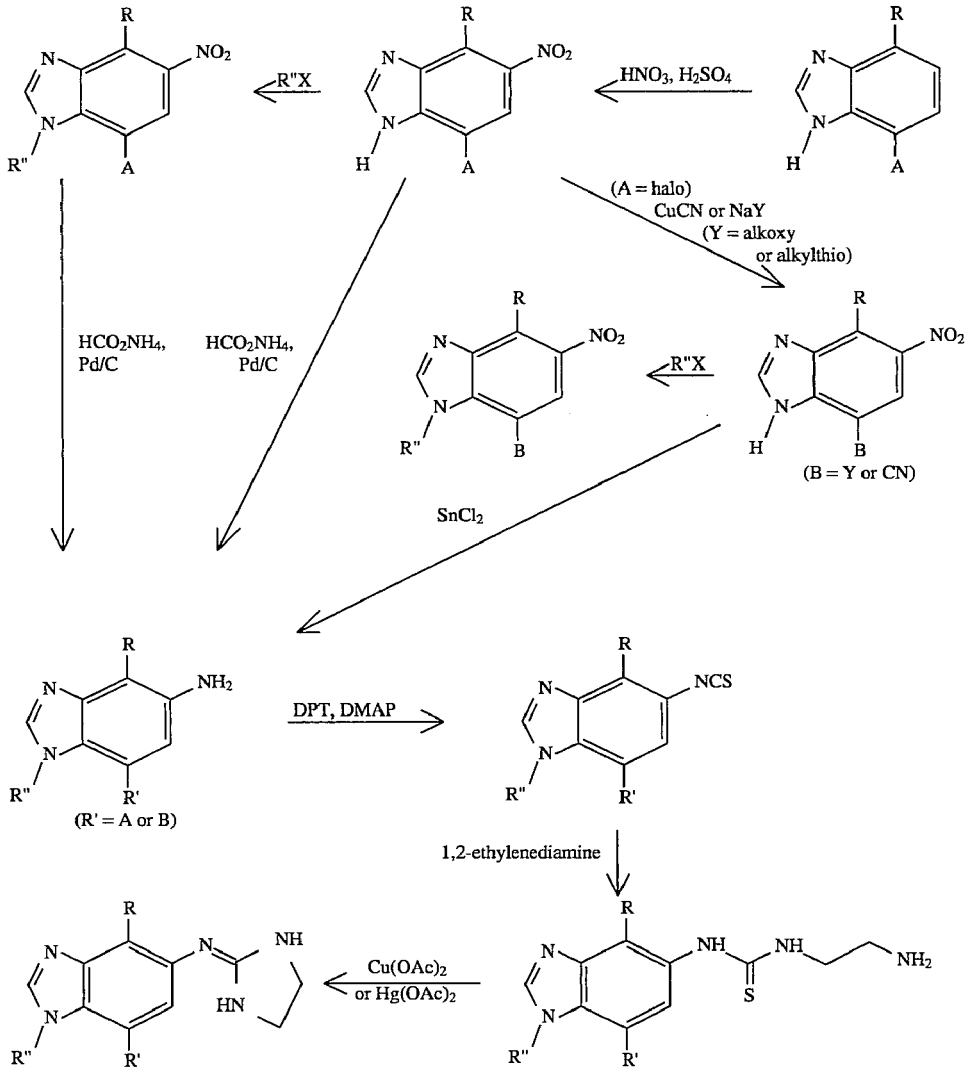
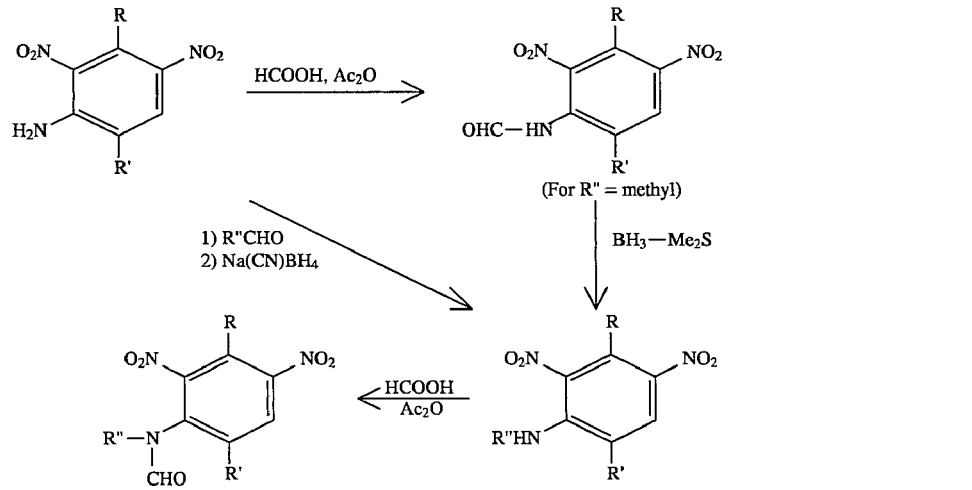
Scheme 2



Scheme 3



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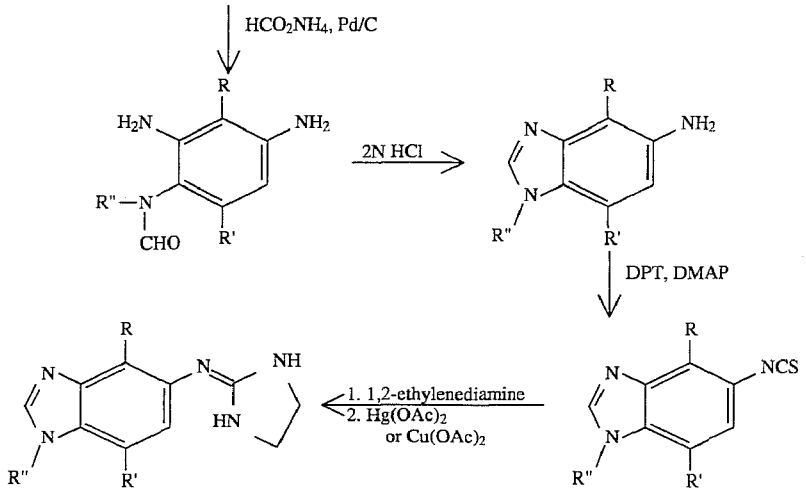
Scheme 3



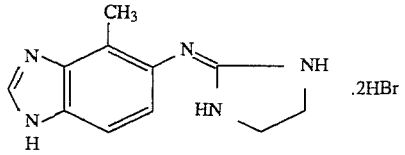
In the above schemes, where R' is alkoxy or alkylthio, the corresponding hydroxy or thiol compounds are derived from the final compounds by using a standard dealkylating procedure (Bhatt, et al., "Cleavage of Ethers", *Synthesis*, 1983, pp. 249–281).

Synthesis Examples

The following non-limiting examples provide details for the synthesis of 5-imidazolinylaminobenzimidazoles:

EXAMPLE 1

Synthesis of 4-methyl-5-(2-imidazolinylamino) benzimidazole dihydrobromide:



2,3-diamino-6-nitrotoluene. To a solution 3-methyl-2,4-dinitroaniline (30 g) in boiling ethanol (750 mL) is added dropwise over 90 minutes a solution of sodium sulfide nonahydrate (109.6 g) in water (750 mL). At the end of the addition, the mixture is refluxed for 30 minutes then poured into ice (2000 g) and allowed to stand until all the ice has melted. The mixture is then extracted with methylene chloride and the organic layer is dried over magnesium sulfate and rotary evaporated. The residue is purified by flash chromatography on silica gel, eluting with methylene chloride to afford 2,3 -diamino-6-nitrotoluene as an orange solid.

4-Methyl-5-nitrobenzimidazole. A mixture of 2,3-diamino-6-nitrotoluene (11.81 g), formic acid (88%, 390 mL) and 12N HCl (38 mL) is heated to reflux for 1 hour. The resulting mixture is cooled to room temperature and rotary evaporated. The residue is diluted with water (200 mL), then basified with ammonium hydroxide (28–30%). The suspension is extracted with ethyl acetate (3×200 mL). The combined extracts are dried over magnesium sulfate ($MgSO_4$) and evaporated to afford 4-methyl-5-nitrobenzimidazole as an orange solid.

1-tert-Butoxycarbonyl-4-methyl-5-nitrobenzimidazole. A suspenion of 4-methyl-5-nitrobenzimidazole (11.25 g), di-tert-butyl-dicarbonate (21.58 g), triethylamine (11.7 mL) and 4-dimethylaminopyridine (DMAP) (0.1 g) in a mixture of methanol (800 mL) and ethyl acetate (400 mL) is stirred at room temperature overnight. The mixture is rotary evaporated and the residue purified by flash chromatography on silica gel, eluting with 10% ethyl acetate in hexane. The product-containing fractions are combined and rotary evaporated to afford a white solid contaminated with a yellow oil. The solid is dissolved in methylene chloride (CH_2Cl_2) and enough hexane is added to cause precipitation. The solid is filtered and washed with 50% methylene chloride/hexane. The filtrate is rotary evaporated and the process repeated until no more clean white solid is obtained by precipitation. The combined solid fractions are dried in vacuo to afford 1 -tert-butoxycarbonyl-4-methyl-5-nitrobenzimidazole as a white solid.

5-Amino-1-tert-butoxycarbonyl-4-methylbenzimidazole. To a solution of 1-tert-butoxycarbonyl-4-methyl-5-nitrobenzimidazole (8 g) in methanol (40 mL)/ethyl acetate (400 mL)is added palladium-on-carbon (Pd/C) (10%, 0.5 g) and ammonium formate (7.27g). The mixture is stirred at 50° C. for 2 hours, then filtered on Celite, with methanol wash of the solids. The filtrate is rotary evaporated and the residue partitioned between water and ethyl acetate. The organic layer is washed with saturated ammonium chloride, dried over magnesium sulfate, filtered and rotary evaporated to afford pure 5-amino-1-tert-butoxycarbonyl-4-methylbenzimidazole as an off-white solid.

1-tert-Butoxycarbonyl-4-methyl-5-benzimidazolyl-isothiocyanate. To a solution of di-2-pyridyl thionocarbonate (DPT) (14.3 g) and 4-dimethylaminopyridine (0.1 g) in CH_2Cl_2 (500 mL) is added dropwise over 30 minutes a solution of 5-amino-1-tert-butoxycarbonyl-4-methylbenzimidazole (7.82 g) in CH_2Cl_2 (250 mL). The mixture is stirred for 15 minutes at room temperature then rotary evaporated. The residue is purified by flash chromatography on silica gel, eluting with 10% ethyl acetate/hexane to afford 1-tert-butoxycarbonyl-4-methyl-5-benzimidazolylisothiocyanate as a white solid.

N-(1-tert-Butoxycarbonyl-4-methyl-5-benzimidazolyl)-N'-2-aminoethylthiourea. A solution of 1-tert-butoxycarbonyl-4-methyl-5-benzimidazolylisothiocyanate (7.0 g) in

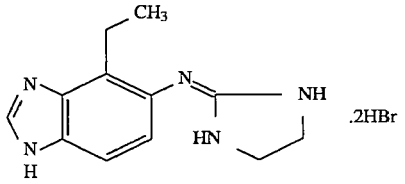
CH_2Cl_2 (600 mL) is added dropwise over 45 minutes to ethylenediamine (8 mL) in solution in CH_2Cl_2 (200 mL). The mixture is stirred for 3 hours at room temperature. Ether (150 mL) is added to the suspension and the mixture is stirred for 10 minutes at room temperature. The solid is filtered. The filtrate is rotary evaporated, the residue diluted with CH_2Cl_2 and reprecipitated with ether to afford a second crop. The combined solids are dried overnight in vacuo to afford N-(1 -tert-butoxycarbonyl-4-methyl-5-benzimidazolyl)-N'-2-aminoethylthiourea as a white solid.

1-tert-Butoxycarbonyl-4-methyl-5-(2-imidazolinylamino)benzimidazole. A mixture of N-(1-tert-butoxycarbonyl-4-methyl-5 -benzimidazolyl)-N'-2-aminoethylthiourea (2.89 g) and mercuric acetate (3.32 g) in methanol (200 mL)/chloroform (100 mL) is stirred at room temperature for 2 hours. The resulting black mixture is filtered on Celite and the filtrate rotary evaporated. The residue is purified by flash chromatography on a short pad of silica gel, eluting with 10% methanol/chloroform containing 1% ammonium hydroxide. The product-containing fractions are collected and rotary evaporated to afford 1 -tert-butoxycarbonyl-4-methyl-5-(2-imidazolinylamino)benzimidazole as a white solid.

4-Methyl-5-(2-imidazolinylamino)benzimidazole dihydrobromide. To a solution of 1-tert-butoxycarbonyl-4-methyl-5-(2-imidazolinylamino)benzimidazole (2.40 g) in glacial acetic acid (50 mL) is added a solution of hydrobromic acid in glacial acetic acid (30%, 6 mL). The mixture is stirred at room temperature and gas evolution is monitored. After the gas evolution has stopped (about 1 hour), the precipitate is filtered and washed with ether. The solid is recrystallized from methanol/ether and dried in vacuo to afford 4-methyl-5-(2-imidazolinylamino)benzimidazole dihydrobromide as a pale rose solid.

EXAMPLE 2

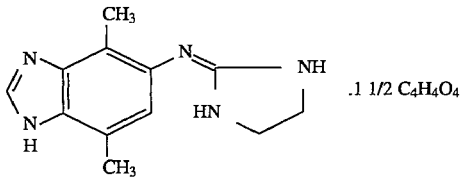
Synthesis of
4-ethyl-5-(2-imidazolinylamino)benzimidazole
dihydrobromide:



4-ethyl-5-(2-imidazolinylamino)benzimidazole dihydrobromide is made in the same manner as 4-methyl-5-(2-imidazolinylamino)benzimidazole dihydrobromide (see Example 1) except that 2-amino-3-ethyl-4-nitroaniline is used in place of 2,3-diamino-6-nitrotoluene.

EXAMPLE 3

Synthesis of
4,7-Dimethyl-5-(2-imidazolinylamino)benzimidazole
sesquifumarate:



4,7-Dimethylbenzimidazole. A mixture of 2,3-diamino-p-xylene (5.1 g), formic acid (88%, 200 mL) and 12N HCl (20 mL) is heated to reflux for 3 hours. The resulting mixture is cooled to room temperature and rotary evaporated. The residue is diluted with water (100 mL), then basified with ammonium hydroxide (28–30%). The suspension is extracted with ethyl acetate (3×100 mL). The combined extracts are dried over $MgSO_4$ and rotary evaporated to afford 4,7-dimethylbenzimidazole as a yellow solid.

4,7-Dimethyl-5-nitrobenzimidazole. To a cold (ice bath) solution of 4,7-dimethylbenzimidazole (1 g) in concentrated sulfuric acid (8 mL) is added dropwise concentrated nitric acid (0.37 mL), over 50 minutes. The mixture is stirred an additional 30 minutes in the ice bath, then poured into a mixture of crushed ice (30 mL) and ammonium hydroxide (30 mL). The resulting mixture is extracted with ethyl acetate. The extract is dried over $MgSO_4$ and rotary evaporated to afford 4,7-dimethyl-5-nitrobenzimidazole as a dark tan solid.

5-Amino-4,7-dimethylbenzimidazole. To a solution of 4,7-dimethyl-5-nitrobenzimidazole (1.17 g) in methanol (150 mL) is added Pd/C (10%, 0.16 g) and ammonium formate (1.31 g). The mixture is stirred at room temperature overnight, then filtered on Celite, with methanol wash of the solids. The filtrate is rotary evaporated and the residue partitioned between water and ethyl acetate. The organic layer is washed with saturated ammonium chloride, dried over magnesium sulfate, filtered and rotary evaporated to afford 5-amino-4,7-dimethylbenzimidazole as a foamy reddish solid.

4,7-Dimethyl-5-benzimidazolylisothiocyanate. To a solution of di-2-pyridyl thionocarbonate (2.29 g) and 4-dimethylaminopyridine (0.03 g) in CH_2Cl_2 (150 mL) is added dropwise over 30 minutes a solution of 5-amino- 4,7-dimethylbenzimidazole (0.816 g) in methanol (50 mL). The mixture is stirred for 3 hours at room temperature, then rotary evaporated. The residue is purified by flash chromatography on silica gel, eluting with a gradient of 50% to 80% ethyl acetate/hexane to afford 4,7-dimethyl-5-benzimidazolylisothiocyanate as a white solid.

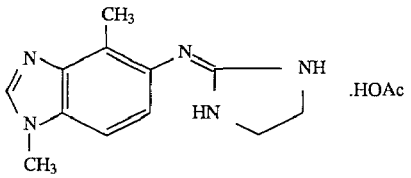
N-(4,7-Dimethyl-5-benzimidazolyl)-N'-2-aminoethylthiourea. A solution of 4,7-dimethyl-5-benzimidazolylisothiocyanate (0.59 g) in CH_2Cl_2 (50 mL)/methanol (5 mL) is added dropwise over 20 minutes to ethylenediamine (1 mL) in solution in CH_2Cl_2 (150 mL). The mixture is stirred for 2 hours at room temperature. The resulting suspension is filtered and the solid is dried overnight in vacuo to afford N-(4,7-dimethyl-5 -benzimidazolyl)-N'-2-aminoethylthiourea as a white solid.

4,7-Dimethyl-5-(2-imidazolinylamino)benzimidazole sesquifumarate. A mixture of N-(4,7-dimethyl-5-benzimidazolyl)-N'-2-aminoethylthiourea (0.77 g) and cupric acetate

(0.81 g) in methanol (100 mL) is stirred at 65°–70° C. for 40 minutes. The mixture is cooled to room temperature, $NaHS.xH_2O$ is added and the resulting mixture is stirred for 10 minutes at room temperature. The mixture is acidified to pH=3 with 1N HCl and filtered on Celite. The filtrate is basified to pH=9 with 50% sodium hydroxide and rotary evaporated. The syrupy residue is diluted with water (20 mL) and lyophilized. The solid residue is purified by flash chromatography on a short pad of silica gel, eluting first with 10% methanol/chloroform containing 0.1% ammonium hydroxide, then 30% methanol/chloroform containing 1% ammonium hydroxide. The product-containing fractions are collected and rotary evaporated. The residue is diluted with water (5 mL) and lyophilized to afford 4,7-dimethyl-5-(2-imidazolinylamino)benzimidazole as a yellow glassy solid. A fumarate salt is obtained by treating a solution of 4,7 -dimethyl-5-(2-imidazolinylamino)benzimidazole in methanol (20 mL) with fumaric acid (0.278 g). The mixture is heated to achieve solubilization, then cooled to room temperature. The precipitate is filtered and recrystallized twice from methanol/water to afford 4,7-dimethyl-5-(2-imidazolinylamino)benzimidazole sesquifumarate.

EXAMPLE 4

Synthesis of 1,4-Dimethyl-5-(2-imidazolinylamino) benzimidazole.HOAc:



2,4-Dinitro-3-methyl-formanilide. To a solution of 2,4-dinitro-3-methylaniline (2 g) in formic acid (99%, 10 mL) heated at 55° C., is added dropwise acetic anhydride (2.5 mL), over 15 minutes. The mixture is stirred for 1 hour at 55° C. then cooled to room temperature and rotary evaporated. The residue is diluted with ethyl acetate (100 mL), washed with saturated $NaHCO_3$, dried over magnesium sulfate and rotary evaporated. The residue is purified by flash chromatography, eluting with chloroform, to afford 2,4-dinitro-3-methyl-formanilide as a white solid.

N,3-Dimethyl-2,4-dinitroaniline. To a solution of 2,4-dinitro-3-methylformanilide (1.15 g) in dry tetrahydrofuran (40 mL) is added borane-dimethyl sulfide complex (1.21 mL). The mixture is refluxed for 2 hours, then cooled in an ice bath; methanol (30 mL) is added and the stirring is maintained for 1 hour at 0° C. The mixture is acidified to pH=2 with concentrated HCl and heated to reflux for 1 hour, diluted with methanol (70 mL) and rotary evaporated. The solid residue is suspended in water (150 mL) and basified to pH=12 with concentrated NaOH. The mixture is extracted with chloroform, and the organic layer is dried over potassium carbonate and rotary evaporated. The residue is purified by flash chromatography on silica gel, eluting with 25% ethyl acetate/hexane to afford N,3-dimethyl-2,4-dinitroaniline as an orange solid.

N,3-Dimethyl-2,4-dinitroformanilide. To a solution of N,3-dimethyl- 2,4-dinitroaniline (0.45 g) in formic acid (99%, 10 mL)/chloroform (4 mL) heated to 55° C., is added dropwise, acetic anhydride (1 mL), in two portions at 1 hour intervals. The mixture is stirred for 5 hours at 55° C., then cooled to room temperature, poured into 1N NaOH (50 mL) and basified to pH=12 with conc. NaOH. The mixture is extracted with methylene chloride, and the organic layer is dried over magnesium sulfate and rotary evaporated. The residue is purified by flash chromatography, eluting with chloroform, to afford N,3-dimethyl-2,4-dinitroformanilide as a white solid.

2,4-Diamino-N,3-dimethylformanilide. To a solution of N,3-dimethyl- 2,4-dinitroformanilide (0.44 g) in methanol (30 mL)/ethyl acetate (10 mL) is added palladium-on-carbon (10%, 95 mg) and ammonium formate (0.93 g), and the mixture is stirred for 2 hours at room temperature. The mixture is filtered on Celite, with methanol wash of the solids, and the filtrate is rotary evaporated. The residue is partitioned between methylene chloride and water. The aqueous layer is extracted 4 times with methylene chloride. The combined extracts are dried over magnesium sulfate and rotary evaporated to afford 2,4-diamino-N,3-dimethylformanilide as a brown solid.

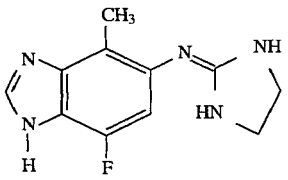
5-Amino-1,4-dimethylbenzimidazole. A suspension of 2,4-diamino-N, 3-dimethylformanilide (0.24 g) in 2N HCl (10 mL) is heated to reflux for 1.5 hours. The mixture is diluted with water (50 mL), basified with 1N NaOH and extracted with ethyl acetate. The organic layer is dried over magnesium sulfate and rotary evaporated to afford 5-amino-1,4-dimethylbenzimidazole.

1,4-Dimethyl-5-benzimidazolylisothiocyanate. To a solution of di-2-pyridyl thionocarbonate (494 mg) and 4-dimethylaminopyridine (0.01 g) in methylene chloride (40 mL) is added dropwise over 30 minutes, a solution of 5-amino-1,4-dimethylbenzimidazole (176 mg) in methylene chloride (20 mL). The mixture is stirred for 3 hours at room temperature, then rotary evaporated. The residue is purified by flash chromatography on silica gel, eluting with 50% ethyl acetate/hexane, to afford 1,4-dimethyl-5 -benzimidazolyl-isothiocyanate as a white solid.

1,4-Dimethyl-5-(2-imidazolinylamino)benzimidazole.HOAc. A solution of 1,4-dimethyl-5-benzimidazolyl-isothiocyanate (210 mg) in methylene chloride (40 mL) is added dropwise over 20 minutes to ethylenediamine (0.35 mL) in solution in methylene chloride (100 mL). The mixture is stirred for 1 hour at room temperature, then rotary evaporated. The residue is dissolved in methanol (70 mL), mercuric acetate (395 mg) is added, and the mixture is stirred at room temperature for 2 hours. The resulting black suspension is filtered on Celite with methanol wash of the solids. The filtrate is rotary evaporated, and the residue is purified by flash chromatography on silica gel, eluting with 10% methanol/chloroform containing 0.1% of ammonium hydroxide. The product-containing fractions are combined and rotary evaporated to yield 1,4-dimethyl-5-(2-imidazolinylamino)benzimidazole.HOAc.

EXAMPLE 5

Synthesis of 7-fluoro-4-methyl-5-(2-imidazolinylamino) benzimidazole:



2,3-Dinitro-4-fluorotoluene. Fuming sulfuric acid (180 mL) is added dropwise to 4-fluoro-2-nitrotoluene (50.21 g) under an argon atmosphere. The internal temperature of the mixture is maintained at 0°–5° C. using an ice/sodium chloride bath. A preformed (ice bath) mixture of fuming nitric acid (30 mL) and fuming sulfuric acid (90 mL) is added dropwise to the previous solution over three hours. The reaction is then allowed to warm to room temperature. After stirring at room temperature for two hours, the mixture is poured slowly into ice and the products are extracted with methylene chloride (4×500 mL). The combined extracts are dried over magnesium sulfate, filtered and rotary evaporated. The crude product is purified by flash chromatography on silica gel, eluting with 5% ethyl acetate/hexane to afford 2,3-dinitro-4-fluorotoluene as a pale yellow solid.

4-Fluoro-7-methylbenzimidazole. A suspension of 2,3-dimethyl-4-fluorotoluene (1 g), iron powder (1.95 g) and palladium-on-carbon (10%, 150 mg) in formic acid (99%, 25 mL) is heated to reflux for 2.5 hours. The resulting mixture is filtered through Celite, with methanol wash of the solids. The filtrate is rotary evaporated and the residue partitioned between water and ethyl acetate. The organic layer is dried over magnesium sulfate, filtered and rotary evaporated to afford 4-fluoro-7-methylbenzimidazole as an off-white solid.

7-Fluoro-4-methyl-5-nitrobenzimidazole. To a cold (ice bath) solution of 4-fluoro-7-methylbenzimidazole (734 mg) in concentrated sulfuric acid (10 mL) is added dropwise concentrated nitric acid (0.22 mL) over 1 hour. The mixture is stirred an additional 15 minutes in the ice bath, then poured in a mixture of crushed ice (20 mL) and ammonium hydroxide (20 mL). The resulting mixture is extracted with ethyl acetate. The extract is dried over magnesium sulfate, filtered and rotary evaporated to afford 7-fluoro-4 -methyl-5-nitrobenzimidazole as a pale yellow solid.

1-tert-Butoxycarbonyl-7-fluoro-4-methyl-5-nitrobenzimidazole. A suspension of 7-fluoro-4-methyl-5-nitrobenzimidazole (0.556 g) di-tert-butyldicarbonate (0.870 g), triethylamine (0.475 mL) and 4-dimethylaminopyridine (0.01 g)in ethyl acetate (100 mL) is stirred at room temperature overnight. The mixture is rotary evaporated and the residue purified by flash chromatography on silica gel, eluting with 10% ethyl acetate/hexane to afford 1-tert-butoxycarbonyl-7-fluoro-4-methyl-5-nitrobenzimidazole as an off-white solid.

5-Amino-1-tert-butoxycarbonyl-7-fluoro-4-methylbenzimidazole. To a solution of 1-tert-butoxycarbonyl-7-fluoro-4-methyl-5-nitrobenzimidazole (0.776 g) in methanol (100 mL)/ethyl acetate (50 mL) is added palladium-on-carbon (10%, 0.1 g) and ammonium formate (0.663 g). The mixture is stirred at room temperature for 5 hours, then filtered on Celite, with methanol wash of the solids. The filtrate is rotary evaporated and the residue partitioned between water and ethyl acetate. The organic layer is dried over magnesium sulfate, filtered and rotary evaporated. The residue is purified by flash chromatography on silica gel, eluting with 25% ethyl acetate/hexane to afford 5-amino-1-tert-butoxycarbonyl-7-fluoro-4-methylbenzimidazole as a yellow oil.

1-tert-Butoxycarbonyl-7-fluoro-4-methyl-5-benzimidazolylisothiocyanate. To a solution of di-2-pyridyl thionocarbonate (0.393 mg) and 4-dimethylaminopyridine (0.01 g) in methylene chloride (100 mL) is added dropwise over 30 minutes a solution of 5-amino-1 -tert-butoxycarbonyl-7-fluoro-4-methylbenzimidazole (0.409 g) in methylene chloride (70 mL). The mixture is stirred at room temperature for 3 hours then rotary evaporated. The residue is purified by flash chromatography on silica gel, eluting with 10% ethyl acetate/hexane to afford 1 -tert-butoxycarbonyl-7-fluoro-4-methyl-5-benzimidazolylisothiocyanate as a white solid.

N-(1-tert-Butoxycarbonyl-7-fluoro-4-methyl-5-benzimidazolyl)-N'-2-aminoethylthiourea. A solution of 1-tert-butoxycarbonyl-7-fluoro-4-methyl-5-benzimidazolylisothiocyanate (0.42 g) in methylene chloride (50 mL) is added dropwise over 15 minutes to 1,2-ethylenediamine (0.45 mL) in solution in methylene chloride (100 mL). The mixture is stirred for 10 minutes at room temperature, then rotary evaporated. The residue is triturated for 30 minutes with ether (100 mL). The resulting white suspension is filtered and the solid is dried in vacuo overnight.

7-Fluoro-4-methyl-5-(2-imidazolinylamino)benzimidazole. A mixture of N-(1-tert-butoxycarbonyl-7-fluoro-4-methyl-5-benzimidazolyl)-N'-2 -aminoethylthio-urea (0.5 g) and mercuric acetate (0.52 g) in methanol (150 mL) is stirred at room temperature for 1 hour. The resulting black mixture is filtered on Celite with methanol wash of the solids. The filtrate is rotary evaporated and the residue filtered through a short pad of silica gel, eluting 25% methanol in chloroform containing 1% of ammonium hydroxide. The product-containing fractions are rotary evaporated, the residue diluted with water (15 mL), filtered through a plug of glass wool and lyophilized to afford 7-fluoro-4-methyl-5-(2-imidazolinylamino)benzimidazole as a pale yellow solid.

Compositions

Another aspect of the subject invention is compositions which comprise a safe and effective amount of a subject compound, or a pharmaceutically-acceptable salt thereof, and a pharmaceutically-acceptable carrier. As used herein, "safe and effective amount" means an amount of the subject compound sufficient to significantly induce a positive modification in the condition to be treated, but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgement. A safe and effective amount of the subject compound will vary with the age and physical condition of the patient being treated, the severity of the condition, the duration of the treatment, the nature of concurrent therapy, the particular pharmaceutically-acceptable carrier utilized, and like factors within the knowledge and expertise of the attending physician.

Compositions of the subject invention preferably comprise from about 0.0001% to about 99% by weight of the subject compound, more preferably from about 0.01% to about 90%; also preferably from about 10% to about 50%, also preferably from about 5% to about 10%, also preferably from about 1% to about 5%, and also preferably from about 0.1% to about 1%.

In addition to the subject compound, the compositions of the subject invention contain a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier", as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a human or lower animal. The term

"compatible", as used herein, means that the components of the composition are capable of being commingled with the subject compound, and with each other, in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the composition under ordinary use situations. Pharmaceutically-acceptable carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the human or lower animal being treated.

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the Tweens®; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

If the subject compound is to be injected, the preferred pharmaceutically-acceptable carrier is sterile, physiological saline, with blood-compatible suspending agent, the pH of which has been adjusted to about 7.4.

The preferred mode of administering the subject compounds is perorally. The preferred unit dosage form is therefore tablets, capsules, lozenges, chewable tablets, and the like. Such unit dosage forms comprise a safe and effective amount of the subject compound, which is preferably from about 0.01 mg to about 200 mg, more preferably from about 0.1 mg to about 50 mg, more preferably still from about 0.5 mg to about 25 mg, also preferably from about 1 mg to about 10 mg. The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for peroral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be readily made by a person skilled in the art.

Peroral compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Such liquid oral compositions preferably comprise from about 0.001% to about 5% of the subject compound, more preferably from about 0.01% to about 0.5%. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, Avicel® RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual and buccal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

A preferred mode of administering the subject compounds is topically to the site where activity is desired: intranasal doses for nasal decongestion, inhalants for asthma, eye drops, gels and creams for ocular disorders, and peroral doses for gastrointestinal disorders.

Preferred compositions of the subject invention include aqueous solutions comprising a safe and effective amount of a subject compound intended for topical intranasal administration. Such compositions preferably comprise from about 0.001% to about 5% of a subject compound, more preferably from about 0.01% to about 0.5%. Such compositions also typically include safe and effective amounts of preservatives, such as benzalkonium chloride and thimerosal; buffers such as phosphate and acetate; tonicity agents such as sodium chloride; antioxidants such as ascorbic acid; aromatic agents; and acids and bases to adjust the pH of these aqueous compositions as needed.

Preferred compositions of the subject invention include aqueous solutions, suspensions, and dry powders comprising a safe and effective amount of a subject compound intended for atomization and topical inhalation administration. Such compositions preferably comprise from about 0.1% to about 50% of a subject compound, more preferably from about 1% to about 20%. Such compositions are typically contained in a container with attached atomizing means. Such compositions also typically include propellants such as chlorofluorocarbons 12/11 and 12/114; solvents such as water, glycerol and ethanol; stabilizers such as ascorbic acid, sodium metabisulfite; preservatives such as cetylpyridinium chloride and benzalkonium chloride; tonicity adjustors such as sodium chloride; and flavoring agents such as sodium saccharin.

Preferred compositions of the subject invention include aqueous solutions comprising a safe and effective amount of a subject compound intended for topical intraocular administration. Such compositions preferably comprise from about 0.0001% to about 5% of a subject compound, more preferably from about 0.01% to about 0.5%. Such compositions also typically include one or more of preservatives, such as benzalkonium chloride, thimerosal, phenylmercuric acetate; vehicles, such as poloxamers, modified celluloses, povidone and purified water; tonicity adjustors, such as sodium chloride, mannitol and glycerin; buffers such as acetate, citrate, phosphate and borate; antioxidants such as sodium metabisulfite, butylated hydroxy toluene and acetyl cysteine; acids and bases may be used to adjust the pH of these formulations as needed.

Preferred compositions of the subject invention include solids, such as tablets and capsules, and liquids, such as solutions, suspensions and emulsions (preferably in soft gelatin capsules), comprising a safe and effective amount of a subject compound intended for topical administration to the gastrointestinal tract by peroral administration. Such compositions preferably comprise from about 0.01 mg to about 100 mg per dose, more preferably from about 0.1 mg to about 5 mg per dose. Such compositions can be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit® coatings, waxes and shellac.

Compositions of the subject invention may optionally include other drug actives. Non-limiting examples of drug actives which may be incorporated in these compositions, include:

Antihistamines, including;

Hydroxyzine preferably at a dosage range of from about 25 to about 400 mg; Doxylamine, preferably at a dosage range of from about 3 to about 75 mg; Pyrilamine, preferably at a dosage range of from about 6.25 to about 200 mg; Chlorpheniramine, preferably at a dosage range of from about 1 to about 24 mg; Phenindamine, preferably at a dosage range of from about 6.25 to about 150 mg; Dexchlorpheniramine, preferably at a dosage range of from about 0.5 to about 12 mg; Dexbrompheniramine, preferably at a dosage range of from about 0.5 to about 12 mg; Clemastine, preferably at a dosage range of from about 1 to about 9 mg; Diphenhydramine, preferably at a dosage range of from about 6.25 to about 300 mg; Azelastine, preferably at a dosage range of from about 140 to about 1,680 ug (when dosed intranasally); 1 to about 8 mg (when dosed orally); Acrivastine, preferably at a dosage range of from about 1 to about 24 mg; Levocarbastine (which can be dosed as an intranasal or ocular medicament), preferably at a dosage range of from about 100 to about 800 ug; Mequitazine, preferably at a dosage range of from about 5 to about 20 mg; Astemizole, preferably at a dosage range of from about 5 to about 20 mg; Ebastine;Loratadine, preferably at a dosage range of from about 5 to about 40 mg; Cetirizine, preferably at a dosage range of from about 5 to about 20 mg; Terfenadine, preferably at a dosage range of from about 30 to about 480 mg; Terfenadine metabolites; Promethazine, preferably at a dosage range of from about 6.25 to about 50 mg; Dimenhydrinate, preferably at a dosage range of from about 12.5 to about 400 mg; Meclizine, preferably at a dosage range of from about 6.25 to about 50 mg; Tripelennamine, preferably at a dosage range of from about 6.25 to about 300 mg; Carbinoxamine, preferably at a dosage range of from about 0.5 to about 16 mg; Cyproheptadine, preferably at a dosage range of from about 2 to about 20 mg; Azatadine, preferably at a dosage range of from about 0.25 to about 2 mg; Brompheniramine, preferably at a dosage range of from about 1 to about 24 mg; Triprolidine, preferably at a dosage range of from about 0.25 to about 10 mg; Cyclizine, preferably at a dosage range of from about 12.5 to about 200 mg; Thonzylamine, preferably at a dosage range of from about 12.5 to about 600 mg; Pheniramine, preferably at a dosage range of from about 3 to about 75 mg; Cyclizine, preferably at a dosage range of from about 12.5 to about 200 mg and others;

Antitussives, including;

Codeine, preferably at a dosage range of from about 2.5 to about 120 mg; Hydrocodone, preferably at a dosage range of from about 2.5 to about 40 mg; Dextromethorphan, preferably at a dosage range of from about 2.5 to about 120 mg; Noscapine, preferably at a dosage range of from about 3 to about 180 mg; Benzonatate, preferably at a dosage range of from about 100 to about 600 mg; Diphenhydramine, preferably at a dosage range of from about 12.5 to about 150 mg; Chlophedianol, preferably at a dosage range of from about 12.5 to about 100 mg; Clobutinol, preferably at a dosage range of from about 20 to about 240 mg; Fominoben, preferably at a dosage range of from about 80 to about 480 mg; Glaucine; Pholcodine, preferably at a dosage range of from about 1 to about 40 mg; Zipeprol, preferably at a dosage range of from about 75 to about 300 mg; Hydromorphone, preferably at a dosage range of from about 0.5 to about 8 mg; Carbetapentane, preferably at a dosage range of from about 15 to about 240 mg; Caramiphen, Levopropoxyphene, preferably at a dosage range of from about 25 to about 200 mg and others;

Antiinflammatories, preferably Non-Steroidal Anti-inflammatories, (NSAIDS) including;

Ibuprofen, preferably at a dosage range of from about 50 to about 3,200 mg; Naproxen, preferably at a dosage range of from about 62.5 to about 1,500 mg; Sodium naproxen, preferably at a dosage range of from about 110 to about 1,650 mg; Ketoprofen, preferably at a dosage range of from about 25 to about 300 mg; Indoprofen, Indomethacin, preferably at a dosage range of from about 25 to about 200mg; Sulindac, preferably at a dosage range of from about 75 to about 400 mg; Diflunisal, preferably at a dosage range of from about 125 to about 1,500 mg; Ketorolac, preferably at a dosage range of from about 10 to about 120 mg; Piroxicam, preferably at a dosage range of from about 10 to about 40 mg; Aspirin, preferably at a dosage range of from about 80 to about 4,000 mg; Meclofenamate, preferably at a dosage range of from about 25 to about 400 mg; Benzydamine, preferably at a dosage range of from about 25 to about 200 mg; Carprofen, preferably at a dosage range of from about 75 to about 300 mg; Diclofenac, preferably at a dosage range of from about 25 to about 200 mg; Etodolac, preferably at a dosage range of from about 200 to about 1,200 mg; Fenbufen, preferably at a dosage range of from about 300 to about 900 mg; Fenoprofen, preferably at a dosage range of from about 200 to about 3,200 mg; Flurbiprofen, preferably at a dosage range of from about 50 to about 300 mg; Mefenamic acid, preferably at a dosage range of from about 250 to about 1,500 mg; Nabumetone, preferably at a dosage range of from about 250 to about 2,000 mg; Phenylbutazone, preferably at a dosage range of from about 100 to about 400 mg; Pirprofen, preferably at a dosage range of from about 100 to about 800 mg; Tolmetin, preferably at a dosage range of from about 200 to about 1,800 mg and others;

Analgesics, including;

Acetaminophen, preferably at a dosage range of from about 80 to about 4,000 mg; and others:

Expectorants/Mucolytics, including;

Guaifenesin, preferably at a dosage range of from about 50 to about 2,400mg; N-Acetylcysteine, preferably at a dosage range of from about 100 to about 600 mg; Ambroxol, preferably at a dosage range of from about 15 to about 120 mg; Bromhexine, preferably at a dosage range of from about 4 to about 64 mg; Terpin hydrate, preferably at a dosage range of from about 100 to about 1,200 mg; Potassium iodide, preferably at a dosage range of from about 50 to about 250 mg and others;

Atropinics, preferably intranasally or orally administered atropinics, including;

Ipratroprium (preferably intranasally), preferably at a dosage range of from about 42 to about 252 ug; Atropine sulfate (preferably oral), preferably at a dosage range of from about 10 to about 1,000 ug; Belladonna (preferably as an extract), preferably at a dosage range of from about 15 to about 45 mg equivalents; Scopolamine, preferably at a dosage range of from about 400 to about 3,200 ug; Scopolamine methobromide, preferably at a dosage range of from about 2.5 to about 20 mg; Homatropine methobromide, preferably at a dosage range of from about 2.5 to about 40 mg; Hyoscyamine (preferably oral), preferably at a dosage range of from about 125 to about 1,000 ug; Isopropramide (preferably oral), preferably at a dosage range of from about 5 to about 20 mg; Orphenadrine (preferably oral), preferably at a dosage range of from about 50 to about 400 mg; Benzalkonium chloride (preferably intranasally) preferably a 0.005 to about 0.1% solution and others;

Mast Cell Stabilizers, preferably intranasally, or orally administered mast cell stabilizers, including;

Cromalyn, preferably at a dosage range of from about 10 to about 60 mg; Nedocromil, preferably at a dosage range of from about 10 to about 60 mg; Oxatamide, preferably at a dosage range of from about 15 to about 120 mg; Ketotifen, preferably at a dosage range of from about 1 to about 4 mg; Lodoxamide, preferably at a dosage range of from about 100 to about 3,000 ug and others;

LT Antagonists, including Zileuton and others;

Methylxanthines, including;

Caffeine, preferably at a dosage range of from about about 65 to about 600 mg; Theophyllene, preferably at a dosage range of from about 25 to about 1,200 mg; Enprofylline; Pentoxifylline, preferably at a dosage range of from about 400 to about 3,600 mg; Aminophylline, preferably at a dosage range of from about 50 to about 800 mg; Dyphylline, preferably at a dosage range of from about 200 to about 1,600 mg and others;

Antioxidants or radical inhibitors, including;

Ascorbic acid, preferably at a dosage range of from about 50 to about 10,000 mg; Tocopherol, preferably at a dosage range of from about 50 to about 2,000 mg; Ethanol, preferably at a dosage range of from about 500 to about 10,000 mg and others;

Steroids, preferably intranasally administered steroids, including:

Beclomethasone, preferably at a dosage range of from about 84 to about 336 ug; Fluticasone, preferably at a dosage range of from about 50 to about 400 ug; Budesonide, preferably at a dosage range of from about 64 to about 256 ug; Mometasone; Triamcinolone, preferably at a dosage range of from about 110 to about 440 ug; Dexamethasone, preferably at a dosage range of from about 168 to about 1,008 ug; Flunisolide, preferably at a dosage range of from about 50 to about 300 ug; Prednisone (preferably oral), preferably at a dosage range of from about 5 to about 60 mg; Hydrocortisone (preferably oral), preferably at a dosage range of from about 20 to about 300 mg and others;

Bronchodilators, preferably for inhalation, including;

Albuterol, preferably at a dosage range of from about 90 to about 1,080 ug; 2 to about 16 mg (if dosed orally); Epinephrine, preferably at a dosage range of from about 220 to about 1,320 ug; Ephedrine, preferably at a dosage range of from about 15 to about 240 mg (if dosed orally); 250 to about 1,000 ug (if dosed intranasally); Metaproterenol, preferably at a dosage range of from about 65 to about 780 ug or 10 to about 80 mg if dosed orally; Terbutaline, preferably at a dosage range of from about 200 to about 2,400 ug; 2.5 to about 20 mg if dosed orally; Isoetharine, preferably at a dosage range of from about 340 to about 1,360 ug; Pirbuterol, preferably at a dosage range of from about 200 to about 2,400 ug; Bitolterol, preferably at a dosage range of from about 370 to about 2,220 ug; Fenoterol, preferably at a dosage range of from about 100 to about 1,200 ug; 2.5 to about 20 mg (if dosed orally); Rimeterol, preferably at a dosage range of from about 200 to about 1,600 ug; Ipratroprium, preferably at a dosage range of from about 18 to about 216 ug (inhalation) and others; and

Antivirals, including;

Amantadine, preferably at a dosage range of from about 50 to about 200 mg; Rimantadine, preferably at a dosage range of from about 50 to about 200 mg; Enviroxime; Nonoxinols, preferably at a dosage range of from about 2 to about 20 mg (preferably an intranasal form); Acyclovir, preferably at a dosage range of from about 200 to about 2,000 mg (oral); 1 to about 10 mg (preferably an intranasal form); Alpha-lnterferon, preferably at a dosage range of from about 3 to about 36 MIU; Beta-Interferon, preferably at a dosage range of from about 3 to about 36 MIU and others;

Ocular Drug actives:

acetylcholinesterase inhibitors, e.g., echothiophate from about 0.03% to about 0.25% in topical solution and others; and

Gastrointestinal actives:

antidiarrheals, e.g., Ioperamide from about 0.1 mg to about 1.0 mg per dose, and bismuth subsalicylate from about 25 mg to about 300 mg per dose and others.

Of course, clearly contemplated and included in the description above are the acid or base addition salts, esters, metabolites, steoisomers and enatiomers of these preferred actives, as well as analogues to these actives that are safe and effective. It is also recognized that an active may be useful for more than one of the above uses, and these uses are clearly contemplated as well. This overlap is recognized in the art and adjusting dosages and the like to fit the indication is well within the perview of the skilled medical practitioner.

Methods

Another aspect of the subject invention involves methods for preventing or treating nasal congestion by administering a safe and effective amount of a subject compound to a human or lower animal experiencing or at risk of experiencing nasal congestion. Such nasal congestion may be associated with human diseases or disorders which include, but are not limited to, seasonal allergic rhinitis, acute upper respiratory viral infections, sinusitis, perennial rhinitis, and vasomotor rhinitis. Each administration of a dose of the subject compound preferably administers a dose within the range of from about 0.001 mg/kg to about 10 mg/kg of a compound, more preferably from about 0.01 mg/kg to about 5 mg/kg, more preferably still from about 0.1 mg/kg to about 1 mg/kg. Peroral administration of such doses is preferred. The frequency of administration of a subject compound according to the subject invention is preferably from about once to about six times daily, more preferably from about 2 times to about 4 times daily. Such doses and frequencies are also preferred for treating other respiratory conditions, such as otitis media, cough, COPD and asthma.

Another aspect of the subject invention involves methods for preventing or treating glaucoma by administering a safe and effective amount of a subject compound to a human or lower animal experiencing or at risk of experiencing glaucoma. Each administration of a dose of the subject compound preferably administers a dose within the range of

from about 0.01 μg/kg to about 10 mg/kg of a compound, more preferably from about 0.001 mg/kg to about 1 mg/kg, more preferably still from about 0.01 mg/kg to about 0.1 mg/kg. Intraocular administration of such doses is preferred. The frequency of administration of a subject compound according to the subject invention is preferably from about once to about six times daily, more preferably from about 2 times to about 4 times daily.

Another aspect of the subject invention involves methods for preventing or treating functional bowel disorders, such as diarrhea, by administering a safe and effective amount of a subject compound to a human or lower animal experiencing or at risk of experiencing diarrhea. Each administration of a dose of the subject compound preferably administers a dose within the range of from about 0.001 mg/kg to about 10 mg/kg of a compound, more preferably from about 0.01 mg/kg to about 5 mg/kg, more preferably still from about 0.1 mg/kg to about 1 mg/kg. Peroral administration of such doses is preferred. The frequency of administration of a subject compound according to the subject invention is preferably from about once to about six times daily, more preferably from about 2 times to about 4 times daily.

Composition and Method Examples

The following non-limiting examples illustrate the compositions and methods of use of the subject invention.

EXAMPLE A

Oral Table Composition

Ingredient	Amount per tablet (mg)
Subject Compound 4	20.0
Microcrystalline cellulose (Avicel PH 102 ®)	80.0
Dicalcium phosphate	96.0
Pyrogenic silica (Cab-O-Sil ®)	1.0
Magnesium stearate	3.0
Total =	200.0

One tablet is swallowed by a patient with nasal congestion. The congestion is substantially diminished.

EXAMPLE B

Chewable Tablet Composition

Ingredient	Amount per tablet (mg)
Subject Compound 1	15.0
Mannitol	255.6
Microcrystalline cellulose (Avicel PH 101 ®)	100.8
Dextrinized sucrose (Di-Pac ®)	199.5
Imitation orange flavor	4.2
Sodium saccharin	1.2
Stearic acid	15.0
Magnesium stearate	3.0
FD&C Yellow #6 dye	3.0
Pyrogenic silica (Cab-O-Sil ®)	2.7
Total =	600.0

One tablet is chewed and swallowed by a patient with nasal congestion. The congestion is substantially reduced.

EXAMPLE C

Sublingual Tablet Composition

Ingredient	Amount per tablet (mg)
Subject Compound 5	2.00
Mannitol	2.00
Microcrystalline cellulose (Avicel PH 101 ®)	29.00
Mint flavorants	0.25
Sodium saccharin	0.08
Total =	33.33

One tablet is placed under the tongue of a patient with nasal congestion and allowed to dissolve. The congestion is rapidly and substantially diminished.

EXAMPLE D

Intranasal Solution Composition

Ingredient	Composition (% w/v)
Subject Compound 3	0.20
Benzalkonium chloride	0.02
Thimerosal	0.002
d-Sorbitol	5.00
Glycine	0.35
Aromatics	0.075
Purified water	q.s.
Total =	100.00

One-tenth of a mL of the composition is sprayed from a pump actuator into each nostril of a patient with nasal congestion. The congestion is substantially diminished.

EXAMPLE E

Intranasal Gel Composition

Ingredient	Composition (% w/v)
Subject Compound 1	0.10
Benzalkonium chloride	0.02
Thimerosal	0.002
Hydroxypropyl methylcellulose (Metolose 65SH4000 ®)	1.00
Aromatics	0.06
Sodium chloride (0.65%)	q.s.
Total =	100.00

One-fifth of a mL of the composition is applied as drops from a dropper into each nostril of a patient with nasal congestion. The congestion is substantially reduced.

EXAMPLE F

Inhalation Aerosol Composition

Ingredient	Composition (% w/v)
Subject Compound 2	5.0
Alcohol	33.0
Ascorbic acid	0.1
Menthol	0.1

-continued

Ingredient	Composition (% w/v)
Sodium Saccharin	0.2
Propellant (F12, F114)	q.s.
Total =	100.0

Two-puffs of the aerosol composition is inhaled from a metered-dose inhaler by a patient with asthma. The asthmatic condition is effectively relieved.

EXAMPLE G

Topical Ophthalmic Composition

Ingredient	Composition (% w/v)
Subject Compound 5	0.10
Benzalkonium chloride	0.01
EDTA	0.05
Hydroxyethylcellulose (Natrosol M ®)	0.50
Sodium metabisulfite	0.10
Sodium chloride (0.9%)	q.s.
Total =	100.0

One-tenth of a mL of the composition is administered directly into each eye of a patient with glaucoma. The intraocular pressure is substantially reduced.

EXAMPLE H

Oral Liquid Composition

Ingredient	Amount/15 mL Dose
Subject Compound 4	15 mg
Chlorpheniramine maleate	4 mg
Propylene glycol	1.8 g
Ethanol (95%)	1.5 mL
Methanol	12.5 mg
Eucalyptus oil	7.55 mg
Flavorants	0.05 mL
Sucrose	7.65 g
Carboxymethylcellulose (CMC)	7.5 mg
Microcrystalline cellulose and Sodium CMC (Avicel RC 591 ®)	187.5 mg
Polysorbate 80	3.0 mg
Glycerin	300 mg
Sorbitol	300 mg
FD&C Red #40 dye	3 mg
Sodium saccharin	22.5 mg
Sodium phosphate monobasic	44 mg
Sodium citrate monohydrate	28 mg
Purified Water	q.s.
Total =	15 mL

One 15 mL dose of the liquid composition is swallowed by a patient with nasal congestion and runny nose due to allergic rhinitis. The congestion and runny nose are effectively reduced.

EXAMPLE J

Oral Liquid Composition

Ingredient	Amount/15 mL Dose
Subject Compound 2	30 mg
Sucrose	8.16 g
Glycerin	300 mg
Sorbitol	300 mg
Methylparaben	19.5 mg
Propylparaben	4.5 mg
Menthol	22.5 mg
Eucalyptus oil	7.5 mg
Flavorants	0.07 mL
FD&C Red #40 dye	3.0 mg
Sodium saccharin	30 mg
Purified water	q.s.
Total =	15 mL

One 15 mL dose of the alcohol-free liquid medication is swallowed by a patient with nasal congestion. The congestion is substantially diminished.

EXAMPLE K

For the relief of nasal congestion due to the common cold, hay fever, or other upper respiratory allergies, or associated with sinusitis; relieves runny nose, sneezing, and itchy watery eyes as may occur in allergic rhinitis. Restores freer breathing through the nose. Adults 12 and over take one tablet every four hours.

	mg/tablet
chlorpheniramine maleate, USP	4 mg
Subject Compound 1	4
microcrystalline cellulose, NF	130
starch 1500, NF	100
magnesium stearate, USP	2
total	240 mg

EXAMPLE L

For the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, and nasal congestion. Adults 12 and over take one tablet every twelve hours.

	mg/tablet
loratadine	5 mg
Subject Compound 2	12
hydroxypropyl methylcellulose, USP	12
magnesium stearate, USP	2
lactose anhydrous, USP	200
total	231 mg

EXAMPLE M

For relief of symptoms associated with the common cold, sinusitis, or flu including nasal congestion, headache, fever, body aches, and pains. Adults 12 and over take two caplets every twelve hours.

	mg/caplet
naproxen sodium anhydrous, USP	220 mg
Subject Compound 3	6
hydroxypropyl methylcellulose, USP	6
magnesium stearate, USP	2
povidone K-30, USP	10
talc, USP	12
microcrystalline cellulose, NF	44
total	300 mg

EXAMPLE N

For relief of nasal/sinus congestion and pressure, sinus headache pain associated with sinusitis, hay fever, upper respiratory allergies, or the common cold. Adults 12 and over take one tablet every six hours.

	mg/tablet
acetaminophen, USP	500 mg
Subject Compound 4	6
hydroxypropyl methylcellulose, USP	6
silicon dioxide, colloidal, NF	30
pregelatinized starch, NF	50
magnesium stearate, USP	4
total	596 mg

EXAMPLE N

For the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, nasal congestion, sinus pain, and headache. Adults 12 and over take two caplets every twelve hours.

	mg/caplet
naproxen sodium anhydrous, USP	220 mg
loratadine	2.5
Subject Compound 5	6
hydroxypropyl methylcellulose, USP	6
magnesium stearate, USP	2
povidone K-30, USP	10.5
talc, USP	12
microcrystalline cellulose, NF	44
total	303 mg

EXAMPLE O

For the relief of symptoms due to the common cold, flu, hay fever, or other upper respiratory allergies, or associated with sinusitis; relieves runny nose, sneezing, and itchy watery eyes as may occur in allergic rhinitis. Relieves headache, fever, body aches, and pains. Restores freer breathing through the nose. Adults 12 and over take two tablets every twelve hours.

	mg/tablet
naproxen sodium anhydrous, USP	220 mg
chlorpheniramine maleate, USP	6
Subject Compound 1	6
hydroxypropyl methylcellulose, USP	12
magnesium stearate, USP	2
povidone K-30, USP	10

-continued

	mg/tablet
talc, USP	12
microcrystalline cellulose, NF	44
total	312 mg

EXAMPLE P

For the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, nasal congestion, sinus pain, and headache. Adults 12 and over take two tablets every six hours.

	mg/tablet
acetaminophen, USP	500 mg
loratadine	1.3
Subject Compound 5	3
hydroxypropyl methylcellulose, USP	3
silicon dioxide, colloidal, NF	30
pregelatinized starch, NF	50
magnesium stearate, USP	2.7
total	590 mg

EXAMPLE Q

For the relief of minor aches, pains, headache, muscular aches, sore throat pain, and fever associated with a cold or flu. Relieves nasal congestion, cough due to minor throat and bronchial irritations, runny nose, and sneezing associated with the common cold. Adults 12 and over take one fluid ounce every six hours.

	mg/fl oz
acetaminophen, USP	1000 mg
doxylamine succinate, USP	12.5
dextromethorphan hydrobromide, USP	30
Subject Compound 2	6
Dow XYS-40010.00 resin	3
high fructose corn syrup	16000
polyethylene glycol, NF	3000
propylene glycol, USP	3000
alcohol, USP	2500
sodium citrate dihydrate, USP	150
citric acid, anhydrous, USP	50
saccharin sodium, USP	20
flavor	3.5
purified water, USP	3500
total	29275 mg

EXAMPLE R

For the relief of minor aches, pains, headache, muscular aches, sore throat pain, and fever associated with a cold or flu. Relieves nasal congestion, cough due to minor throat and bronchial irritations, runny nose, and sneezing associated with the common cold. Adults 12 and over take one fluid ounce every six hours.

	mg/fl oz
naproxen sodium anhydrous, USP	220 mg
doxylamine succinate, USP	12.5

-continued

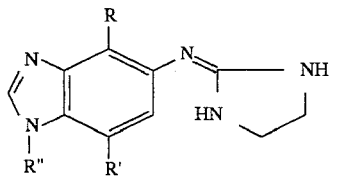
	mg/fl oz
dextromethorphan hydrobromide, USP	30
Subject Compound 1	6
Dow XYS-40010.00 resin	3
high fructose corn syrup	16000
polyethylene glycol, NF	3000
propylene glycol, USP	3000
alcohol, USP	2500
sodium citrate dihydrate, USP	150
citric acid, anhydrous, USP	50
saccharin sodium, USP	20
flavor	3.5
purified water, USP	3800
total	28795 mg

Other examples of combination actives are contemplated. Examples of medicaments which can be combined with the primary active are included in U.S. Pat. No. 4,552,899 to Sunshine, et al., hereby incorporated by reference. All other references referred to throughout this specification are hereby incorporated by reference.

While particular embodiments of the subject invention have been described, it will be obvious to those skilled in the art that various changes and modifications of the subject invention can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

What is claimed is:

1. A pharmaceutical composition comprising the compound having the following structure:



wherein:

(a) R is unsubstituted alkanyl or alkenyl having from 1 to about 3 carbon atoms;

(b) R' is selected from the group consisting of hydrogen; unsubstituted alkanyl or alkenyl having from 1 to about 3 carbon atoms; unsubstituted alkylthio or alkoxy having from 1 to about 3 carbon atoms; hydroxy; thiol; cyano; and halo;

(c) R" is selected from the group consisting of hydrogen, methyl, ethyl and i-propyl;

and one or more actives chosen from the group consisting of an antitussive, mast cell stabilizer, LT antagonist, expectorant/muycolytic, antioxidant or radical inhibitor, steroid, bronchodilator, antiviral, analgesic, antiinflammatory, gastrointestinal and ocular active.

2. A pharmaceutical composition according to claim **1** further comprising an analgesic.

3. A pharmaceutical composition according to claim **1** further comprising an antiinflammatory.

4. A pharmaceutical composition according to claim **1** further comprising an antihistamine.

5. A pharmaceutical composition according to claim **1** further comprising an muycolytic/expectorant.

6. A pharmaceutical composition according to claim **1** further comprising an antitussive.

7. A pharmaceutical composition according to claim **1** further comprising a mast cell stabilizer.

8. A pharmaceutical composition according to claim **1** further comprising a LT antagonist.

9. A pharmaceutical composition according to claim **1** further comprising an antioxidant or radical inhibitor.

10. A pharmaceutical composition according to claim **1** further comprising asteroid.

11. A pharmaceutical composition according to claim **1** further comprising a bronchodilator.

12. A pharmaceutical composition according to claim **1** further comprising an antitussive.

13. A pharmaceutical composition according to claim **1** further comprising an antiviral.

14. A pharmaceutical composition according to claim **1** further comprising an ocular drug.

15. A pharmaceutical composition according to claim **15** further comprising a gastrointestinal active.

* * * * *

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Proprietors: Banner Life Sciences, LCC
Opponents: Beate Dieckhoff
Our Ref.: BD.01.17.EIN

NOTICE OF OPPOSITION

On behalf of

Beate Dieckhoff

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51375 Leverkusen

Germany (DE)

an opposition is filed herewith pursuant to Art. 99 (1) EPC against the European Patent

EP 1 863 458 B1

(European Patent Application No. 06 737 018.9).

Publication and Mention of the Grant:	September 14, 2016
Title of the Patent:	Solvent system for enhancing the solubility of pharmaceutical agents
Proprietor:	Banner Life Sciences, LLC High Point North Carolina 27265 USA

The opposition fee in the amount of € 785.00 is paid online today.

I. Requests

1. The opposition is directed against all claims of 1 863 458 B1 (hereinafter also referred to as "the Contested Patent"). It is requested that the Contested Patent be revoked in its entirety with effect for all designated EPC Contracting and Extension States.

2. The opposition is based on the grounds that

   (a) the subject matter of the Contested Patent is not patentable within the terms of Articles 52 to 57 EPC (see Article 100(a) EPC); specifically, the subject matter is not novel and/or not based on an inventive step (Articles 54 and 56 EPC).

   (b) the Contested Patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (see Article 100(b) EPC).

   (c) The subject-matter of the Contested Patent extends beyond the content of the application as filed (see Article 100 (c) EPC).

3. If the Opposition Division feels unable to grant the above request for revocation on the basis of our written submission(s), oral proceedings are hereby requested in accordance with Article 116 (1) EPC.

II. Documents referred to in the present opposition

4. The following references are submitted herewith:

D1: US 5,360,615 published on November 1, 1994 (prior art according to Art. 54 (2) EPC)

D2: WO 2006/096580 A (application of the Contested Patent as originally filed)

D3: US 2001/007668 A, published on July 12, 2001 (prior art according to Art. 54 (2) EPC)

D4 US 5,541,210, published on July 30, 1996 (prior art according to Art. 54 (2) EPC)

D5: Experiments regarding the Contested Patent filed by the Patentee on September 16, 2011 during the examination procedure

D6: Experiments regarding the Contested Patent filed by the Patentee on March 26, 2012 with the substantiation of the appeal

D7: Technical data sheet for PEG-600

D8: Beyer, Walter – Lehrbuch der organischen Chemie, 21. Edition, Stuttgart, Hirzel, 1988, page 280

D9: Excerpt from the German Wikipedia weppage on Milchsäure (lactic acid)

D10: Beyer, Walter – Lehrbuch der organischen Chemie, 21. Edition, Stuttgart, Hirzel, 1988, page 260

D11 Excerpt from the U.S. weppage pharmacopeia on PEG (lactic acid)

D12 Excerpt from the English Wikipedia weppage on citric acid

D13 Beyer Walter, Lehrbuch der organischen Chemie, 21. Edition, Stuttgart, Hirzel, 1988, page 283

III. The subject matter of the Contested Patent

5. The Contested Patent comprises thirteen claims, of which two are independent claims.

5.1 Independent claim 1 relates to

Feature 1.1 a softgel capsule comprising a fill material wherein the fill material

Feature 1.2 (a) naproxen sodium;

Feature 1.3 (b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid

Feature 1.3.1 in an amount from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

Feature 1.4 (c) polyethylene glycol;

Feature 1.5 (d) water; and

Feature 1.6 (e) a solubilizer selected from the group consisting of glycerin

5.2. The dependent claims 2 to 12 disclose the following features:

Feature 2.1 (b) is citric acid or lactic acid.

Feature 3.1 (b) is lactic acid.

Feature 4.1 polyethylene glycol is present in an amount from 10% to 80% by weight.

Feature 5.1 the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

Feature 6.1 water is present in an amount from 1% to 18% by weight.

Feature 7.1 further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, and combinations thereof.

Feature 8.1 the solubilizer is present in an amount from 1% to 10% by weight.

Feature 9.1 the fill material is liquid.

Feature 10.1 A capsule of any of the preceding claims for use as a medicament.

Feature 11.1 A method of making the capsule comprising

(a) mixing components (a), (b), (c), (d), and (e) as defined; and

(b) encapsulating the mixture in a soft gel capsule.

Feature 12.1 The method, wherein step (a) is conducted at a temperature from

5.3 Independent claim 13 relates to the use of

Feature 13.1 (a) naproxen sodium;

Feature 13.2 (b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid

Feature 13.2.1 in an amount from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

Feature 13.3 (c) polyethylene glycol;

Feature 13.4 (d) water; and

Feature 13.5 (e) a solubilizer selected from the group consisting of glycerin

Feature 13.6 in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

IV. Unallowable Extension of the Contested Patent (Art. 123(2) EPC)

6. The subject-matter of claims 11 and 12 of the Contested Patent extend beyond the content of the application as filed.

IV.1 Claim 11

7. Claim 11 states:

A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c), (d) and (e) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

8. It seems the patentee considered page 8, line 25 to page 9, line 2 of the application as originally filed (D2) as basis for this claim. The passage reads (emphasis added):

The fill material is prepared by mixing the agent (such as a salt of the

drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight. Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

9. This passage clearly mentions that the mixing is conducted at a specific temperature range (50 to 70 °C). Furthermore, this passage also specifies the amounts of the pharmaceutical agent, water, polyethylene glycol, and the solubilizers used.

10. All these limitations are missing in claim 11 of the Contested Patent which is therefore not in accordance with the requirement of Article 123(2) EPC.

IV.2 Claim 12

11. Claim 12 refers to claim 11 and limits the temperature in step (a) to the range of from 50 to 70 °C. This means this claim resolves one of the issues raised with regards to the unallowable extension of claim 11.

12. However, the subject-matter of this claim still extends beyond the subject matter as originally filed as it does not contain the specific amounts for the pharmaceutical agent, water, polyethylene glycol, and the solubilizers disclosed in the relevant paragraph of the application as filed. Consequently, claim 12 of the Contested Patent is not in accordance with the requirements of Article 123(2) EPC.

V. Lack of sufficiency of disclosure

13. The Contested Patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art:

V.1 Claim 7

14. In claim 7 the further presence of one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives,

surfactants, and combinations thereof is required.

15. The Contested Patent does not provide any explanation to the meaning of crystallization inhibitors, bulk filling agents and bioavailability enhancers. Therefore, a person skilled in the art would not know how to obtain a softgel capsule containing one of these additional excipients.

VI. Missing novelty of the subject matter of the claims of the Contested Patent

VI.1 Missing novelty of independent claim 1

16. Independent claim 1 is not novel in view of document D4. Document D4 is related to various pharmaceutical compositions. These compositions are preferably in soft gelatin capsules (cf. column, 19, line 4; feature 1.1). The composition used in Example R (column 28 to 29 of document D4) is shown below.

	mg/fl oz
naproxen sodium anhydrous, USP	220 mg
doxylamine succinate, USP	12.5
dextromethorphan hydrobromide, USP	30
Subject Compound 1	6
Dow XYS-40010.00 resin	3
high fructose corn syrup	16000
polyethylene glycol, NF	3000
propylene glycol, USP	3000
alcohol, USP	2500
sodium citrate dihydrate, USP	150
citric acid, anhydrous, USP	50
saccharin sodium, USP	20
flavor	3.5
purified water, USP	3800
total	28795 mg

Table 1: Composition of Example R of document D4.

17. It comprises naproxen sodium (feature 1.2), citric acid (feature 1.3), polyethylene glycol (feature 1.4), water (feature 1.5) and propylene glycol (feature 1.6).

18. In this example 220 mg naproxen sodium (0.87 mmol) and 50 mg citric acid (0.26 mmol) are used. This corresponds to 0.30 mol equivalents citric acid per mol naproxen sodium (feature 1.3.1).

19. Consequently, all features of independent claim 1 are disclosed in document D4.

VI.2 Missing novelty of claim 2

20. Feature 2.1 requires component (b) to be citric acid or lactic acid. In Example R of document D4 citric acid is used (see argumentation above). Consequently, claim 2 is also not novel in view of document D4.

VI.3 Missing novelty of claim 4

21. Feature 4.1 requires the compound (c) (polyethylene glycol) to be present in an amount from 10% to 80% by weight.

22. In example R of document D4 3000 mg polyethylene glycol are present and the total mass of all components is 28795 mg. This means polyethylene glycol is present in an amount of 10.41%, which is within the feature of claim 4. Consequently, the subject matter of claim 4 is not novel in view of document D4.

VI.4 Missing novelty of claim 5

23. Feature 5.1 limits the molecular weight of PEG between 300 and 1500.

24. In example R of document D4 "PEG NF" is used. The "NF" refers to the National Formulary, which together with the USP comprises the US Pharmacopeia. The molecular weight of PEG according to the US Pharmacopeia is within the range claimed in claim 5 (cf. document D11, first table on pages 1 and 2, which lists PEG with a molecular weight from 200 to 2100[1])

VI.4 Missing novelty of claim 6

25. Feature 6.1 requires the compound (d) (water) to be present in an amount from 1% to 18% by weight.

26. In example R of document D4 3800 mg of water is present and the total mass of all components is 28795 mg. This means water is present in an amount of 13% by weight, which is according to claim 6. Accordingly, the subject matter of claim 6 is not novel in view of document D4.

VI.5 Missing novelty of claim 7

27. Feature 7.1 requires the further presence of one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, and combinations thereof.

28. According to the Contested Patent solubilizers are the compounds mentioned in

[1] Document D11 is an article from the weppage pharmacopeia dated June 13, 2017; i.e. it was published after the priority date of the Contested Patent. However, the properties of PEG mentioned therein (i.e. molecular weight) did not change from the priority date of the Contested Patent.

feature 1.6 (glycerin, polyvinylpyrrolidone and propylene glycol). As outlined before example R of document D4 comprises such a solubilizer (propylene glycol). Consequently, claim 7 is not novel in view of document D4.

VI.6 Missing novelty of claim 8

29. Feature 8.1 requires that the compound (e) (solubilizer) is present in an amount from 1% to 10% by weight.

30. In example R of document D4 3000 mg of the solubilizer propylene glycol is used and the total mass of all components is 28795 mg. This means the solubilizer is present in an amount of 10.41% by weight. Consequently, claim 8 is not novel in view of this example.

VI.7 Missing novelty of claim 9

31. Feature 9.1 requires the fill material to be liquid.

32. The fill material disclosed in example R of document D4 is liquid. With regards to this example it is disclosed that the patient should "[...] take one fluid ounce every six hours" (cf. document D4, column 28, lines 60-61). This means the material is liquid and claim 9 is not novel in view of document D4.

VI.8 Missing novelty of claim 10

33. Feature 10.1 requires a capsule of any of the preceding claims for use as a medicament.

34. With regards to example R document D4 clearly discloses that this example is for the relief of minor aches and pains and also mentions a prescribable amount (cf. document D4, column 28, lines 55-61). This means it is used as a medicament and the claim 10 is not novel in view of document D4.

VI.9 Missing novelty of independent claim 13

35. Independent claim 13 addresses the use of the same filling contained in features 1.2 to 1.6 of claim 1 in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

36. As outlined above (see argumentation in V.1) all features of independent claim 13 are not novel in view of document D4.

VII. Lack of inventive step of the subject matter of the claims of the Contested Patent

37. In addition to being not novel the Contested Patent is also not inventive.

38. Before addressing the inventiveness of the Contested Patent the Experiments filed by the patentee will be assessed in the following:

VII.1 Experiments filed by the Patentee

39. The application as filed does not contain any experimental results. The twelve examples disclosed therein merely disclose various compositions for the fill material without evidencing any technical effect.

40. In the course of the Examination the patentee filed new experiments on September 16, 2011 and on March 26, 2012. These experiments will be discussed in the following.

VII.1.1 Experiments filed on September, 16, 2011 (document D5)

41. These experiments were filed prior to the scheduled oral proceedings before the Examining Division regarding the patent application of the Contested Patent. In these experiments, the patentee tried to show that compositions according to the application form very small amounts of PEG-naproxen-esters over (up to) several years.

42. The fill material and the active ingredients used in these experiments are listed in the table below:

Active Ingredients

Ingredient	Amount per Capsule
naproxen sodium	220mg

Fill Excipients

Ingredient	Amount (mg) per Capsule
Lactic Acid	44.0
Propylene Glycol	17.7
Povidone K-30	17.7
Polyethylene Glycol 600	580.6

Table 2: active ingredient and fill excipients used in the experiments filed by the Patentee on September 16, 2011 (document D5).

43. According to document D5, the composition is used within a capsule (feature 1.1) and as shown in the table its fill consists of naproxen sodium (feature 1.2), lactic acid (feature 1.3), propylene glycol (feature 1.6), povidone K-30 and polyethylene glycol 600 (feature 1.4). The molar equivalent of lactic acid to naproxen sodium is 0.56 (feature 1.3.1). Independent Claim 13 and its features literally and/or inherently correspond to claim 1 and are, therefore also fulfilled.

44. In these experiments water is not part of the fill material; water is only mentioned as part of the gelatin shell. According to the Contested Patent (claims as granted), the fill material must comprise water (feature 1.5). Therefore, these experiments are not according to the alleged invention of the Contested Patent.

45. For these capsules the patentee observed hardly any ester formation over the course of up to three years (less than 1%). It is no surprise that in such an experimental setup hardly any ester formation is observed.

46. Most of the naproxen sodium will be present as solid due to the lack of water for solubilisation and solid naproxen sodium will not react to form PEG-naproxen-ester. Consequently, it is no surprise that hardly any PEG-ester formation is observed in this experimental setup.

47. In addition, the patentee does not provide any comparative examples or comparative data from the closest prior art that would allow these results to be put

into context.

VII.1.2 Experiments filed on March 26, 2012 (document D6)

48. This set of experiments was submitted as part of the substantiation of the appeal against the refusal of the patent application. In this set of experiments the patentee is trying to prove that formulations according to the application form less PEG-naproxen-esters than formulations according to the prior art document D1. The results are summarized in 15 samples according to the alleged invention (samples #1 to #15) and 6 comparative examples which are (allegedly) according to prior art document D1 (samples #16 to #21).

49. In the experiments (allegedly) according to the Contested Patent the components (naproxen sodium, HCl or lactic acid or citric acid in different equivalents, water and PEG-600) are mixed and the mixture is analyzed both visually and by HPLC. After "accelerated stress conditions" (1 week at 60 °C) the mixture is analyzed both visually and by HPLC again.

50. Regarding these experiments it must be noted that the claim set of the patent application at the time of these experiments was different than the claim set of the Contested Patent. Consequently, these experiments are not according to the Contested Patent as outlined in the following:

51. According to the Contested Patent various acids are listed as feature 1.3 and hydrochloric acid is not among these acids. However, in six of the experiments (samples #1 to #6) hydrochloric acid is used and; consequently, these experiments are not according to the Contested Patent.

52. All experiments, which are (allegedly) according to the alleged invention (samples #1 to #15) lack a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof (feature 1.6).

53. As a summary it can be noted that the samples #1 to #15 lack feature 1.6 (solubilizer). Furthermore, samples #1 to #6 lack feature 1.3 and use HCl instead of an acid selected from the list disclosed. The six samples which use HCl (samples #1 to #6) and; therefore lack both features 1.3 and 1.6 will not be considered in the forthcoming discussion. In the following it will be shown that most of the remaining samples (#7 to #15) cannot be considered as valid experiments:

54. Of these experiments only sample #11 is a homogeneous solution after mixing the components. After "stress treatment" only samples #8 and #11 are homogeneous solutions. The other samples (allegedly) according to the alleged invention contain precipitate and/or are a suspension. All samples according to the prior art (samples #16 to #21) are clear solutions.

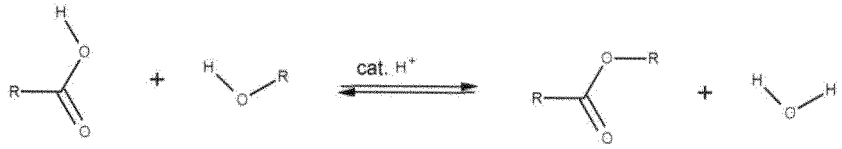
55. The patentee argued (cf. decision T 0826/12, page 4, second paragraph) that the absence of these solubilizers is the reason for the presence of inhomogeneous solutions and that these samples, although not suitable for encapsulation in a softgel capsule, would still demonstrate an improvement over document D1 with respect to the decreased production of PEG-naproxen-esters.

56. Based on the teaching of the Contested Patent and this statement of the patentee the effect of these solubilizers must be to enhance the solubility of the naproxen sodium. PEG-600 is completely soluble in water (cf. document D7, page 1, 5th item in the table). Therefore, the precipitate comprises undissolved sodium naproxen and – most likely – undissolved acid as well.

57. To show that the experiments must be disregarded from a scientific point of view some basics regarding the formation of esters in general have to be considered:

58. <u>The Ester formation</u>

59. The Ester formation between an acid and an alcohol is an equilibrium reaction, which is catalyzed by acids. Besides the ester, a molecule of water is also formed in the reaction (see general reaction scheme below).



Reaction scheme 1: Ester formation.

60. For purposes of this discussion the ester formation reaction will be analyzed using the principle of Le Chatelier: When the (initial) concentration of a starting material (such as the acid above) is decreased, the reaction mixture will be shifted towards the starting materials (this means "the left side" of the reaction scheme) and less products (like the ester) will be present at the equilibrium of the reaction.

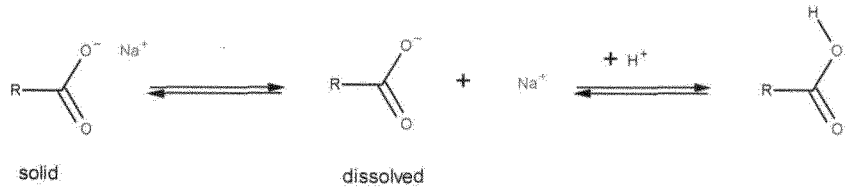
61. Likewise, when the (initial) concentration of a product (like water) is increased the reaction mixture will also be shifted towards the starting materials (the "left side"

of the reaction scheme), this means more starting materials and less products (like ester) will be present at the equilibrium of the reaction.

62. The effect of different concentrations of the starting material will be discussed in paragraphs [66] to [70]. The effect of different product concentrations will be discussed in paragraphs [71] to [77]. Furthermore, competing reactions will be discussed in paragraphs [78] to [84] and some general remarks are provided in paragraphs [85] to [91].

63. Different initial concentrations of the starting materials - naproxen

64. As discussed before in document D6 naproxen sodium is used. In most samples it is not fully dissolved. Only a fraction is, and only this dissolved fraction can form the acid (see reaction scheme 2) and participate in the formation of PEG-naproxen-esters.



Reaction scheme 2: Equilibrium between solid and dissolved naproxen and free acid.

65. This means that the ester formation of those compositions that contain solid naproxen precipitate (most samples allegedly according to the alleged invention) cannot be compared to those compositions that do not contain any solid (the samples according to the closest prior art). The starting concentration of the acid is lower in the former than in the latter. Therefore, the solid naproxen compositions must result in a lower concentration of the PEG-naproxen-ester when these formulations ultimately reach equilibrium than those that do not contain any solid.

66. Only two samples that are according to the alleged invention of the Contested Patent do not contain solids and, therefore, might be of some scientific relevance (samples #8 and #11). Both examples use the same acid (lactic acid) at 0.6 equivalents.

67. It is also worth noting that the initial concentrations of the starting materials differ

greatly between the individual experiments.[2] This makes any comparison with regard to the amount of ester formed in any given formulation even more unreliable.

68. Different initial concentration of the products – water

69. Besides the initial concentration of the starting materials, the initial concentration of the products is also important when evaluating an equilibrium reaction like the ester formation discussed in document D6. As mentioned before, when the initial concentration of a product (for example water) is increased, the equilibrium will shift towards the left of the reaction scheme (i.e. the starting materials) and the equilibrium concentration of the products is therefore reduced.

70. In the current set of experiments the patentee used much higher water concentrations for the only two relevant experiments (samples #8 and #11) compared to the initial water concentration of the comparative examples (samples #16 to #21). This is shown in the following tables:

Sample #	naproxen sodium (g)	naproxen (free acid) (g)	naproxen [mmol]	50% KOH (g)	(H_2O) (g)	H_2O [mmol]	PEG (g)	n (PEG) [mmol]
8	7,15		28,35		1,30	71,89	15,05	25,09
11	5,52		21,88		1,03	57,18	17,34	28,90
16		6,50	28,22	0,33	0,17	9,16	17,89	29,82
17		6,50	28,22	0,96	0,48	26,56	16,68	27,80
18		6,51	28,27	1,59	0,80	44,24	15,36	25,60
19		5,03	21,83	0,29	0,14	7,94	19,56	32,59
20		5,10	22,15	0,76	0,38	21,01	18,58	30,97
21		5,13	22,30	1,23	0,62	34,14	17,54	29,23

Table 2: Content of the relevant compositions (data from document D6).

71. The data from this table is based on the experimental data submitted by the patentee. In addition the table contains the molar amounts of the compounds (calculated by the Opponent) and the initial mass of water used in the comparative experiments (calculated by the Opponent based on the fact that the patentee used 50% KOH – which means 50% of the mass of the KOH solution is water).

[2] This assessment is based on a rough calculation, assuming that all liquid stems from PEG and water, both have a density of 1.0g/mL and the mixture has a density of 1.0 g/mL as well. The difference in concentration will also be observed for a more sophisticated calculation.

72. Just by comparing the masses listed in this table it should be obvious that samples #8 and #11 must have a much higher water concentration than the samples according to the closest prior art (samples #16 to#21). Samples #8 and #11 contain (on average) 1.2 g water while the comparative examples contain (on average) 0.4 g water. This corresponds to a factor of 3 difference between them.

73. In order to visualize the difference in water concentration the molar amounts listed in the table above where used to calculate the corresponding concentrations. This calculation was conducted under the assumption that all liquid stems from PEG and water, both have a density of 1.0 g/mL, and the mixture has a density of 1.0 g/mL as well. It should be obvious that the general trend in concentrations will also be observed for a more sophisticated calculation as the amount of PEG is basically constant for all experiments, whereas the amount of water differs significantly. The following concentrations were calculated:

Sample #	**c (naproxen) [mol/L]**	**c (PEG) [mol/L]**	**c (H_2O) [mmol/L]**
8	1,73	0,92	79,21
11	1,19	0,94	56,07
16	1,56	0,99	9,14
17	1,64	0,97	27,89
18	1,75	0,95	49,34
19	1,11	0,99	7,26
20	1,17	0,98	19,96
21	1,23	0,97	33,87

Table 3: Concentrations of the relevant compounds.

74. In the two experiments which are allegedly according to the alleged invention of the Contested Patent (samples #8 and #11), a much higher initial concentration of water is present than in the comparative experiments (samples #16 to #21). Due to the much higher initial concentrations of water (a product in the ester formation) a shift of the equilibrium towards the starting material will be observed. Consequently it is not surprising that less PEG-ester was observed in the reactions according to the application of the Contested Patent.

75. Competing reactions

76. In addition, the examples (allegedly) according to the alleged invention (samples #7 to #15) offer competing reaction pathways which are not available for the

samples (allegedly) according to the closest prior art (samples #16 to #21).

77. The acids used in the examples #7 to #15 are lactic acid and citric acid. They possess the following structures (see figure below):

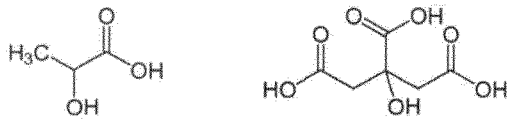


Figure 1: Structures of lactic acid (left) and citric acid (right)

78. These acids contain one (lactic acid) or three (citric acids) carboxy groups and one hydroxyl-group.

79. The carboxy- groups can (and will) compete with the carboxy group of the naproxen in forming PEG-esters. This means the carboxy-groups of these "acids" (lactic- and citric acid) will react with the hydroxyl-group of PEG forming PEG-"acid"-esters. This competing reaction will reduce the concentration of PEG (compared to reactions without such an acid), and this competing reaction will also produce a molecule of water per molecule of PEG-"acid"-ester formed. The influence of the water concentration on the formation of PEG-naproxen-esters has been discussed before.

80. The acids also contain a hydroxyl-group and will compete with the hydroxyl-group of PEG. This means the naproxen can react either with a hydroxyl-group of PEG or with a hydroxyl group of the acid. Again, this competing reaction will result in the formation of water and any naproxen which reacts to form a naproxen-acid-ester cannot form a PEG-naproxen-ester. Consequently, a lower concentration of the PEG-naproxen-ester is to be expected.

81. In addition lactic acid is also known to form cyclic lactides and intermolecular (poly)esters (cf. document D8, last reaction scheme and the text starting from 4 lines above this reaction scheme and document D9, 3rd and 4th paragraph[3]). This intermolecular reaction will increase the water concentration as one molecule of water is formed for each intermolecular lactic ester formed.

82. Additional remarks

[3] Document D9 is an article from the weppage Wikipedia dated June 13, 2017; i.e. it was published after the priority date of the Contested Patent. However, the information disclosed therein only summarizes a general fact which is obvious to the person skilled in the art.

83. The examples according to the current invention use naproxen sodium, whereas the comparison experiments use naproxen in the presence of potassium hydroxide. It is unclear to us why the patentee used potassium hydroxide. In our opinion a proper comparison would require the use of sodium hydroxide. The use of sodium hydroxide as hydroxide species is explicitly mentioned in claim 4 of document D1.

84. The comparison examples #16 and #19 contain less than 1% weight of water (0.7% and 0.6% respectively). However, document D1 requires the presence of 1% to 20% water by weight. Consequently, these examples are not according to the teaching of document D1 and cannot be considered as comparative examples.

85. The patentee does not provide any information on the margin of error and the number of significant figures. Thus, any information provided is meaningless. But even when all these flaws are ignored and the determined amounts of PEG-naproxen-ester are compared there is no advantage and/or the advantage is negligible. 89. The amount of PEG-naproxen-esters formed in the experiments according to the alleged invention of the Contested Patent after mixing is between 0.0021% (sample #14) and 0.0087% (sample 13). After stress induction the amount determined is between 0% and 0.0107% (sample #14).

86. In the samples (allegedly) according to the prior art, between 0.0144% (sample #19) and 0.0178% (sample #16) PEG-naproxen-ester is determined after mixing. Between 0.0093% and 0.0140% is determined after stress induction (samples #19 and #21).

87. This means that after stress induction the experiments according to the closest prior art might actually form less PEG-naproxen-ester than specific experiments (allegedly) according to the alleged invention of the Contested Patent.

88. Conclusion regarding the experiments filed on March 26, 2012 (document D6)

89. The experiments are about the equilibrium concentrations of an ester which is formed. This formation is an (acid catalyzed) equilibrium reaction between an acid and an alcohol forming an ester and water. According to the principle of Le Chatelier the equilibrium concentrations of the individual compounds is depending on the (initial) concentration of the starting materials and the products. Our main objections with regards to these experiments are:

i. The starting materials are undissolved in some experiments resulting in a much lower initial concentration of the starting materials.

ii. The initial concentration of both starting materials differ between different experiments.

iii. The initial concentration of the product water differs siginificantly.

iv. In the experiments according to the Contested Patent competing reactions are possible. These competing reactions will (for example) form water and reduce the concentration of one of the starting materials.

VII.2. Alleged technical effects

90. As shown in the previous section the alleged technical effect (suppression of PEG-esters) was not shown. It is established case law that alleged advantages cannot be taken into consideration as long as they are not evidenced. The case law of the Board of Appeals elaborates on this principle (Case law of the board of appeals, 8th edition, July 2016 – Section I. D. 4.2):

> According to the case law of the boards of appeal, alleged advantages to which the patent proprietor/ applicant merely refers, without offering sufficient evidence to support the comparison with the closest prior art, cannot be taken into consideration in determining the problem underlying the invention and therefore in assessing inventive step (see **T 20/81**, OJ 1982, 217; **T 181/82**, OJ 1984, 401; **T 124/84**, **T 152/93**, **T 912/94**, **T 284/96**, **T 325/97**, **T 1051/97**). In **T 1027/08**, the board added that there was no reason to deviate from this case law as it was based on the understandable rule that a patent can only properly be granted for a solution claimed as non-obvious **if** it actually has the alleged effect (see also in this chapter I.D.4.6).
>
> In view of the absence of any data confirming the alleged improvement, such an effect could not be taken into account in the formulation of the technical problem (**T 2044/09**).

91. In the following considerations we assume that the Opposition Division agrees with our assessment regarding the lacking proof for a technical effect in the experiments conducted by the patentee. However, afterwards we will also present arguments regarding the lack of inventive step for the unlikely case that the Opposition Division disagrees with our assessment and considers the experimental data to show the alleged effect.

92. In case the Opposition Division concurs with our argumentation, the task of the Contested Patent can only be to provide an alternative.

VII.3 Example R of document D4 as closest prior art

93. The Contested Patent does not show any technical effect and merely lists components for the fill material of a softgel capsule. The Contested Patent can only be considered to provide an alternative to the prior art. Example R of document D4 can be considered as the closest prior art. This example was already discussed with regards to the lacking novelty of the Contested Patent.

94. In accordance with T597/07 and T131/01 the Opponent will not discuss the inventiveness of claims 1, 2, 4, 6, 7, 8, 9, 10 and 13 in view of document D4 as those claims were already considered as being not novel in view of this document. However, in case the Opposition Division does not concur with the arguments regarding the novelty of one or more of these claims the Opponent will reserve the right to file a substantial argument regarding the lack of inventive step for any one of these claims at a later point in time.

VII.3.1 Lacking inventive step for claim 3

95. Claim 3 of the Contested Patent limits the acids used to lactic acid. There is no effect attributed to lactic acid in comparison to the citric acid used in document D4; therefore, it is obvious to the person skilled in the art that the citric acid can be replaced with a similar acid like lactic acid. Both acids can be considered similar as both contain a hydroxyl-group and at least one carboxyl-group and possess a similar pKa-value (cf. document D13, roughly in the middle of the right page for the pKs-value of lactic acid and document D12, page 2, table on the right, fourth characteristic from the bottom for the pKa-value of citric acid[4]).

VII.3.3. Lacking inventive step for claim 11

96. Claim 11 of the Contested Patent is related to a method of making the capsules of claim 1. This method comprises the mixing of the components and their encapsulation in a softgel capsule.

97. The method mentioned in this claim is inherently disclosed in the closest prior art example. It discloses a mixture according to claim 1 of the Contested Patent and discloses the use of such mixtures in softgel capsules. It should be obvious for the person skilled in the art that such capsules can be prepared by mixing the components in a first step and encapsulating them in a second step. Consequently, this claim cannot be considered as inventive.

---

[4] Document D12 is an article from the weppage Wikipedia dated June 13, 2017; i.e. it was published after the priority date of the Contested Patent. However, the pKa-value disclosed therein is a general fact which was known to the person skilled in the art.

VII.3.4 Lacking inventive step for claim 12

98. Claim 12 of the Contested Patent refers to claim 11 and further limits the temperature during the mixing of from 50 to 70 °C.

99. The use of elevated temperatures to enhance a mixing process is obvious to a person skilled in the art. The use of elevated temperatures for the mixing step for similar composition are (for example) disclosed in documents D3 (cf. paragraph [0041]) and D1 (cf. column 10, lines 67 to 68). Claim 12 of the Contested Patent is therefore not inventive.

VII.4 Lacking inventiveness in view of document D1

100. In case the Opposition Division does not follow our arguments regarding the experiments and is of the opinion that the experiments show that less PEG-naproxen-ester is formed when compositions according to the alleged invention are used we will show that the Contested Patent is, nevertheless, not inventive.

101. In document D1 an acidic agent (naproxen, cf. claim 8) and a base (for example NaOH, cf. claim 4) is present in an aqueous environment. The base is present from 0.1 to less than 1.0 molar equivalents. PEG and solubilizers are present as well (cf. claim 6).

102. Naproxen and sodium hydroxide will react in an acid/base reaction and a mixture of acidic naproxen and deprotonated naproxen sodium will be present in solution.

103. In the contested Patent a mixture of naproxen sodium, an acid, polyethylene glycol, water and a solubilizer is present. The acid is present in an amount from 0.2 to 1.0 molar equivalents. The acid is selected from a list but all acids bear a carboxyl-group.

104. Naproxen sodium will react in an acid/base reaction and a mixture of acidic naproxen and deprotonated naproxen sodium will be present in solution (as in document D1 cf. paragraph [107] above)

105. This means the distinguishing feature is the addition of an acid bearing a carboxyl-group.

106. The distinguishing result is the formation of less PEG-naproxen-ester.

107. If the formation of PEG-naproxen-esters was considered a problem and a person skilled in the art wanted to suppress this formation (starting from document D1) he

would have analyzed the ester formation reaction in general and would have considered that:

i. Esters can be hydrolysed by the addition of an acid (cf. document D10, first two sentences).

Consequently, the addition of acids is obvious.

108. In addition, if the formation of PEG-naproxen-esters was considered an issue he would also have considered adding molecules containing carboxylic groups (this means acids according to the invention of the Contested Patent). These carboxylic groups would react with PEG and form carboxyl-PEG-esters and water. This would reduce the concentration of PEG which can form PEG-naproxen-esters. Furthermore, the synthesized water will – according to the principle of Le Chatelier – reduce the equilibrium concentration of PEG-naproxen-esters (and any other ester).

109. Therefore, the addition of molecules that contain (at least one) carboxy-group is obvious as well. Consequently, claim 1 cannot be considered as inventive over document D1.

VII.4.1 Dependent claims

110. The dependent claims are also not inventive in view of document D1.

111. In claim 2 the list of acids is reduced to citric acid or lactic acid and in claim 3 it is further reduced to lactic acid.

112. Both of these acids contain a hydroxyl-group and carboxyl-group(s). If the formation of PEG-naproxen-esters was considered an issue the person skilled in the art would have considered adding molecules which also contain a hydroxyl group. These hydroxyl groups would react with naproxen to form an ester and water. This would reduce the concentration of naproxen which can form PEG-naproxen-esters. Furthermore, the synthesized water will reduce the equilibrium concentration of PEG-naproxen-esters. These effects were discussed earlier with regards to the experiments of document D6.

113. The addition of molecules that possess both carboxy-groups and hydroxy groups (like maleic acid) would be especially beneficial. Such molecules can form esters both with PEG and naproxen (while also forming water), will form intermolecular esters, which will release water as well, and, furthermore, can hydrolyse esters.

These effects have been discussed earlier with regards to the experiments of document D6.

114. The use of such acids is therefore obvious when the hydrolysis of PEG-naproxen-esters and/or a lower formation of PEG-naproxen-ester is desired.

115. In claim 4 the amount of PEG is restricted from 10% to 80% by weight. Claim 1 of document D1 discloses the presence of 10% to 80% by weight PEG. Consequently, claim 4 is not inventive in view of document D1.

116. In claim 5 the molecular weight of PEG is restricted to between 300 and 1500. In claim 5 of document D1 the molecular weight of PEG is restricted to between 200 and 100000. Consequently, claim 5 is not inventive in view of document D1.

117. In claim 6 the amount of water is limited to 1% to 18% by weight. In claim 1 of document D1 the amount of water is limited to 1% to 20% by weight. Consequently, claim 6 is not inventive in view of document D1.

118. In claim 7 the further presence of various additional compounds is required. In claim 1 of document D1 the presence of water (solvent) is required. Consequently, claim 7 is not inventive in view of document D1.

119. In claim 8 the amount of solubilizer (like glycerin) is restricted to an amount from 1% to 10% by weight. In claim 2 of document D1 the amount of glycerin (solubilizer) is restricted to an amount from 4% to 12%. Consequently, claim 8 is not inventive in view of document D1.

120. In claim 9 the fill material of the capsule is required to be liquid. In claim 1 of document D1 it is mentioned that it concerns solutions (this means liquids) which are suitable for encapsulation. Consequently, claim 9 is not inventive in view of document D1.

121. In claim 10 the capsule is limited for use as a medicament. Document D1 is related to pharmaceutical acceptable solutions (cf. claim 1). Consequently, claim 10 is not inventive in view of document D1.

122. Claim 11 of the Contested Patent is related to a method of making the capsules of claim 1. This method comprises the mixing of the components and their encapsulation in a softgel capsule. Claim 12 of the Contested Patent refers to claim 11 and further limits the temperature during the mixing of from 50 to 70 °C. The use of such a process including the elevated temperatures to enhance the

mixing process is obvious to a person skilled in the art. The use of such a process at 60°C is disclosed in document D1 (cf. column 10, lines 67 to 68). Consequently, claims 11 and 12 are not inventive in view of document D1.

VII.4.2 Independent claim 13

123. Independent claim 13 is basically identical to independent claim 1. Due to the reasons outlined with regards to claim 1 claim 13 is also not inventive in view of document D1.

VII.4.3 Inventiveness in view of document D1 – conclusion

124. Based on the previous assessments the independent claims, as well as the dependent claim, are not inventive in view of document D1.

VIII. Conclusion

125. The above-given explanations show that the revocation of the Contested Patent is justified.

Bernard Lohmanns
Patent Attorney

Europäisches Patentamt
European Patent Office
Office européen des brevets

Acknowledgement of receipt

We hereby acknowledge receipt of the Notice of Opposition:

Submission number	5363237
Application number	EP06737018.9
Patent number	EP1863458
Date of receipt	14 June 2017
Your reference	BD.01.17.EIN
Opponent	DIECKHOFF, Beate
Title	SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

Documents submitted

package-data.xml	ep-opposition-data.xml
ep-oppo.pdf (6 p.)	OPPO.pdf\OPPOSITION - BD.01.17.EIN.pdf (24 p.)
Published-Evidence-1.pdf\D1 - US5360615A.pdf (10 p.)	Published-Evidence-2.pdf\D2 - WO2006096580A1.pdf (22 p.)
Published-Evidence-3.pdf\D3 - US2001007668A1.pdf (10 p.)	Published-Evidence-4.pdf\D4 - US5541210A.pdf (16 p.)
Published-Evidence-5.pdf\D8 - Beyer Walter, Lehrbuch der organischen Chemie.pdf (1 p.)	Published-Evidence-6.pdf\D9 - excerpt from the Wikipedia on Milchsäure (lactic acid).pdf (6 p.)
Published-Evidence-7.pdf\D10 - Beyer Walter, Lehrbuch der organischen Chemie page 260.pdf (1 p.)	Published-Evidence-8.pdf\D11 - Polyethylene Glycol USP.pdf (5 p.)
Published-Evidence-9.pdf\D12 - excerpt from the Wikipedia weppage on citric acid.pdf (8 p.)	Published-Evidence-10.pdf\D13 - Beyer Walter, Lehrbuch der organischen Chemie page 283.pdf (1 p.)

	Other-evidence-1.pdf\D5 - Experiments 2011.pdf (5 p.) Other-evidence-3.pdf\D7 - solubility of PEG600.pdf (2 p.)	Other-evidence-2.pdf\D6 - Experiments 2012.pdf (8 p.)

Submitted by	CN=Bernard Lohmanns 50454
Method of submission	Online
Date and time receipt generated	14 June 2017, 12:14 (CEST)
Message Digest	D3:D9:2C:C3:79:6B:76:7F:33:41:FB:3F:FC:31:6B:8F:7A:F0:3A:1E

Correction by the EPO of errors in debit instructions filed by eOLF
Errors in debit instructions filed by eOLF that are caused by the editing of Form 1038E entries or the continued use of outdated software (all forms) may be corrected automatically by the EPO, leaving the payment date unchanged (see decision T 152/82, OJ EPO 1984, 301 and point 6.3 ff ADA, Supplement to OJ EPO 10/2007).

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Date
26.06.2017

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 1466 / 1863458
Applicant/Proprietor	
Banner Life Sciences, LLC	

Communication of a notice of opposition

You are hereby informed of a notice of opposition to the European patent specified above (see attached copy in the enclosure). The documents specified as patent documents in the notice of opposition are available for inspection via the European Patent Register at **www.epo.org/register**. Should you wish to receive these documents in paper format, they will be supplied to you free of charge if specifically requested on receipt of this communication (see OJ EPO 2009, 434).

If oral proceedings are to take place, parties are advised to check the electronic file via European Patent Register in advance of the hearing to ensure they are in possession of all relevant documents.

An invitation to file observations and to file amendments, where appropriate, to the description, claims and drawings (R. 79(1) EPC) will be issued separately.

The period within which such observations may be filed will not be fixed until the following conditions are met:

(a) the opposition period has expired;

(b) the notice of opposition has been examined for certain formal requirements (R. 77 EPC).

For the Examining Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

Enclosure: Notice of opposition

O1 : Beate Dieckhhoff with cited documents - non patent literature.

Europäisches Patentamt
European Patent Office
Office européen des brevets

Notice of opposition to a European patent

I. Patent opposed

Patent No.	EP1863458
Application No.	EP06737018.9
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	14 September 2016
Title of the invention	SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS

II. Proprietor of the patent

first named in the patent specification	Banner Life Sciences, LLC
Opponent's or representative's reference	BD.01.17.EIN

III. Opponent

Name	DIECKHOFF Beate
Address:	Dünnwalder Grenzweg 20 51375 Leverkusen Germany
State of residence or of principal place of business	Germany
Country of nationality	Germany
Multiple opponents (see additional sheet)	☐

IV. Authorisation

1. Representative

	Lohmanns Bernard	
Address of place of business	Benrather Schlossallee 49-53 40597 Düsseldorf Germany	
Telephone/Fax	0211 - 86531-0	0211 - 86531-11
E-mail:	mail@patlaw.de	

Multiple representatives (see additional sheet) ☐

Authorisation(s)

is/are enclosed ☐

has/have been registered under No. ☐

V. Opposition is filed against

the patent as a whole ☒

claim(s) No(s).

VI. Grounds for opposition:

Opposition is based on the following grounds:

(a) the subject-matter of the European patent opposed is not patentable (Art. 100(a) EPC) because:

- it is not new (Art. 52(1); Art. 54 EPC) ☒
- it does not involve an inventive step (Art. 52(1); Art. 56 EPC) ☒
- patentability is excluded on other grounds, namely articles ☐

(b) the patent opposed does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (Art. 100(b) EPC; see Art. 83 EPC). ☒

(c) the subject-matter of the patent opposed extends beyond the content of the application/of the earlier application as filed (Art. 100(c) EPC, see Art. 123(2) EPC). ☒

VII. Facts (Rule 76(2)(c) EPC)

presented in support of the opposition are submitted herewith on an attached document ☒

VIII. Other requests:

- Oral proceedings are hereby requested auxiliarily.

IX. Evidence presented

D1	Patent document	US5,360,615 (A) , 01.11.1994 original file name: D1 - US5360615A.pdf attached as: Published-Evidence-1.pdf
D10	Non-patent literature - book	Beyer, Walter, "Lehrbuch der organischen Chemie" Stutgart: Hirzel, 1988, Ed. 21. particular relevance: page 260 original file name: D10 - Beyer Walter, Lehrbuch der organischen Chemie page 260.pdf attached as: Published-Evidence-7.pdf
D11	Non-patent literature - internet	Wikipedia , "Excerpt from the U.S. weppage pharmacopeia on PEG (lactic acid)" , [cited 13.06.2017] Available from: [http://www.pharmacopeia.cn/v29240/usp29nf24s0_m66430.html] original file name: D11 - Polyethylene Glycol USP.pdf attached as: Published-Evidence-8.pdf
D12	Non-patent literature - internet	Wikipedia, "Excerpt from the English Wikipedia weppage on citric acid" , [cited 13.06.2017] Available from: [https://en.wikipedia.org/w/index.php?title=Citric_acid&oldid=784172966] original file name: D12 - excerpt from the Wikipedia weppage on citric acid.pdf attached as: Published-Evidence-9.pdf
D13	Non-patent literature - book	Beyer, Walter, "Lehrbuch der organischen Chemie" Stuttgart: Hirzel, 1988, Ed. 21 particular relevance: page 283 original file name: D13 - Beyer Walter, Lehrbuch der organischen Chemie page 283.pdf attached as: Published-Evidence-10.pdf
D2	Patent document	WO 2016/096580 (A1) , 14.09.2006 original file name: D2 - WO2006096580A1.pdf attached as: Published-Evidence-2.pdf
D3	Patent document	US2001/0007668 (A1) , 12.07.2001 original file name: D3 - US2001007668A1.pdf attached as: Published-Evidence-3.pdf
D4	Patent document	US5,541,210 (A) , 30.07.1996 original file name: D4 - US5541210A.pdf attached as: Published-Evidence-4.pdf
D5	Other evidence	Experiments regarding the Contested Patent filed by the Patentee on September 16, 2011 during the examination procedure original file name: D5 - Experiments 2011.pdf attached as: Other-evidence-1.pdf
D6	Other evidence	Experiments regarding the Contested Patent filed by the Patentee on March 26, 2012 with the substantiation of the appeal original file name: D6 - Experiments 2012.pdf attached as: Other-evidence-2.pdf
D7	Other evidence	Technical data sheet for PEG-600

		original file name: D7 - solubility of PEG600.pdf attached as: Other-evidence-3.pdf
D8	Non-patent literature - book	Beyer, Walter, "Lehrbuch der organischen Chmie" Stuttgart: Hirzel, 1988, Ed. 21 particular relevance: page 280 original file name: D8 - Beyer Walter, Lehrbuch der organischen Chemie.pdf attached as: Published-Evidence-5.pdf
D9	Non-patent literature - internet	Wikipedia , "Excerpt from the German Wikipedia weppage on Milchsäure (lactic acid)" , [cited 13.06.2017] Available from: [https://de.wikipedia.org/w/index.php?title=Milchsäure&oldid=165775114] original file name: D9 - excerpt from the Wikipedia on Milchsäure (lactic acid).pdf attached as: Published-Evidence-6.pdf

X. Payment

Mode of payment	Debit from deposit account

The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated in the fees section below.

Currency:	EUR
Deposit account number:	28003075
Account holder:	Bernard Lohmanns

Refunds

Any refunds should be made to EPO deposit account:	28003075
Account holder:	Bernard Lohmanns

Fees

	Factor applied	Fee schedule	Amount to be paid
010 Opposition fee	1	785.00	785.00
Total:		EUR	785.00

	A Forms	Details:	System file name:
A-1	Form for notice of opposition		ep-oppo.pdf

	B Attached document files	Original file name:	System file name:
B-1	1. Facts and arguments	OPPOSITION - BD.01.17.EIN.pdf	OPPO.pdf

	C Attached evidence files	Original file name:	System file name:
C-1	1. Patent document	D1 - US5360615A.pdf	Published-Evidence-1.pdf
C-2	2. Patent document	D2 - WO2006096580A1.pdf	Published-Evidence-2.pdf
C-3	3. Patent document	D3 - US2001007668A1.pdf	Published-Evidence-3.pdf
C-4	4. Patent document	D4 - US5541210A.pdf	Published-Evidence-4.pdf
C-5	1. Non-patent literature - book	D8 - Beyer Walter, Lehrbuch der organischen Chemie.pdf	Published-Evidence-5.pdf
C-6	2. Non-patent literature - book	D10 - Beyer Walter, Lehrbuch der organischen Chemie page 260.pdf	Published-Evidence-7.pdf

C-7	3. Non-patent literature - book	D13 - Beyer Walter, Lehrbuch der organischen Chemie page 283.pdf	Published-Evidence-10.pdf
C-8	4. Non-patent literature - internet	D9 - excerpt from the Wikipedia on Milchsäure (lactic acid).pdf	Published-Evidence-6.pdf
C-9	5. Non-patent literature - internet	D11 - Polyethylene Glycol USP.pdf	Published-Evidence-8.pdf
C-10	6. Non-patent literature - internet	D12 - excerpt from the Wikipedia weppage on citric acid.pdf	Published-Evidence-9.pdf
C-11	1. Other evidence	D5 - Experiments 2011.pdf	Other-evidence-1.pdf
C-12	2. Other evidence	D6 - Experiments 2012.pdf	Other-evidence-2.pdf
C-13	3. Other evidence	D7 - solubility of PEG600.pdf	Other-evidence-3.pdf

Signature of opponent or representative

Place	**Düsseldorf**
Date:	**14 June 2017**
Signed by:	**Bernard Lohmanns 50454**
Capacity:	**(Bernard Lohmanns)**

PA B. Lohmanns, Benrather Schlossallee 49-53, D-40597 Düsseldorf

Europäisches Patentamt
80298 München

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14 June 2017 BL/JW

Opposition against European Patent No. 1 863 458 (06737018.9)
Proprietors: Banner Life Sciences, LCC
Opponents: Beate Dieckhoff
Our Ref.: BD.01.17.EIN

NOTICE OF OPPOSITION

On behalf of

Beate Dieckhoff

Dünnwalder Grenzweg 20

51375 Leverkusen

Germany (DE)

an opposition is filed herewith pursuant to Art. 99 (1) EPC against the European Patent

EP 1 863 458 B1

(European Patent Application No. 06 737 018.9).

Publication and Mention of the Grant:	September 14, 2016
Title of the Patent:	Solvent system for enhancing the solubility of pharmaceutical agents
Proprietor:	Banner Life Sciences, LLC High Point North Carolina 27265 USA

The opposition fee in the amount of € 785.00 is paid online today.

I. Requests

1. The opposition is directed against all claims of 1 863 458 B1 (hereinafter also referred to as "the Contested Patent"). It is requested that the Contested Patent be revoked in its entirety with effect for all designated EPC Contracting and Extension States.

2. The opposition is based on the grounds that

   (a) the subject matter of the Contested Patent is not patentable within the terms of Articles 52 to 57 EPC (see Article 100(a) EPC); specifically, the subject matter is not novel and/or not based on an inventive step (Articles 54 and 56 EPC).

   (b) the Contested Patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (see Article 100(b) EPC).

   (c) The subject-matter of the Contested Patent extends beyond the content of the application as filed (see Article 100 (c) EPC).

3. If the Opposition Division feels unable to grant the above request for revocation on the basis of our written submission(s), oral proceedings are hereby requested in accordance with Article 116 (1) EPC.

II. Documents referred to in the present opposition

4. The following references are submitted herewith:

D1: US 5,360,615 published on November 1, 1994 (prior art according to Art. 54 (2) EPC)

D2: WO 2006/096580 A (application of the Contested Patent as originally filed)

D3: US 2001/007668 A, published on July 12, 2001 (prior art according to Art. 54 (2) EPC)

D4 US 5,541,210, published on July 30, 1996 (prior art according to Art. 54 (2) EPC)

D5: Experiments regarding the Contested Patent filed by the Patentee on September 16, 2011 during the examination procedure

D6: Experiments regarding the Contested Patent filed by the Patentee on March 26, 2012 with the substantiation of the appeal

D7: Technical data sheet for PEG-600

D8: Beyer, Walter – Lehrbuch der organischen Chemie, 21. Edition, Stuttgart, Hirzel, 1988, page 280

D9: Excerpt from the German Wikipedia weppage on Milchsäure (lactic acid)

D10: Beyer, Walter – Lehrbuch der organischen Chemie, 21. Edition, Stuttgart, Hirzel, 1988, page 260

D11 Excerpt from the U.S. weppage pharmacopeia on PEG (lactic acid)

D12 Excerpt from the English Wikipedia weppage on citric acid

D13 Beyer Walter, Lehrbuch der organischen Chemie, 21. Edition, Stuttgart, Hirzel, 1988, page 283

III. The subject matter of the Contested Patent

5. The Contested Patent comprises thirteen claims, of which two are independent claims.

5.1 Independent claim 1 relates to

Feature 1.1 a softgel capsule comprising a fill material wherein the fill material

Feature 1.2 (a) naproxen sodium;

Feature 1.3 (b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid

Feature 1.3.1 in an amount from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

Feature 1.4 (c) polyethylene glycol;

Feature 1.5 (d) water; and

Feature 1.6 (e) a solubilizer selected from the group consisting of glycerin

5.2. The dependent claims 2 to 12 disclose the following features:

Feature 2.1 (b) is citric acid or lactic acid.

Feature 3.1 (b) is lactic acid.

Feature 4.1 polyethylene glycol is present in an amount from 10% to 80% by weight.

Feature 5.1 the polyethylene glycol is one or more polyethylene glycols with a molecular weight between 300 and 1500.

Feature 6.1 water is present in an amount from 1% to 18% by weight.

Feature 7.1 further comprising one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, and combinations thereof.

Feature 8.1 the solubilizer is present in an amount from 1% to 10% by weight.

Feature 9.1 the fill material is liquid.

Feature 10.1 A capsule of any of the preceding claims for use as a medicament.

Feature 11.1 A method of making the capsule comprising

(a) mixing components (a), (b), (c), (d), and (e) as defined; and

(b) encapsulating the mixture in a soft gel capsule.

Feature 12.1 The method, wherein step (a) is conducted at a temperature from

5.3 Independent claim 13 relates to the use of

Feature 13.1 (a) naproxen sodium;

Feature 13.2 (b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid

Feature 13.2.1 in an amount from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;

Feature 13.3 (c) polyethylene glycol;

Feature 13.4 (d) water; and

Feature 13.5 (e) a solubilizer selected from the group consisting of glycerin

Feature 13.6 in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

IV. Unallowable Extension of the Contested Patent (Art. 123(2) EPC)

6. The subject-matter of claims 11 and 12 of the Contested Patent extend beyond the content of the application as filed.

IV.1 Claim 11

7. Claim 11 states:

A method of making the capsule of claim 1 comprising

(a) mixing components (a), (b), (c), (d) and (e) as defined in claim 1; and

(b) encapsulating the mixture in a softgel capsule.

8. It seems the patentee considered page 8, line 25 to page 9, line 2 of the application as originally filed (D2) as basis for this claim. The passage reads (emphasis added):

The fill material is prepared by mixing the agent (such as a salt of the

drug), the deionizing agent, water, and polyethylene glycol at a temperature of 50°C to 70°C. The resulting solution is encapsulated using the appropriate gel mass. The pharmaceutical agent is present in an amount from about 10% to about 50% by weight. The deionizing agent is present in an amount from about 0.2 to 1.0 mole per mole of the pharmaceutical agent. Water is present in an amount from about 1% to about 20% by weight and polyethylene glycol is present in amount from about 10% to about 80% by weight. Optionally, propylene glycol and/or polyvinyl pyrrolidone are present in an amount from about 1% to about 10%.

9. This passage clearly mentions that the mixing is conducted at a specific temperature range (50 to 70 °C). Furthermore, this passage also specifies the amounts of the pharmaceutical agent, water, polyethylene glycol, and the solubilizers used.

10. All these limitations are missing in claim 11 of the Contested Patent which is therefore not in accordance with the requirement of Article 123(2) EPC.

IV.2 Claim 12

11. Claim 12 refers to claim 11 and limits the temperature in step (a) to the range of from 50 to 70 °C. This means this claim resolves one of the issues raised with regards to the unallowable extension of claim 11.

12. However, the subject-matter of this claim still extends beyond the subject matter as originally filed as it does not contain the specific amounts for the pharmaceutical agent, water, polyethylene glycol, and the solubilizers disclosed in the relevant paragraph of the application as filed. Consequently, claim 12 of the Contested Patent is not in accordance with the requirements of Article 123(2) EPC.

V. Lack of sufficiency of disclosure

13. The Contested Patent does not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art:

V.1 Claim 7

14. In claim 7 the further presence of one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives,

surfactants, and combinations thereof is required.

15. The Contested Patent does not provide any explanation to the meaning of crystallization inhibitors, bulk filling agents and bioavailability enhancers. Therefore, a person skilled in the art would not know how to obtain a softgel capsule containing one of these additional excipients.

VI. Missing novelty of the subject matter of the claims of the Contested Patent

VI.1 Missing novelty of independent claim 1

16. Independent claim 1 is not novel in view of document D4. Document D4 is related to various pharmaceutical compositions. These compositions are preferably in soft gelatin capsules (cf. column, 19, line 4; feature 1.1). The composition used in Example R (column 28 to 29 of document D4) is shown below.

	mg/fl oz
naproxen sodium anhydrous, USP	220 mg
doxylamine succinate, USP	12.5
dextromethorphan hydrobromide, USP	30
Subject Compound 1	6
Dow XYS-40010.00 resin	3
high fructose corn syrup	16000
polyethylene glycol, NF	3000
propylene glycol, USP	3000
alcohol, USP	2500
sodium citrate dihydrate, USP	150
citric acid, anhydrous, USP	50
saccharin sodium, USP	20
flavor	3.5
purified water, USP	3800
total	28795 mg

Table 1: Composition of Example R of document D4.

17. It comprises naproxen sodium (feature 1.2), citric acid (feature 1.3), polyethylene glycol (feature 1.4), water (feature 1.5) and propylene glycol (feature 1.6).

18. In this example 220 mg naproxen sodium (0.87 mmol) and 50 mg citric acid (0.26 mmol) are used. This corresponds to 0.30 mol equivalents citric acid per mol naproxen sodium (feature 1.3.1).

19. Consequently, all features of independent claim 1 are disclosed in document D4.

VI.2 Missing novelty of claim 2

20. Feature 2.1 requires component (b) to be citric acid or lactic acid. In Example R of document D4 citric acid is used (see argumentation above). Consequently, claim 2 is also not novel in view of document D4.

VI.3 Missing novelty of claim 4

21. Feature 4.1 requires the compound (c) (polyethylene glycol) to be present in an amount from 10% to 80% by weight.

22. In example R of document D4 3000 mg polyethylene glycol are present and the total mass of all components is 28795 mg. This means polyethylene glycol is present in an amount of 10.41%, which is within the feature of claim 4. Consequently, the subject matter of claim 4 is not novel in view of document D4.

VI.4 Missing novelty of claim 5

23. Feature 5.1 limits the molecular weight of PEG between 300 and 1500.

24. In example R of document D4 "PEG NF" is used. The "NF" refers to the National Formulary, which together with the USP comprises the US Pharmacopeia. The molecular weight of PEG according to the US Pharmacopeia is within the range claimed in claim 5 (cf. document D11, first table on pages 1 and 2, which lists PEG with a molecular weight from 200 to 2100[1])

VI.4 Missing novelty of claim 6

25. Feature 6.1 requires the compound (d) (water) to be present in an amount from 1% to 18% by weight.

26. In example R of document D4 3800 mg of water is present and the total mass of all components is 28795 mg. This means water is present in an amount of 13% by weight, which is according to claim 6. Accordingly, the subject matter of claim 6 is not novel in view of document D4.

VI.5 Missing novelty of claim 7

27. Feature 7.1 requires the further presence of one or more excipients selected from the group consisting of plasticizers, crystallization inhibitors, wetting agents, bulk filling agents, solubilizers, bioavailability enhancers, solvents, dyes, preservatives, surfactants, and combinations thereof.

28. According to the Contested Patent solubilizers are the compounds mentioned in

[1] Document D11 is an article from the weppage pharmacopeia dated June 13, 2017; i.e. it was published after the priority date of the Contested Patent. However, the properties of PEG mentioned therein (i.e. molecular weight) did not change from the priority date of the Contested Patent.

feature 1.6 (glycerin, polyvinylpyrrolidone and propylene glycol). As outlined before example R of document D4 comprises such a solubilizer (propylene glycol). Consequently, claim 7 is not novel in view of document D4.

VI.6 Missing novelty of claim 8

29. Feature 8.1 requires that the compound (e) (solubilizer) is present in an amount from 1% to 10% by weight.

30. In example R of document D4 3000 mg of the solubilizer propylene glycol is used and the total mass of all components is 28795 mg. This means the solubilizer is present in an amount of 10.41% by weight. Consequently, claim 8 is not novel in view of this example.

VI.7 Missing novelty of claim 9

31. Feature 9.1 requires the fill material to be liquid.

32. The fill material disclosed in example R of document D4 is liquid. With regards to this example it is disclosed that the patient should "[...] take one fluid ounce every six hours" (cf. document D4, column 28, lines 60-61). This means the material is liquid and claim 9 is not novel in view of document D4.

VI.8 Missing novelty of claim 10

33. Feature 10.1 requires a capsule of any of the preceding claims for use as a medicament.

34. With regards to example R document D4 clearly discloses that this example is for the relief of minor aches and pains and also mentions a prescribable amount (cf. document D4, column 28, lines 55-61). This means it is used as a medicament and the claim 10 is not novel in view of document D4.

VI.9 Missing novelty of independent claim 13

35. Independent claim 13 addresses the use of the same filling contained in features 1.2 to 1.6 of claim 1 in the manufacture of a medicament in the form of a capsule for administration of the naproxen sodium to a patient in need thereof.

36. As outlined above (see argumentation in V.1) all features of independent claim 13 are not novel in view of document D4.

VII. Lack of inventive step of the subject matter of the claims of the Contested Patent

37. In addition to being not novel the Contested Patent is also not inventive.

38. Before addressing the inventiveness of the Contested Patent the Experiments filed by the patentee will be assessed in the following:

VII.1 Experiments filed by the Patentee

39. The application as filed does not contain any experimental results. The twelve examples disclosed therein merely disclose various compositions for the fill material without evidencing any technical effect.

40. In the course of the Examination the patentee filed new experiments on September 16, 2011 and on March 26, 2012. These experiments will be discussed in the following.

VII.1.1 Experiments filed on September, 16, 2011 (document D5)

41. These experiments were filed prior to the scheduled oral proceedings before the Examining Division regarding the patent application of the Contested Patent. In these experiments, the patentee tried to show that compositions according to the application form very small amounts of PEG-naproxen-esters over (up to) several years.

42. The fill material and the active ingredients used in these experiments are listed in the table below:

Active Ingredients

Ingredient	Amount per Capsule
naproxen sodium	220mg

Fill Excipients

Ingredient	Amount (mg) per Capsule
Lactic Acid	44.0
Propylene Glycol	17.7
Povidone K-30	17.7
Polyethylene Glycol 600	580.6

Table 2: active ingredient and fill excipients used in the experiments filed by the Patentee on September 16, 2011 (document D5).

43. According to document D5, the composition is used within a capsule (feature 1.1) and as shown in the table its fill consists of naproxen sodium (feature 1.2), lactic acid (feature 1.3), propylene glycol (feature 1.6), povidone K-30 and polyethylene glycol 600 (feature 1.4). The molar equivalent of lactic acid to naproxen sodium is 0.56 (feature 1.3.1). Independent Claim 13 and its features literally and/or inherently correspond to claim 1 and are, therefore also fulfilled.

44. In these experiments water is not part of the fill material; water is only mentioned as part of the gelatin shell. According to the Contested Patent (claims as granted), the fill material must comprise water (feature 1.5). Therefore, these experiments are not according to the alleged invention of the Contested Patent.

45. For these capsules the patentee observed hardly any ester formation over the course of up to three years (less than 1%). It is no surprise that in such an experimental setup hardly any ester formation is observed.

46. Most of the naproxen sodium will be present as solid due to the lack of water for solubilisation and solid naproxen sodium will not react to form PEG-naproxen-ester. Consequently, it is no surprise that hardly any PEG-ester formation is observed in this experimental setup.

47. In addition, the patentee does not provide any comparative examples or comparative data from the closest prior art that would allow these results to be put

into context.

VII.1.2 Experiments filed on March 26, 2012 (document D6)

48. This set of experiments was submitted as part of the substantiation of the appeal against the refusal of the patent application. In this set of experiments the patentee is trying to prove that formulations according to the application form less PEG-naproxen-esters than formulations according to the prior art document D1. The results are summarized in 15 samples according to the alleged invention (samples #1 to #15) and 6 comparative examples which are (allegedly) according to prior art document D1 (samples #16 to #21).

49. In the experiments (allegedly) according to the Contested Patent the components (naproxen sodium, HCl or lactic acid or citric acid in different equivalents, water and PEG-600) are mixed and the mixture is analyzed both visually and by HPLC. After "accelerated stress conditions" (1 week at 60 °C) the mixture is analyzed both visually and by HPLC again.

50. Regarding these experiments it must be noted that the claim set of the patent application at the time of these experiments was different than the claim set of the Contested Patent. Consequently, these experiments are not according to the Contested Patent as outlined in the following:

51. According to the Contested Patent various acids are listed as feature 1.3 and hydrochloric acid is not among these acids. However, in six of the experiments (samples #1 to #6) hydrochloric acid is used and; consequently, these experiments are not according to the Contested Patent.

52. All experiments, which are (allegedly) according to the alleged invention (samples #1 to #15) lack a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof (feature 1.6).

53. As a summary it can be noted that the samples #1 to #15 lack feature 1.6 (solubilizer). Furthermore, samples #1 to #6 lack feature 1.3 and use HCl instead of an acid selected from the list disclosed. The six samples which use HCl (samples #1 to #6) and; therefore lack both features 1.3 and 1.6 will not be considered in the forthcoming discussion. In the following it will be shown that most of the remaining samples (#7 to #15) cannot be considered as valid experiments:

54. Of these experiments only sample #11 is a homogeneous solution after mixing the components. After "stress treatment" only samples #8 and #11 are homogeneous solutions. The other samples (allegedly) according to the alleged invention contain precipitate and/or are a suspension. All samples according to the prior art (samples #16 to #21) are clear solutions.

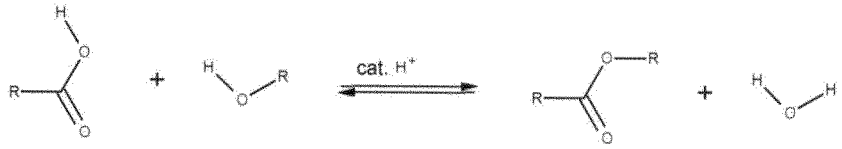
55. The patentee argued (cf. decision T 0826/12, page 4, second paragraph) that the absence of these solubilizers is the reason for the presence of inhomogeneous solutions and that these samples, although not suitable for encapsulation in a softgel capsule, would still demonstrate an improvement over document D1 with respect to the decreased production of PEG-naproxen-esters.

56. Based on the teaching of the Contested Patent and this statement of the patentee the effect of these solubilizers must be to enhance the solubility of the naproxen sodium. PEG-600 is completely soluble in water (cf. document D7, page 1, 5th item in the table). Therefore, the precipitate comprises undissolved sodium naproxen and – most likely – undissolved acid as well.

57. To show that the experiments must be disregarded from a scientific point of view some basics regarding the formation of esters in general have to be considered:

58. <u>The Ester formation</u>

59. The Ester formation between an acid and an alcohol is an equilibrium reaction, which is catalyzed by acids. Besides the ester, a molecule of water is also formed in the reaction (see general reaction scheme below).



Reaction scheme 1: Ester formation.

60. For purposes of this discussion the ester formation reaction will be analyzed using the principle of Le Chatelier: When the (initial) concentration of a starting material (such as the acid above) is decreased, the reaction mixture will be shifted towards the starting materials (this means "the left side" of the reaction scheme) and less products (like the ester) will be present at the equilibrium of the reaction.

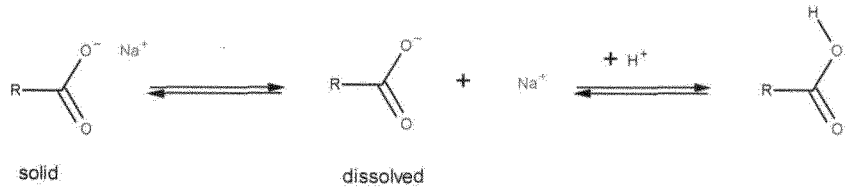
61. Likewise, when the (initial) concentration of a product (like water) is increased the reaction mixture will also be shifted towards the starting materials (the "left side"

of the reaction scheme), this means more starting materials and less products (like ester) will be present at the equilibrium of the reaction.

62. The effect of different concentrations of the starting material will be discussed in paragraphs [66] to [70]. The effect of different product concentrations will be discussed in paragraphs [71] to [77]. Furthermore, competing reactions will be discussed in paragraphs [78] to [84] and some general remarks are provided in paragraphs [85] to [91].

63. Different initial concentrations of the starting materials - naproxen

64. As discussed before in document D6 naproxen sodium is used. In most samples it is not fully dissolved. Only a fraction is, and only this dissolved fraction can form the acid (see reaction scheme 2) and participate in the formation of PEG-naproxen-esters.



Reaction scheme 2: Equilibrium between solid and dissolved naproxen and free acid.

65. This means that the ester formation of those compositions that contain solid naproxen precipitate (most samples allegedly according to the alleged invention) cannot be compared to those compositions that do not contain any solid (the samples according to the closest prior art). The starting concentration of the acid is lower in the former than in the latter. Therefore, the solid naproxen compositions must result in a lower concentration of the PEG-naproxen-ester when these formulations ultimately reach equilibrium than those that do not contain any solid.

66. Only two samples that are according to the alleged invention of the Contested Patent do not contain solids and, therefore, might be of some scientific relevance (samples #8 and #11). Both examples use the same acid (lactic acid) at 0.6 equivalents.

67. It is also worth noting that the initial concentrations of the starting materials differ

greatly between the individual experiments.[2] This makes any comparison with regard to the amount of ester formed in any given formulation even more unreliable.

68. Different initial concentration of the products – water

69. Besides the initial concentration of the starting materials, the initial concentration of the products is also important when evaluating an equilibrium reaction like the ester formation discussed in document D6. As mentioned before, when the initial concentration of a product (for example water) is increased, the equilibrium will shift towards the left of the reaction scheme (i.e. the starting materials) and the equilibrium concentration of the products is therefore reduced.

70. In the current set of experiments the patentee used much higher water concentrations for the only two relevant experiments (samples #8 and #11) compared to the initial water concentration of the comparative examples (samples #16 to #21). This is shown in the following tables:

Sample #	naproxen sodium (g)	naproxen (free acid) (g)	naproxen [mmol]	50% KOH (g)	(H_2O) (g)	H_2O [mmol]	PEG (g)	n (PEG) [mmol]
8	7,15		28,35		1,30	71,89	15,05	25,09
11	5,52		21,88		1,03	57,18	17,34	28,90
16		6,50	28,22	0,33	0,17	9,16	17,89	29,82
17		6,50	28,22	0,96	0,48	26,56	16,68	27,80
18		6,51	28,27	1,59	0,80	44,24	15,36	25,60
19		5,03	21,83	0,29	0,14	7,94	19,56	32,59
20		5,10	22,15	0,76	0,38	21,01	18,58	30,97
21		5,13	22,30	1,23	0,62	34,14	17,54	29,23

Table 2: Content of the relevant compositions (data from document D6).

71. The data from this table is based on the experimental data submitted by the patentee. In addition the table contains the molar amounts of the compounds (calculated by the Opponent) and the initial mass of water used in the comparative experiments (calculated by the Opponent based on the fact that the patentee used 50% KOH – which means 50% of the mass of the KOH solution is water).

[2] This assessment is based on a rough calculation, assuming that all liquid stems from PEG and water, both have a density of 1.0g/mL and the mixture has a density of 1.0 g/mL as well. The difference in concentration will also be observed for a more sophisticated calculation.

72. Just by comparing the masses listed in this table it should be obvious that samples #8 and #11 must have a much higher water concentration than the samples according to the closest prior art (samples #16 to#21). Samples #8 and #11 contain (on average) 1.2 g water while the comparative examples contain (on average) 0.4 g water. This corresponds to a factor of 3 difference between them.

73. In order to visualize the difference in water concentration the molar amounts listed in the table above where used to calculate the corresponding concentrations. This calculation was conducted under the assumption that all liquid stems from PEG and water, both have a density of 1.0 g/mL, and the mixture has a density of 1.0 g/mL as well. It should be obvious that the general trend in concentrations will also be observed for a more sophisticated calculation as the amount of PEG is basically constant for all experiments, whereas the amount of water differs significantly. The following concentrations were calculated:

Sample #	**c (naproxen) [mol/L]**	**c (PEG) [mol/L]**	**c (H_2O) [mmol/L]**
8	1,73	0,92	79,21
11	1,19	0,94	56,07
16	1,56	0,99	9,14
17	1,64	0,97	27,89
18	1,75	0,95	49,34
19	1,11	0,99	7,26
20	1,17	0,98	19,96
21	1,23	0,97	33,87

Table 3: Concentrations of the relevant compounds.

74. In the two experiments which are allegedly according to the alleged invention of the Contested Patent (samples #8 and #11), a much higher initial concentration of water is present than in the comparative experiments (samples #16 to #21). Due to the much higher initial concentrations of water (a product in the ester formation) a shift of the equilibrium towards the starting material will be observed. Consequently it is not surprising that less PEG-ester was observed in the reactions according to the application of the Contested Patent.

75. Competing reactions

76. In addition, the examples (allegedly) according to the alleged invention (samples #7 to #15) offer competing reaction pathways which are not available for the

samples (allegedly) according to the closest prior art (samples #16 to #21).

77. The acids used in the examples #7 to #15 are lactic acid and citric acid. They possess the following structures (see figure below):

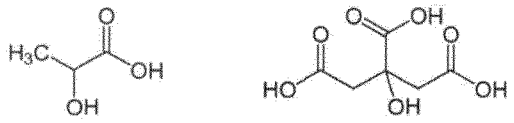


Figure 1: Structures of lactic acid (left) and citric acid (right)

78. These acids contain one (lactic acid) or three (citric acids) carboxy groups and one hydroxyl-group.

79. The carboxy- groups can (and will) compete with the carboxy group of the naproxen in forming PEG-esters. This means the carboxy-groups of these "acids" (lactic- and citric acid) will react with the hydroxyl-group of PEG forming PEG-"acid"-esters. This competing reaction will reduce the concentration of PEG (compared to reactions without such an acid), and this competing reaction will also produce a molecule of water per molecule of PEG-"acid"-ester formed. The influence of the water concentration on the formation of PEG-naproxen-esters has been discussed before.

80. The acids also contain a hydroxyl-group and will compete with the hydroxyl-group of PEG. This means the naproxen can react either with a hydroxyl-group of PEG or with a hydroxyl group of the acid. Again, this competing reaction will result in the formation of water and any naproxen which reacts to form a naproxen-acid-ester cannot form a PEG-naproxen-ester. Consequently, a lower concentration of the PEG-naproxen-ester is to be expected.

81. In addition lactic acid is also known to form cyclic lactides and intermolecular (poly)esters (cf. document D8, last reaction scheme and the text starting from 4 lines above this reaction scheme and document D9, 3rd and 4th paragraph[3]). This intermolecular reaction will increase the water concentration as one molecule of water is formed for each intermolecular lactic ester formed.

82. Additional remarks

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[3] Document D9 is an article from the weppage Wikipedia dated June 13, 2017; i.e. it was published after the priority date of the Contested Patent. However, the information disclosed therein only summarizes a general fact which is obvious to the person skilled in the art.

83. The examples according to the current invention use naproxen sodium, whereas the comparison experiments use naproxen in the presence of potassium hydroxide. It is unclear to us why the patentee used potassium hydroxide. In our opinion a proper comparison would require the use of sodium hydroxide. The use of sodium hydroxide as hydroxide species is explicitly mentioned in claim 4 of document D1.

84. The comparison examples #16 and #19 contain less than 1% weight of water (0.7% and 0.6% respectively). However, document D1 requires the presence of 1% to 20% water by weight. Consequently, these examples are not according to the teaching of document D1 and cannot be considered as comparative examples.

85. The patentee does not provide any information on the margin of error and the number of significant figures. Thus, any information provided is meaningless. But even when all these flaws are ignored and the determined amounts of PEG-naproxen-ester are compared there is no advantage and/or the advantage is negligible. 89. The amount of PEG-naproxen-esters formed in the experiments according to the alleged invention of the Contested Patent after mixing is between 0.0021% (sample #14) and 0.0087% (sample 13). After stress induction the amount determined is between 0% and 0.0107% (sample #14).

86. In the samples (allegedly) according to the prior art, between 0.0144% (sample #19) and 0.0178% (sample #16) PEG-naproxen-ester is determined after mixing. Between 0.0093% and 0.0140% is determined after stress induction (samples #19 and #21).

87. This means that after stress induction the experiments according to the closest prior art might actually form less PEG-naproxen-ester than specific experiments (allegedly) according to the alleged invention of the Contested Patent.

88. Conclusion regarding the experiments filed on March 26, 2012 (document D6)

89. The experiments are about the equilibrium concentrations of an ester which is formed. This formation is an (acid catalyzed) equilibrium reaction between an acid and an alcohol forming an ester and water. According to the principle of Le Chatelier the equilibrium concentrations of the individual compounds is depending on the (initial) concentration of the starting materials and the products. Our main objections with regards to these experiments are:

i. The starting materials are undissolved in some experiments resulting in a much lower initial concentration of the starting materials.

ii. The initial concentration of both starting materials differ between different experiments.

iii. The initial concentration of the product water differs siginificantly.

iv. In the experiments according to the Contested Patent competing reactions are possible. These competing reactions will (for example) form water and reduce the concentration of one of the starting materials.

VII.2. Alleged technical effects

90. As shown in the previous section the alleged technical effect (suppression of PEG-esters) was not shown. It is established case law that alleged advantages cannot be taken into consideration as long as they are not evidenced. The case law of the Board of Appeals elaborates on this principle (Case law of the board of appeals, 8th edition, July 2016 – Section I. D. 4.2):

> According to the case law of the boards of appeal, alleged advantages to which the patent proprietor/ applicant merely refers, without offering sufficient evidence to support the comparison with the closest prior art, cannot be taken into consideration in determining the problem underlying the invention and therefore in assessing inventive step (see **T 20/81**, OJ 1982, 217; **T 181/82**, OJ 1984, 401; **T 124/84**, **T 152/93**, **T 912/94**, **T 284/96**, **T 325/97**, **T 1051/97**). In **T 1027/08**, the board added that there was no reason to deviate from this case law as it was based on the understandable rule that a patent can only properly be granted for a solution claimed as non-obvious **if** it actually has the alleged effect (see also in this chapter I.D.4.6).
>
> In view of the absence of any data confirming the alleged improvement, such an effect could not be taken into account in the formulation of the technical problem (**T 2044/09**).

91. In the following considerations we assume that the Opposition Division agrees with our assessment regarding the lacking proof for a technical effect in the experiments conducted by the patentee. However, afterwards we will also present arguments regarding the lack of inventive step for the unlikely case that the Opposition Division disagrees with our assessment and considers the experimental data to show the alleged effect.

92. In case the Opposition Division concurs with our argumentation, the task of the Contested Patent can only be to provide an alternative.

VII.3 Example R of document D4 as closest prior art

93. The Contested Patent does not show any technical effect and merely lists components for the fill material of a softgel capsule. The Contested Patent can only be considered to provide an alternative to the prior art. Example R of document D4 can be considered as the closest prior art. This example was already discussed with regards to the lacking novelty of the Contested Patent.

94. In accordance with T597/07 and T131/01 the Opponent will not discuss the inventiveness of claims 1, 2, 4, 6, 7, 8, 9, 10 and 13 in view of document D4 as those claims were already considered as being not novel in view of this document. However, in case the Opposition Division does not concur with the arguments regarding the novelty of one or more of these claims the Opponent will reserve the right to file a substantial argument regarding the lack of inventive step for any one of these claims at a later point in time.

VII.3.1 Lacking inventive step for claim 3

95. Claim 3 of the Contested Patent limits the acids used to lactic acid. There is no effect attributed to lactic acid in comparison to the citric acid used in document D4; therefore, it is obvious to the person skilled in the art that the citric acid can be replaced with a similar acid like lactic acid. Both acids can be considered similar as both contain a hydroxyl-group and at least one carboxyl-group and possess a similar pKa-value (cf. document D13, roughly in the middle of the right page for the pKs-value of lactic acid and document D12, page 2, table on the right, fourth characteristic from the bottom for the pKa-value of citric acid[4]).

VII.3.3. Lacking inventive step for claim 11

96. Claim 11 of the Contested Patent is related to a method of making the capsules of claim 1. This method comprises the mixing of the components and their encapsulation in a softgel capsule.

97. The method mentioned in this claim is inherently disclosed in the closest prior art example. It discloses a mixture according to claim 1 of the Contested Patent and discloses the use of such mixtures in softgel capsules. It should be obvious for the person skilled in the art that such capsules can be prepared by mixing the components in a first step and encapsulating them in a second step. Consequently, this claim cannot be considered as inventive.

---

[4] Document D12 is an article from the weppage Wikipedia dated June 13, 2017; i.e. it was published after the priority date of the Contested Patent. However, the pKa-value disclosed therein is a general fact which was known to the person skilled in the art.

VII.3.4 Lacking inventive step for claim 12

98. Claim 12 of the Contested Patent refers to claim 11 and further limits the temperature during the mixing of from 50 to 70 °C.

99. The use of elevated temperatures to enhance a mixing process is obvious to a person skilled in the art. The use of elevated temperatures for the mixing step for similar composition are (for example) disclosed in documents D3 (cf. paragraph [0041]) and D1 (cf. column 10, lines 67 to 68). Claim 12 of the Contested Patent is therefore not inventive.

VII.4 Lacking inventiveness in view of document D1

100. In case the Opposition Division does not follow our arguments regarding the experiments and is of the opinion that the experiments show that less PEG-naproxen-ester is formed when compositions according to the alleged invention are used we will show that the Contested Patent is, nevertheless, not inventive.

101. In document D1 an acidic agent (naproxen, cf. claim 8) and a base (for example NaOH, cf. claim 4) is present in an aqueous environment. The base is present from 0.1 to less than 1.0 molar equivalents. PEG and solubilizers are present as well (cf. claim 6).

102. Naproxen and sodium hydroxide will react in an acid/base reaction and a mixture of acidic naproxen and deprotonated naproxen sodium will be present in solution.

103. In the contested Patent a mixture of naproxen sodium, an acid, polyethylene glycol, water and a solubilizer is present. The acid is present in an amount from 0.2 to 1.0 molar equivalents. The acid is selected from a list but all acids bear a carboxyl-group.

104. Naproxen sodium will react in an acid/base reaction and a mixture of acidic naproxen and deprotonated naproxen sodium will be present in solution (as in document D1 cf. paragraph [107] above)

105. This means the distinguishing feature is the addition of an acid bearing a carboxyl-group.

106. The distinguishing result is the formation of less PEG-naproxen-ester.

107. If the formation of PEG-naproxen-esters was considered a problem and a person skilled in the art wanted to suppress this formation (starting from document D1) he

would have analyzed the ester formation reaction in general and would have considered that:

i. Esters can be hydrolysed by the addition of an acid (cf. document D10, first two sentences).

Consequently, the addition of acids is obvious.

108. In addition, if the formation of PEG-naproxen-esters was considered an issue he would also have considered adding molecules containing carboxylic groups (this means acids according to the invention of the Contested Patent). These carboxylic groups would react with PEG and form carboxyl-PEG-esters and water. This would reduce the concentration of PEG which can form PEG-naproxen-esters. Furthermore, the synthesized water will – according to the principle of Le Chatelier – reduce the equilibrium concentration of PEG-naproxen-esters (and any other ester).

109. Therefore, the addition of molecules that contain (at least one) carboxy-group is obvious as well. Consequently, claim 1 cannot be considered as inventive over document D1.

VII.4.1 Dependent claims

110. The dependent claims are also not inventive in view of document D1.

111. In claim 2 the list of acids is reduced to citric acid or lactic acid and in claim 3 it is further reduced to lactic acid.

112. Both of these acids contain a hydroxyl-group and carboxyl-group(s). If the formation of PEG-naproxen-esters was considered an issue the person skilled in the art would have considered adding molecules which also contain a hydroxyl group. These hydroxyl groups would react with naproxen to form an ester and water. This would reduce the concentration of naproxen which can form PEG-naproxen-esters. Furthermore, the synthesized water will reduce the equilibrium concentration of PEG-naproxen-esters. These effects were discussed earlier with regards to the experiments of document D6.

113. The addition of molecules that possess both carboxy-groups and hydroxy groups (like maleic acid) would be especially beneficial. Such molecules can form esters both with PEG and naproxen (while also forming water), will form intermolecular esters, which will release water as well, and, furthermore, can hydrolyse esters.

These effects have been discussed earlier with regards to the experiments of document D6.

114. The use of such acids is therefore obvious when the hydrolysis of PEG-naproxen-esters and/or a lower formation of PEG-naproxen-ester is desired.

115. In claim 4 the amount of PEG is restricted from 10% to 80% by weight. Claim 1 of document D1 discloses the presence of 10% to 80% by weight PEG. Consequently, claim 4 is not inventive in view of document D1.

116. In claim 5 the molecular weight of PEG is restricted to between 300 and 1500. In claim 5 of document D1 the molecular weight of PEG is restricted to between 200 and 100000. Consequently, claim 5 is not inventive in view of document D1.

117. In claim 6 the amount of water is limited to 1% to 18% by weight. In claim 1 of document D1 the amount of water is limited to 1% to 20% by weight. Consequently, claim 6 is not inventive in view of document D1.

118. In claim 7 the further presence of various additional compounds is required. In claim 1 of document D1 the presence of water (solvent) is required. Consequently, claim 7 is not inventive in view of document D1.

119. In claim 8 the amount of solubilizer (like glycerin) is restricted to an amount from 1% to 10% by weight. In claim 2 of document D1 the amount of glycerin (solubilizer) is restricted to an amount from 4% to 12%. Consequently, claim 8 is not inventive in view of document D1.

120. In claim 9 the fill material of the capsule is required to be liquid. In claim 1 of document D1 it is mentioned that it concerns solutions (this means liquids) which are suitable for encapsulation. Consequently, claim 9 is not inventive in view of document D1.

121. In claim 10 the capsule is limited for use as a medicament. Document D1 is related to pharmaceutical acceptable solutions (cf. claim 1). Consequently, claim 10 is not inventive in view of document D1.

122. Claim 11 of the Contested Patent is related to a method of making the capsules of claim 1. This method comprises the mixing of the components and their encapsulation in a softgel capsule. Claim 12 of the Contested Patent refers to claim 11 and further limits the temperature during the mixing of from 50 to 70 °C. The use of such a process including the elevated temperatures to enhance the

mixing process is obvious to a person skilled in the art. The use of such a process at 60°C is disclosed in document D1 (cf. column 10, lines 67 to 68). Consequently, claims 11 and 12 are not inventive in view of document D1.

VII.4.2 Independent claim 13

123. Independent claim 13 is basically identical to independent claim 1. Due to the reasons outlined with regards to claim 1 claim 13 is also not inventive in view of document D1.

VII.4.3 Inventiveness in view of document D1 – conclusion

124. Based on the previous assessments the independent claims, as well as the dependent claim, are not inventive in view of document D1.

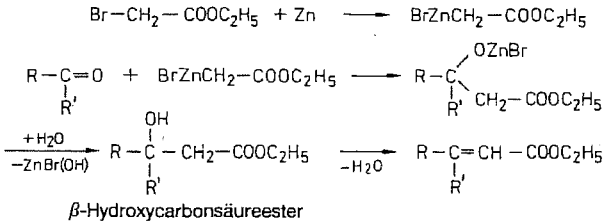
VIII. Conclusion

125. The above-given explanations show that the revocation of the Contested Patent is justified.

Bernard Lohmanns
Patent Attorney

D8

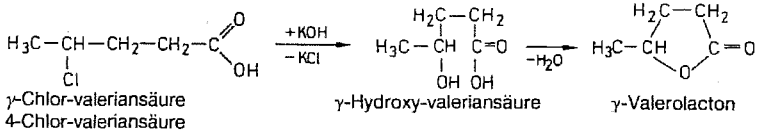
nicht mit der Estergruppe. Bei der Hydrolyse des Addukts entstehen zunächst β-Hydroxycarbonsäureester, die jedoch leicht unter Wasseraustritt in die α,β-ungesättigten Carbonsäureester übergehen, z. B.



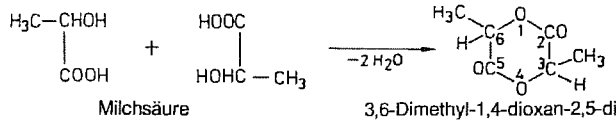
Aldehyde (R'=H) reagieren im allgemeinen leichter als Ketone. Die Reaktion wird meist durch geringe Zusätze von Iod katalysiert.

Diese metallorganische Variante der Aldoladdition kann auf breiter Basis zu Synthesen verwendet werden. Als Carbonylkomponente kommen aliphatische und aromatische Aldehyde sowie aliphatische, cyclische oder aromatische Ketone in Frage (vgl. auch *Ivanoff*-Reaktion), als „Methylenkomponente" unverzweigte und verzweigte aliphatische α, β oder γ-Bromcarbonsäureester.

2.29.4.3 γ- und δ-Hydroxysäuren erhält man *durch alkalische Hydrolyse der* γ- bzw. *δ-Halogencarbonsäuren.* Sie können jedoch nur in Form ihrer Alkalisalze isoliert werden, da sie beim Ansäuern sofort unter Wasseraustritt in γ- bzw. δ-Lactone übergehen, z. B.

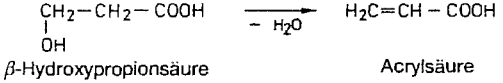


Eigenschaften. Die Hydroxysäuren sind in Wasser leichter, in Ether schwerer löslich als die zugehörigen Carbonsäuren. In Analogie zum Halogen in den Halogencarbonsäuren erhöht besonders die α-ständige Hydroxylgruppe – wenn auch in geringerem Maß – die *Acidität* der Hydroxysäuren (*−I-Effekt*). Ihr chemisches Verhalten ist durch das gleichzeitige Auftreten der alkoholischen Hydroxyl- und der Carboxylgruppe charakterisiert. Sie geben somit die für beide Funktionen spezifischen Umsetzungen.
Beim Erhitzen spalten die Hydroxysäuren Wasser ab und bilden je nach der Stellung der OH-Gruppe nachstehende Verbindungen:
Aus *α-Hydroxysäuren* entstehen unter intermolekularer Wasserabspaltung ringförmige Lactide, z. B.

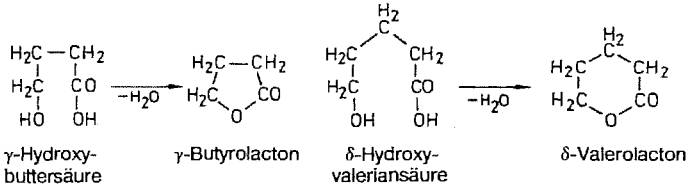


Der Name *Lactide* ist von der Milchsäure (*Acidum lacticum*) abgeleitet, an der diese Reaktion zuerst beobachtet wurde.

β-Hydroxysäuren spalten intramolekular Wasser ab unter Bildung α,β-ungesätt Carbonsäuren, z. B.



γ- bzw. *δ-Hydroxysäuren* gehen – zuweilen schon bei Raumtemperatur – unter molekularer Wasserabspaltung in γ- bzw. *δ-Lactone über, z. B.*



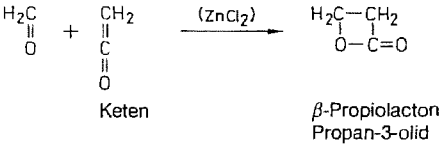
Analog cyclisieren sich γ-Thiolcarbonsäuren spontan zu *γ-Thiolactonen.*

2.29.5 Lactone

Die Lactone sind als *innere Ester* der Hydroxycarbonsäuren aufzufassen, und zwa terscheidet man α-, β-, γ-, δ- und höhergliedrige Lactone. Die aus den aliphatis Carbonsäuren entstehenden Lactone werden durch Anhängen der Endung *-olid* a Namen des *nicht hydroxylierten Kohlenwasserstoffes* mit der gleichen Zahl von Ko wasserstoffatomen benannt. Dabei wird die Positionsziffer des am Ringschluß bet ten C-Atoms vor der Endung angegeben, z. B. Propan-3-olid = β-Propiolacton, 7-H decen-16-olid = Ambrettolid, Pentadecan-15-olid = Exaltolid.
Während die α-Lactone im allgemeinen nur in Lösung nachgewiesen werden kön und die β-Lactone[2] sich nur mit Hilfe spezieller Verfahren darstellen lassen, entst die γ- und die δ-Lactone leicht aus den entsprechenden Hydroxysäuren. Die wic sten Vertreter sind *γ-Butyrolacton* sowie γ- und *δ-Valerolacton.*

Darstellung. Außer durch die allgemeinen Darstellungsverfahren gewinnt man e Lactone technisch auf folgende Weise:

2.29.5.1 *β-Propiolacton* (Hydracrylolacton) wird *durch Cycloaddition* aus Keten Formaldehyd in wasserfreiem Medium bei Gegenwart von Zinkchlorid darge (Ausbeute 90%):



[1] Vgl. *O. L. Chapman* et al., J. Amer. Chem. Soc. *94,* 1365 (1972); ein trifluoralkylsubstitu α-Lacton ist isoliert worden: Chem. Comm. *1982,* 362.
[2] Vgl. *H. E. Zaugg,* β-Lactones, Org. Reactions *8,* 305 (1954); *K. Kröper, Houben-Weyl,* Meth

D9

Milchsäure

aus Wikipedia, der freien Enzyklopädie

Milchsäure (lat. *acidum lacticum*) ist eine Hydroxycarbonsäure, also eine Alkansäure, die sowohl eine Carboxygruppe als auch eine Hydroxygruppe besitzt. Sie wird deswegen auch als **2-Hydroxypropionsäure** bezeichnet, nach den Nomenklaturempfehlungen der IUPAC ist jedoch die Bezeichnung **2-Hydroxypropansäure** zu verwenden. Die Salze und Ester der Milchsäure heißen Lactate.

Inhaltsverzeichnis

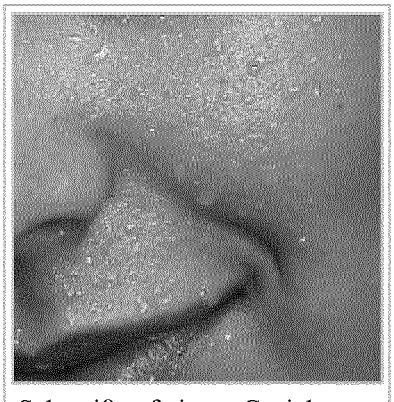
Geschichte

Milchsäure wurde historisch sowohl in Europa wie auch in Asien zur Säuerung und Konservierung von Lebensmitteln, insbesondere für Milch (Sauermilch), Gemüse (z. B. Sauerkraut) und auch zur Herstellung von Silagen als Futtermittel bereits seit Jahrhunderten oder Jahrtausenden genutzt.

Die erste Entdeckung und Isolierung der Milchsäure geht auf den schwedischen Chemiker Carl Wilhelm Scheele im Jahr 1780 zurück, der sie aus saurer Milch in Form eines braunen Sirups isolierte.[5] Die Fleischmilchsäure [L-(+)-Milchsäure] wurde von Jöns Jakob Berzelius im Jahr 1808 entdeckt und ihre Struktur 1873 von Johannes Wislicenus aufgeklärt. Henri Braconnot, ein französischer Chemiker, fand im Jahre 1813 heraus, dass Milchsäure in einem Fermentationsprozess hergestellt werden kann.[5] 1856 entdeckte Louis Pasteur die Milchsäurebakterien und entwickelte das Grundverständnis für die Milchsäuregärung. Die großtechnische Produktion von Milchsäure begann 1881 in den USA,[5] und 1895 machte auch Boehringer Ingelheim die Entdeckung, wie Milchsäure mit Hilfe von Bakterien in großen Mengen hergestellt werden konnte.

Vorkommen

L-(+)-Milchsäure kommt in Schweiß, Blut, Speichel sowie im Muskelserum, in der Niere und Galle vor. Das Racemat, eine 1:1-Mischung aus D- und L-Milchsäure, findet sich z. B. in Sauermilch- und Molkeprodukten, Tomatensaft und Bier. Bei allen Produkten, die per Milchsäuregärung haltbar gemacht werden, ist der Anteil der beiden Enantiomeren abhängig vom verwendeten Bakterienstamm und den Reaktionsbedingungen.

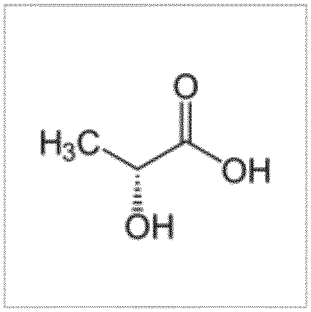


Schweiß auf einem Gesicht

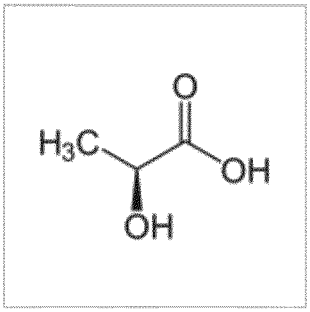
Auch Pilze erzeugen Milchsäure, z. B. Vertreter der Gattungen Rhizopodus, Allomyces und Blastocladiella.[6]

Eigenschaften

Aufgrund ihrer unterschiedlichen optischen Aktivität wird die D-(−)-Milchsäure (Syn.: (*R*)-Milchsäure) auch als *linksdrehende Milchsäure* und die L-(+)-Milchsäure (Syn.: (*S*)-Milchsäure) auch als *rechtsdrehende Milchsäure* bezeichnet. Racemische Milchsäure ist ein 1:1-Gemisch aus (*R*)- und (*S*)-Milchsäure.



D-Milchsäure

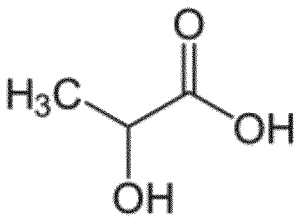


L-Milchsäure

Milchsäure ist in Form von Lactat ein wichtiges Zwischenprodukt im Stoffwechsel, zum Beispiel als Produkt beim Abbau von Zuckern durch die Milchsäuregärung. Weltweit werden jährlich etwa 250.000 Tonnen (Stand 2010) Milchsäure industriell produziert,[7] die vor allem in der Lebensmittelindustrie sowie zur Herstellung von Polylactiden (PLA; auch: *Polymilchsäuren*) genutzt werden.

Der spezifische Drehwinkel beträgt für D-Milchsäure bei 20 °C $[\alpha]_D^{20} = -2{,}6$ (H_2O) und für L-Milchsäure $[\alpha]_D^{20} = +2{,}6$ (H_2O). Bei 15 °C wird für L-Milchsäure ein Drehwinkel $[\alpha]_D^{15} = +3{,}82$ (H_2O)[2] gemessen.

Milchsäure bildet intermolekular Ester. Unter

Strukturformel	
	
Strukturformel ohne Angabe der Stereochemie	
Allgemeines	
Name	Milchsäure
Andere Namen	■ 2-Hydroxypropansäure ■ 2-Hydroxypropionsäure ■ (*R*)-Milchsäure ■ (*S*)-Milchsäure ■ (*RS*)-Milchsäure ■ DL-Milchsäure ■ (±)-Milchsäure ■ E 270
Summenformel	$C_3H_6O_3$
CAS-Nummer	■ 50-21-5 ■ 10326-41-7 (D-Milchsäure) ■ 79-33-4 (L-Milchsäure) ■ 598-82-3 (Racemat)
PubChem	612 (https://pubchem.ncbi.nlm.nih.gov/compound/612)
ATC-Code	G01AD01 (http://www.whocc.no/atc_ddd_index/?code=G01AD01)
Kurzbeschreibung	farblose, fast geruchlose, ölige Flüssigkeit (Racemat)[1]
Eigenschaften	
Molare Masse	90,08 $g \cdot mol^{-1}$
Aggregatzustand	flüssig (Racemat) fest (D-/L-Milchsäure)[1]
Dichte	1,21 $g \cdot cm^{-3}$ (Racemat)[1]
Schmelzpunkt	■ 17 °C (Racemat)[2] ■ 53 °C (D-/L-Milchsäure/Enantiomere)[2]

Abspaltung von Wasser entsteht als Dimer Lactoylmilchsäure, die beim längeren Stehen oder beim Erhitzen zu Polymilchsäure weiterverestert. Diese Makromoleküle erreichen jedoch keine relevanten Kettenlängen, um das Produkt technisch verwerten zu können.

In wässriger Milchsäurelösung liegt ein chemisches Gleichgewicht zwischen Milchsäure und ihren durch intermolekularer Wasserabspaltung entstehenden Polyester (Estoliden) vor. In 90%iger Milchsäurelösung findet man etwa 70 % als freie Säure und 20 % als ihre Estolide vor. Aus zwei Milchsäuremolekülen entstehen unter Ringschluss und Abspaltung von zwei Wassermolekülen Dilactid mit einem sechsgliedrigen Ring (Dilacton). Diese Verbindung wird in wässriger Milchsäurelösung jedoch nicht beobachtet. Aus Dilactiden lassen sich mittels Ringöffnungspolymerisation hochwertige Polyester erzeugen. Der entstehende Kunststoff ist biologisch abbaubar und zudem immunologisch neutral.

Siedepunkt	122 °C (20 hPa) (Racemat)[1]
Dampfdruck	10 Pa (25 °C)[1]
pK_s-Wert	3,90 (25 °C, Racemat)[2]
Löslichkeit	■ vollständig mischbar mit Wasser[1] ■ löslich in Ethanol[2]
Brechungsindex	1,4392 (20 °C; Racemat)[3]
Sicherheitshinweise	
Bitte die eingeschränkte Gültigkeit der Gefahrstoffkennzeichnung bei Arzneimitteln beachten	
GHS-Gefahrstoffkennzeichnung [1]  **Gefahr**	
H- und P-Sätze	H: 315-318 P: 280-305+351+338 [1]
Toxikologische Daten	3.543 mg·kg^{-1} (LD_{50}, Ratte, oral)[4]
Soweit möglich und gebräuchlich, werden SI-Einheiten verwendet. Wenn nicht anders vermerkt, gelten die angegebenen Daten bei Standardbedingungen. Brechungsindex: Na-D-Linie, 20 °C	

Herstellung

Die Herstellung von Milchsäure kann sowohl biotechnologisch über eine Fermentation von Kohlenhydraten (Zucker, Stärke) wie auch synthetisch auf der Basis petrochemischer Rohstoffe (Acetaldehyd) erfolgen.

Fermentative Herstellung

Etwa 70 bis 90 % der Weltproduktion an Milchsäure wird derzeit fermentativ hergestellt,[8] wobei beide reinen Enantiomere kommerziell durch Fermentationsverfahren mit Milchsäurebakterien in signifikanten Mengen produziert werden.[9] Biologisch entsteht bei der mikrobiellen Fermentation durch Milchsäurebakterien häufig das Racemat der Milchsäure (50:50-Gemisch) bis zu Produkten mit Anteilen von 51 bis 90 % L-Milchsäure.[10]

Industriell erfolgt die Herstellung von Sauermilchprodukten durch Vergärung von Milch oder Molke vor allem durch die *Lactobacillus*-Arten *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus delbrueckii subsp. bulgaricus* (*Lactobacillus bulgaricus*) und *Lactobacillus helveticus*, weiterhin durch *Streptococcus salivarius subsp. thermophilus* (*Streptococcus thermophilus*) und *Lactococcus lactis*.[11] Für industriell genutzte Milchsäure werden Zuckerdicksaft oder Stärkehydrolysate und *Lactobacillus delbrueckii* sowie Pentose-haltige Sulfitablaugen und *Lactobacillus pentosus* verwendet.[12] Die Bakterienstämme werden nach ihrer Eigenart eingeteilt, Glucose nur zu Lactat oder auch zu anderen Produkten zu vergären: *homofermentative* Arten, wie *Lactobacillus casei* und *Lactococcus lactis*, bilden pro Mol Glucose zwei Mol Lactat, während *heterofermentative* Arten, wie *Leuconostoc mesenteroides* und *Lactobacillus brevis*, neben einem Mol Lactat pro Mol Glucose auch Essigsäure, Kohlenstoffdioxid und Ethanol produzieren.[10]

Synthetische Herstellung

Synthetisch wird Milchsäure durch Wasseranlagerung an Cyanwasserstoff (Blausäure, HCN) hergestellt. Großtechnisch spielt dabei nur die Synthese von Milchsäure aus Acetaldehyd mit Cyanwasserstoff über Lactonitril eine gewisse Rolle. Letzteres wird über den Einsatz von Salzsäure hydrolysiert, wobei neben der Milchsäure Ammoniumchlorid entsteht. Dieser Syntheseweg wird von dem japanischen Unternehmen Musashino als letztem Großproduzenten für synthetische Milchsäure realisiert.[5]

Verwendung

Ernährung, Futter- und Genussmittel

Joghurt und andere Sauermilchprodukte basieren auf Milchsäuregärung.

Eine Reihe von Lebensmitteln werden direkt durch Milchsäuregärung hergestellt. Darunter fallen vor allem die Sauermilchprodukte wie Sauermilch, Joghurt, Kefir und Buttermilch. Diese werden durch Infektion von pasteurisierter Milch mit Starterkulturen der Milchsäurebakterien hergestellt. Weitere Produkte sind lactofermentierte Gemüse wie Sauerkraut, rote Bete in einigen Borschtsch-Varianten oder Gimchi sowie Sauerteig und entsprechend Sauerteigprodukte. Auch Silagen, durch Vergärung haltbar gemachte Frischfuttermittel, basieren auf der Milchsäuregärung.[10]

Als Lebensmittelzusatzstoff trägt Milchsäure die Bezeichnung E 270. Sie wird in der Lebens- und Genussmittelindustrie vielfältig als Säuerungsmittel eingesetzt, so etwa in Backwaren, Süßwaren und vereinzelt in Limonaden. Durch die Änderung des pH-Wertes in den Lebensmitteln auf einen pH von etwa 4 kommt es zu einer Konservierung der Lebensmittel, da eine Besiedlung mit anderen Mikroorganismen weitgehend ausgeschlossen wird.[10]

In Form der Salze Calciumlactat oder Calciumlactatgluconat kann sie zudem zur Calciumanreicherung zugesetzt werden.

Stoffliche Nutzung

Einkaufsbeutel aus PLA-Biokunststoff

Milchsäure ist das Monomer der Polylactide bzw. Polymilchsäuren (PLA), die als biologisch abbaubare Biokunststoffe vielfältige Verwendung finden.

Milchsäure wirkt antibakteriell und wird deshalb Flüssigseifen, Reinigern und Geschirrspülmitteln zugegeben. Die Desinfektionswirkung entfaltet sie optimal bei einem pH-Wert von 3 bis 4.[13] Sie wurde und wird auch als Mittel zur Schwangerschaftsverhütung eingesetzt.[14]

Milchsäure wird als Kalklöser in der Gerberei zum Entkalken von Häuten verwendet. Auch in der Textilindustrie und der Druckerei wird sie hierzu eingesetzt.

Imker nutzen Milchsäure zur Behandlung von Bienen gegen die Varroamilbe.[15] Arachnologen verwenden Milchsäure, um die präparierte Epigyne von Spinnenweibchen oder andere Chitinstrukturen aufzuhellen und um Gewebereste

aufzulösen.

Die Pharmazeutische Technologie nutzt Milchsäure, um wasserunlösliche Arzneistoffe in Salze der Milchsäure (Lactate) umzuwandeln; diese sind besser wasserlöslich (Beispiel: Ciprofloxacin).[16]

In der Kosmetik wird Milchsäure in Hautcremes und anderen Produkten zur Behandlung von Akne genutzt.

Physiologie

Bei starker Betätigung der Skelettmuskulatur kann es zum Anstieg des Blut-Lactatgehaltes von 5 mg/dl auf 100 mg/dl kommen. Die Ursache ist, dass bei anaeroben Bedingungen, wie beispielsweise bei schneller Betätigung der Skelettmuskulatur, Energie in Form von NAD^+ aus der Reduktion von Pyruvat mittels der Lactatdehydrogenase für die Fortführung der Glykolyse gewonnen werden muss. Die dabei anfallende Milchsäure (Lactat und H^+) wird über den Monocarboxylat-Transporter 1 aus den Zellen geschwemmt. Dieser Vorgang wurde früher als Ursache des Muskelkaters verstanden, jedoch wird diese Theorie heute größtenteils als falsch betrachtet.

Für den Menschen ist die rechtsdrehende L-(+)-Milchsäure die physiologische. Oral eingenommen wird sie im Organismus schneller abgebaut als die linksdrehende D-(−)-Milchsäure.[17]

Weblinks

Commons: Milchsäure (https://commons.wikimedia.org/wiki/Category:Lactic_acid?uselang=de) – Sammlung von Bildern, Videos und Audiodateien
Wiktionary: Milchsäure – Bedeutungserklärungen, Wortherkunft, Synonyme, Übersetzungen

- Kathrin Einschütz: *Wirksamkeitsprüfung verschiedener Verfahren zur Verminderung der Keimbelastung auf Handgeräten der Fleischgewinnung.* Dissertation. FU Berlin, 2004 urn:nbn:de:kobv:188-2004002043 (http://nbn-resolving.de/urn:nbn:de:kobv:188-2004002043) (Antibakterielle und konservierende Eigenschaften der Milchsäure)
- 3D-Darstellung beider Milchsäuremoleküle zum Vergleich (L- und D-Milchsäure) (http://www.cup.uni-muenchen.de/cicum/tutor/enantio/milchsre.html)

Einzelnachweise

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Normdaten (Sachbegriff): GND: 4114596-3 | LCCN: sh85073866 | NDL: 00568760

Abgerufen von „https://de.wikipedia.org/w/index.php?title=Milchsäure&oldid=165775114“

Kategorien: ATC-G01 | Ätzender Stoff | Reizender Stoff | Alpha-Hydroxycarbonsäure | Arzneistoff | Antioxidationsmittel | Säuerungsmittel

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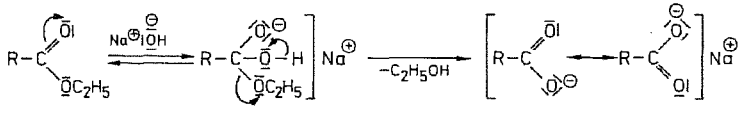
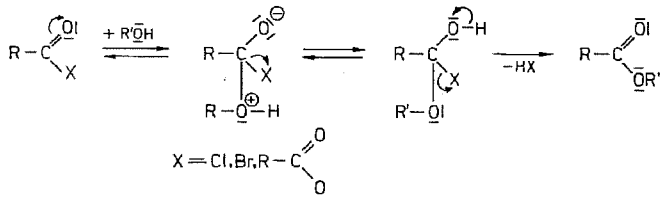
D10

Die Hydrolyse der Ester zu Carbonsäuren kann sowohl im sauren als auch im alkalischen Medium durchgeführt werden. Die *saure* Verseifung verläuft in Abhängigkeit von der Struktur des Alkylrestes in umgekehrter Richtung wie die säurekatalysierten Veresterungen (s. S. 259). Bei der *alkalischen* Verseifung der Ester greift zunächst ein *Hydroxid-Ion* das C-Atom der Alkoxycarbonylgruppe *nucleophil* an. Das entstehende Additionsprodukt stabilisiert sich dann unter Alkoholabspaltung zum Natriumsalz der Carbonsäure (*Additions-Eliminierungs-Mechanismus*):



Der Vorzug der alkalischen Esterverseifung besteht darin, daß der letzte Schritt praktisch irreversibel ist, wodurch die Hydrolyse quantitativ erfolgt. Da das Alkali bei der Reaktion verbraucht wird, ist mindestens ein Äquivalent Base erforderlich.
Die auf S. 151 beschriebene Reaktion des Methylsulfinylcarbanions mit Carbonsäureestern verläuft analog.

2.28.4.2 *Durch Umsetzung von Säurechloriden oder -anhydriden mit Alkoholen:*



Diese Reaktionen verlaufen nach dem *Additions-Eliminierungs-Mechanismus* meist quantitativ.

2.28.4.3 *Aus Silbersalzen der Carbonsäuren mit Alkylhalogeniden:*

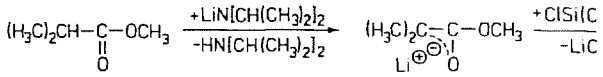
Diese Methode ist teuer und wird nur dann angewendet, wenn die direkte Veresterung versagt oder schlechte Ausbeuten liefert.

2.28.4.4 *Essigsäureethylester* wird technisch aus Acetaldehyd nach dem *Tischtschenko*-Verfahren gewonnen.

Eigenschaften. Die niederen Glieder der Carbonsäureester sind farblose Flüssigkeiten von fruchtartigem Geruch, die höheren sind geruchlos. Sie reagieren neutral, sind spezifisch leichter als Wasser und in diesem nur wenig löslich. Im Gegensatz zu den Carbonsäuren sind ihre Ester nicht assoziiert (keine H-Brücken!) und sieden daher tiefer als die entsprechenden Säuren, z. B. *Essigsäureethylester* bei 77 °C (350 K).
In Analogie zur Hydrolyse der Ester ist mit Alkoholen eine *Alkoholyse* möglich, z. B.

2.28.4.5 Derartige **Umesterungen** verlaufen unter dem katalyt
ralsäuren oder Laugen, zuweilen schon bei Raumtemperatu
gungen gelingt die Umesterung in Gegenwart von „Titanate
che funktionelle Gruppen, die mit Säuren oder Laugen reag
Art der Umesterung intakt[1].

2.28.4.6 Carbonsäureester, die am α-C-Atom mindestens ein
in Analogie zu den Ketonen *Enolate* bilden, aus denen die
Ketenacetale dargestellt werden können, z. B. aus Isobutter
thiumdiisopropylamid und Chlortrimethylsilan:



Das *Dimethylketen-methyl-trimethylsilylacetal* ist präparativ w
pen-Transfer-Polymerisation.

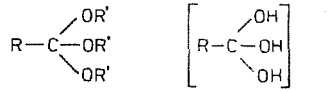
2.28.4.7 *Reduktion der Carbonsäureester zu primären Alkohole*
denen Wegen möglich, und zwar durch Reduktion mit Nat
***veault-Blanc*-Reduktion**), mit Lithiumaluminiumhydrid ode
ferchromit-Kontakt:

Mit *Grignard*-Verbindungen geben die Carbonsäureester *tertiäre* Alkol

Verwendung. Die Säureester, vor allem Ethyl- und Butylacetat
tel für Nitrocellulose und Harze in der Lackindustrie sowie als
kondensationen. Einige Ester werden als künstliche Aromen
z. B. Ethylformiat (Rum, Arrak), Isobutylacetat (Banane),
Ethylbutyrat (Ananas) und Isopentylbutyrat (Birne).

2.28.5 Orthocarbonsäureester

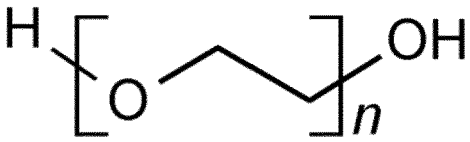
Neben den einfachen Carbonsäureestern lassen sich unter b
auch *Orthoester* darstellen, denen folgende Konstitution zukom



Orthoester Orthocarbonsäuren

[1] Vgl. P. Seebach et al., Tetrahedron Lett. [Rest illegible]

Polyethylene Glycol



Poly(oxy-1,2-ethanediyl), α-hydro-ω-hydroxy-.
Polyethylene glycol [*25322-68-3*].

» Polyethylene Glycol is an addition polymer of ethylene oxide and water, represented by the formula:

$$H(OCH_2CH_2)_nOH,$$

in which *n* represents the average number of oxyethylene groups. The average molecular weight is not less than 95.0 percent and not more than 105.0 percent of the labeled nominal value if the labeled nominal value is below 1000; it is not less than 90.0 percent and not more than 110.0 percent of the labeled nominal value if the labeled nominal value is between 1000 and 7000; it is not less than 87.5 percent and not more than 112.5 percent of the labeled nominal value if the labeled nominal value is above 7000. It may contain a suitable antioxidant.

Packaging and storage— Preserve in tight containers.

Labeling— Label it to state, as part of the official title, the average nominal molecular weight of the Polyethylene Glycol. Label it to indicate the name and quantity of any added antioxidant.

Completeness and color of solution— A solution of 5 g of Polyethylene Glycol in 50 mL of water is colorless; it is clear for liquid grades and not more than slightly hazy for solid grades.

Viscosity ⟨ 911 ⟩ — Determine its viscosity, using a capillary viscosimeter giving a flow time of not less than 200 seconds, and a liquid bath maintained at 98.9 ± 0.3° C (210° F). The viscosity is within the limits specified in the accompanying table. For a Polyethylene Glycol not listed in the table, calculate the limits by interpolation.

Nominal Average Molecular Weight	Viscosity Range, Centistokes	Nominal Average Molecular Weight	Viscosity Range, Centistokes
200	3.9 to 4.8	2200	43 to 56
300	5.4 to 6.4	2300	46 to 60
400	6.8 to 8.0	2400	49 to 65
500	8.3 to 9.6	2500	51 to 70
600	9.9 to 11.3	2600	54 to 74
700	11.5 to 13.0	2700	57 to 78
800	12.5 to 14.5	2800	60 to 83
900	15.0 to 17.0	2900	64 to 88
1000	16.0 to 19.0	3000	67 to 93
1100	18.0 to 22.0	3250	73 to 105
1200	20.0 to 24.5	3350	76 to 110
1300	22.0 to 27.5	3500	87 to 123

Nominal Average Molecular Weight	Viscosity Range, Centistokes	Nominal Average Molecular Weight	Viscosity Range, Centistokes
1400	24 to 30	3750	99 to 140
1450	25 to 32	4000	110 to 158
1500	26 to 33	4250	123 to 177
1600	28 to 36	4500	140 to 200
1700	31 to 39	4750	155 to 228
1800	33 to 42	5000	170 to 250
1900	35 to 45	5500	206 to 315
2000	38 to 49	6000	250 to 390
2100	40 to 53	6500	295 to 480
		7000	350 to 590
		7500	405 to 735
		8000	470 to 900

Average molecular weight—

Phthalic anhydride solution— Place 49.0 g of phthalic anhydride into an amber bottle, and dissolve in 300 mL of pyridine from a freshly opened bottle or that has been freshly distilled over phthalic anhydride. Shake vigorously until completely dissolved. Add 7 g of imidazole, swirl carefully to dissolve, and allow to stand for 16 hours before using.

Test preparation for liquid Polyethylene Glycols— Carefully introduce 25.0 mL of the *Phthalic anhydride solution* into a dry, heat-resistant pressure bottle. Add an accurately weighed amount of the specimen, equivalent to its expected average molecular weight divided by 160. Insert the stopper in the bottle, and wrap it securely in a cloth bag.

Test preparation for solid Polyethylene Glycols— Carefully introduce 25.0 mL of *Phthalic anhydride solution* into a dry, heat-resistant pressure bottle. Add an accurately weighed amount of the specimen, equivalent to its expected molecular weight divided by 160; however, because of limited solubility, do not use more than 25 g. Add 25 mL of pyridine, from a freshly opened bottle or that has been freshly distilled over phthalic anhydride, swirl to dissolve, insert the stopper in the bottle, and wrap it securely in a cloth bag.

Procedure— Immerse the bottle in a water bath maintained at a temperature between 96° and 100°, to the same depth as that of the mixture in the bottle. Remove the bottles from the bath after 5 minutes, and, without unwrapping, swirl for 30 seconds to homogenize. Heat in the water bath for 30 minutes (60 minutes for Polyethylene Glycols having molecular weights of 3000 or higher), then remove from the bath, and allow it to cool to room temperature. Uncap the bottle carefully to release any pressure, remove from the bag, add 10 mL of water, and swirl thoroughly. Wait 2 minutes, add 0.5 mL of a solution of phenolphthalein in pyridine (1 in 100), and titrate with 0.5 N sodium hydroxide VS to the first pink color that persists for 15 seconds, recording the volume, in mL, of 0.5 N sodium hydroxide required as *S*. Perform a blank determination on 25.0 mL of *Phthalic anhydride solution* plus any additional pyridine added to the bottle, and record the volume, in mL, of 0.5 N sodium hydroxide required as *B*. Calculate the average molecular weight by the formula:

$$[2000W]/[(B - S)(N)],$$

in which W is the weight, in g, of the Polyethylene Glycol taken for the *Test preparation; (B – S)* is the difference between the volumes of 0.5 N sodium hydroxide consumed by the blank and by the specimen, and N is the normality of the sodium hydroxide solution.

pH ⟨ 791 ⟩ **:** between 4.5 and 7.5, determined potentiometrically, in a solution prepared by dissolving 5.0 g of Polyethylene Glycol in 100 mL of carbon dioxide-free water and adding 0.30 mL of saturated potassium chloride solution.

Residue on ignition ⟨ 281 ⟩ **:** not more than 0.1%, a 25-g specimen and a tared platinum dish being used, and the residue being moistened with 2 mL of sulfuric acid.

Heavy metals ⟨ 231 ⟩ — Mix 4.0 g with 5.0 mL of 0.1 N hydrochloric acid, and dilute with water to 25 mL: the limit is 5 ppm.

Limit of free ethylene oxide and 1,4-dioxane—

Stripped polyethylene glycol 400— Into a 5000-mL 3-neck, round-bottom flask equipped with a stirrer, a gas dispersion tube, and a vacuum outlet, place 3000 g of Polyethylene Glycol 400. At room temperature, evacuate the flask carefully to a pressure of less than 1 mm of mercury, applying the vacuum slowly while observing for excessive foaming due to entrapped gases. After any foaming has subsided and while stirring continuously, sparge with nitrogen, allowing the pressure to rise to 10 mm of mercury. [NOTE—The 10-mm value is a guideline. Deviations from this value only affect the total time required to strip the Polyethylene Glycol 400.] Continue stripping for a minimum of 1 hour. [NOTE—Completeness of the stripping procedure should be verified by making a headspace injection of the stripped polyethylene glycol 400.] Shut off the vacuum pump, and bring the flask pressure back to atmospheric pressure while maintaining nitrogen sparging. Remove the gas dispersion tube with the gas still flowing, and then turn off the gas flow. Transfer the *Stripped polyethylene glycol 400* to a suitable nitrogen-filled container.

Standard preparation— [*Caution—Ethylene oxide and 1,4-dioxane are toxic and flammable. Prepare these solutions in a well-ventilated fume hood.*] Transfer 4.90 g of *Stripped polyethylene glycol 400* to a tared 22-mL pressure headspace vial that can be sealed. Add 48 µL of 1,4-dioxane, equivalent to 50 mg of 1,4-dioxane, from a syringe, seal, and cap the vial. Using the special handling described in the following, complete the preparation. Ethylene oxide is a gas at room temperature. It is usually stored in a lecture-type gas cylinder or small metal pressure bomb. Chill the cylinder in a refrigerator before use. Transfer about 5 mL of the liquid ethylene oxide to a 100-mL beaker chilled in wet ice. Using a gas-tight syringe that has been chilled in a refrigerator, transfer 57 µL of the liquid ethylene oxide, equivalent to 50 mg of ethylene oxide, to the mixture contained in the headspace vial, and mix. With the aid of a syringe, transfer about 2 mL of this solution to a 5-mL beaker. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with *Stripped polyethylene glycol 400* to volume, and mix. Transfer 10 mL of this solution to a 100-mL volumetric flask, dilute with *Stripped polyethylene glycol 400* to volume, and mix to obtain a *Standard preparation* having known concentrations of 10 µg per g for both ethylene oxide and 1,4-dioxane. Transfer 1.0 mL of the *Standard preparation* to a 22-mL pressure headspace vial, seal with a silicone septum with or without a pressure relief star spring and a pressure relief safety aluminum sealing cap, and crimp the cap closed with a cap-sealing tool.

Resolution solution— Transfer 4.90 g of *Stripped polyethylene glycol 400* to a 22-mL pressure headspace vial. Pipet 50 µL of acetaldehyde into the vial. Using the special handling described under *Standard preparation*, transfer about 50.0 µL of liquid ethylene oxide into the vial. Immediately seal the vial, and shake. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with *Stripped polyethylene glycol 400* to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with *Stripped polyethylene glycol 400* to volume, and mix. Transfer 1.0 mL of this *Resolution solution* to a 22-mL pressure headspace vial; and seal, cap, and crimp as directed for the *Standard preparation.*

Test preparation— Transfer 1.0 g of Polyethylene Glycol, to a 22-mL pressure headspace vial; and seal, cap, and crimp as directed for the *Standard preparation.*

Chromatographic system (see Chromatography ⟨ 621 ⟩)— The gas chromatograph is equipped with a balanced pressure automatic headspace sampler and a flame-ionization detector and contains a 0.32-mm × 50-m fused-silica capillary column containing bonded phase G27 in a 5-µm film thickness. The column temperature is programmed from 70° to 250° at 10° per minute, with the injection port at 85° and the detector at 250°. The carrier gas is helium at a flow rate of about 2.9 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for acetaldehyde and 1.0 for ethylene oxide; and the resolution, *R,* between the acetaldehyde peak and the ethylene oxide peak is not less than 1.3.

Procedure— Place the vials containing the *Standard preparation* and the *Test preparation* into the automated sampler, and heat the vials at a temperature of 80° for 30 minutes. Using a 2-mL gas syringe preheated in an oven at 90°, separately inject 1.0 mL of the headspace from each vial into the chromatograph, record the chromatogram, and measure the areas for the major peaks. [NOTE—A headspace apparatus that automatically transfers the measured amount of headspace may be used to perform the injection.] The relative retention times for ethylene oxide and 1,4-dioxane are about 1.0 and 3.4, respectively. The peak areas for ethylene oxide and 1,4-dioxane in the chromatogram of the *Test preparation* are not greater than those of the corresponding peaks in the chromatogram of the *Standard preparation,* corresponding to not more than 10 µg per g of ethylene oxide and not more than 10 µg per g of 1,4-dioxane.

Limit of ethylene glycol and diethylene glycol (for Polyethylene Glycol having a nominal molecular weight less than 450)—

Standard preparation— Prepare an aqueous solution containing 500 µg each of ethylene glycol and of diethylene glycol per mL.

Test preparation— Transfer about 4 g of Polyethylene Glycol, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see Chromatography ⟨ 621 ⟩)— The gas chromatograph is equipped with a flame-ionization detector and a 3-mm × 1.5-m stainless steel column packed with 12% G13 on support S1NS. The carrier gas is nitrogen or another suitable inert gas, flowing at a rate of 50 mL per minute. The column temperature is maintained at about 140°, the injection port temperature is maintained at about 250°, and the flame-ionization detector temperature is maintained at 280°.

Procedure— Inject a volume (about 2.0 µL) of the *Standard preparation* into the chromatograph, and record the chromatogram, adjusting the operational conditions to obtain peaks not less than 10 cm in height. Measure the heights of the first (ethylene glycol) and second (diethylene glycol) peaks, and record the values as P_1 and P_2, respectively. Inject a volume (about 2.0 µL) of the *Test preparation* into the chromatograph, and record the chromatogram under the same conditions as those employed for the *Standard preparation.* Measure the heights of the first (ethylene glycol) and second (diethylene glycol) peaks, and record the values as p_1 and p_2, respectively. Calculate the percentage of ethylene glycol in the portion of Polyethylene Glycol taken by the formula:

$$(C_1\, p_1)/(P_1 W),$$

in which C_1 is the concentration, in µg per mL, of ethylene glycol in the *Standard preparation;* and W is the weight, in mg, of Polyethylene Glycol taken. Calculate the percentage of diethylene glycol in the portion of Polyethylene Glycol taken by the formula:

$$(C_2\, p_2)/(P_2 W),$$

in which C_2 is the concentration, in µg per mL, of diethylene glycol in the *Standard preparation:* not more than 0.25% of the sum of ethylene glycol and diethylene glycol is found.

Limit of ethylene glycol and diethylene glycol (for Polyethylene Glycol having a nominal molecular weight 450 or above but not more than 1000)—

Ceric ammonium nitrate solution— Dissolve 6.25 g of ceric ammonium nitrate in 100 mL of 0.25 N nitric acid. Use within 3 days.

Standard preparation— Transfer 62.5 mg of diethylene glycol to a 25-mL volumetric flask, dissolve in a mixture of equal volumes of freshly distilled acetonitrile and water, dilute with the same mixture to volume, and mix.

Test preparation— Dissolve 50.0 g of Polyethylene Glycol in 75 mL of diphenyl ether, previously warmed, if necessary, just to melt the crystals, in a 250-mL distilling flask. Slowly distill at a pressure of 1 mm to 2 mm of mercury, into a receiver graduated to 100 mL in 1-mL subdivisions, until 25 mL of distillate has been collected. Add 20.0 mL of water to the distillate, shake vigorously, and allow the layers to separate. Cool in an ice bath to solidify the diphenyl ether and facilitate its removal. Filter the separated aqueous layer, wash the diphenyl ether with 5.0 mL of ice-cold water, pass the washings through the filter, and collect the filtrate and washings in a 25-mL volumetric flask. Warm to room temperature, dilute with water to volume, if necessary, and mix. Mix this solution with 25.0 mL of freshly distilled acetonitrile in a glass-stoppered, 125-mL conical flask.

Procedure— Transfer 10.0 mL each of the *Standard preparation* and the *Test preparation* to separate 50-mL flasks, each containing 15.0 mL of *Ceric ammonium nitrate solution,* and mix. Within 2 to 5 minutes, concomitantly determine the absorbances of the solutions in 1-cm cells at the wavelength of maximum absorbance at about 450 nm, with a suitable spectrophotometer, using a blank consisting of a mixture of 15.0 mL of *Ceric ammonium nitrate solution* and 10.0 mL of a mixture of equal volumes of freshly distilled acetonitrile and water: the absorbance of the solution from the *Test preparation* does not exceed that of the solution from the *Standard preparation,* corresponding to not more than 0.25% of combined ethylene glycol and diethylene glycol.

Organic volatile impurities, *Method IV* ⟨ 467 ⟩ **:** meets the requirements for chloroform, methylene chloride, and trichloroethylene.

Residual solvents ⟨ 467 ⟩ **:** meets the requirements.
(Official January 1, 2007)

Auxiliary Information— *Staff Liaison* : Hong Wang, Ph.D. , Senior Scientific Associate
Expert Committee : (EM205) Excipient Monographs 2

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Citric acid

From Wikipedia, the free encyclopedia

D12

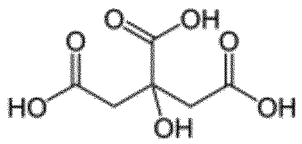
Citric acid is a weak organic tricarboxylic acid having the chemical formula $C_6H_8O_7$. It occurs naturally in citrus fruits. In biochemistry, it is an intermediate in the citric acid cycle, which occurs in the metabolism of all aerobic organisms.

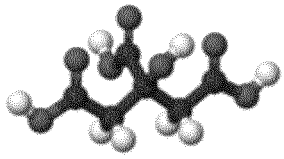
More than a million tons of citric acid are manufactured every year. It is used widely as an acidifier, as a flavoring and chelating agent.[7]

A **citrate** is a derivative of citric acid; that is, the salts, esters, and the polyatomic anion found in solution. An example of the former, a salt is trisodium citrate; an ester is triethyl citrate. When part of a salt, the formula of the citrate ion is written as $C_6H_5O_7^{3-}$ or $C_3H_5O(COO)_3^{3-}$.

Contents

Citric acid

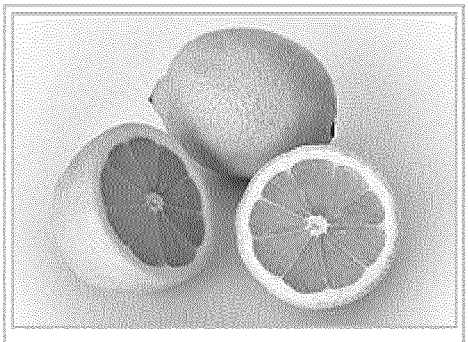




Names	
Preferred IUPAC name 2-Hydroxypropane-1,2,3-tricarboxylic acid	
Other names Citric acid	
Identifiers	
CAS Number	77-92-9 (http://www.commonchemistry.org/ChemicalDetail.aspx?ref=77-92-9) ✓
3D model (JSmol)	Interactive image (http://chemapps.stolaf.edu/jmol/jmol.php?model=OC%28%3DO%29CC%28O%29%28C%28%3DO%29O%29CC%28%3DO%29O)
ChEBI	CHEBI:30769 (https://www.ebi.ac.uk/chebi/searchId.do?chebiId=30769) ✓
ChemSpider	305 (http://www.chemspider.com/Chemical-Structure.305.html) ✓
DrugBank	DB04272 (https://www.drugbank.ca/drugs/DB04272) ✓
ECHA InfoCard	100.000.973 (https://echa.europa.eu/substance-information/-/substanceinfo/100.000.973)
EC Number	201-069-1
E number	E330 (antioxidants, ...)
IUPHAR/BPS	2478 (http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?tab=summary&ligandId=2478)
KEGG	D00037 (http://www.kegg.jp/entry/D00037) ✓
PubChem CID	22230 (monohydrate) 311, 22230 (monohydrate) (https://pubchem.ncbi.nlm.nih.gov/compound/311,)
RTECS number	GE7350000
UNII	XF417D3PSL (https://fdasis.nlm.nih.gov/srs/srsdirect.jsp?regno=XF417D3PSL) ✓

Natural occurrence and

industrial production



Lemons, oranges, limes, and other citrus fruits possess high concentrations of citric acid

Citric acid exists in greater than trace amounts in a variety of fruits and vegetables, most notably citrus fruits. Lemons and limes have particularly high concentrations of the acid; it can constitute as much as 8% of the dry weight of these fruits (about 47 g/L in the juices[8]).[a] The concentrations of citric acid in citrus fruits range from 0.005 mol/L for oranges and grapefruits to 0.30 mol/L in lemons and limes. Within species, these values vary depending on the cultivar and the circumstances in which the fruit was grown.

Industrial-scale citric acid production first began in 1890 based on the Italian citrus fruit industry, where the juice was treated with hydrated lime (calcium hydroxide) to precipitate calcium citrate, which was isolated and converted back to the acid using diluted sulfuric acid.[9] In 1893, C. Wehmer discovered *Penicillium* mold could produce citric acid from sugar. However, microbial production of citric acid did not become industrially important until World War I disrupted Italian citrus exports.

In 1917, American food chemist James Currie discovered certain strains of the mold *Aspergillus niger* could be efficient citric acid producers, and the pharmaceutical company Pfizer began industrial-level production using this technique two years later, followed by Citrique Belge in 1929. In this production

InChI	
	InChI=1S/C6H8O7/c7-3(8)1-6(13,5(11)12)2-4(9)10/h13H,1-2H2,(H,7,8)(H,9,10)(H,11,12) ✓ Key: KRKNYBCHXYNGOX-UHFFFAOYSA-N ✓
	InChI=1/C6H8O7/c7-3(8)1-6(13,5(11)12)2-4(9)10/h13H,1-2H2,(H,7,8)(H,9,10)(H,11,12) Key: KRKNYBCHXYNGOX-UHFFFAOYAM
SMILES	
	OC(=O)CC(O)(C(=O)O)CC(=O)O
Properties	
Chemical formula	$C_6H_8O_7$
Molar mass	192.12 g·mol^{-1}
Appearance	crystalline white solid
Odor	odorless
Density	1.665 g/cm^3 (anhydrous) 1.542 g/cm^3 (18 °C, monohydrate)
Melting point	156 °C (313 °F; 429 K)
Boiling point	310 °C (590 °F; 583 K) decomposes from 175 °C[1]
Solubility in water	117.43 g/100 mL (10 °C) 147.76 g/100 mL (20 °C) 180.89 g/100 mL (30 °C) 220.19 g/100 mL (40 °C) 382.48 g/100 mL (80 °C) 547.79 g/100 mL (100 °C)[2]
Solubility	soluble in alcohol, ether, ethyl acetate, DMSO insoluble in C_6H_6, $CHCl_3$, CS_2, toluene[1]
Solubility in ethanol	62 g/100 g (25 °C)[1]
Solubility in amyl acetate	4.41 g/100 g (25 °C)[1]
Solubility in diethyl ether	1.05 g/100 g (25 °C)[1]
Solubility in 1,4-Dioxane	35.9 g/100 g (25 °C)[1]
log P	−1.64
Acidity (pK_a)	pKa_1 = 3.13[3] pKa_2 = 4.76[3] pKa_3 = 6.39,[4] 6.40[5]
Refractive index (n_D)	1.493–1.509 (20 °C)[2] 1.46 (150 °C)[1]
Viscosity	6.5 cP (50% aq. sol.)[2]
Structure	
Crystal structure	Monoclinic
Thermochemistry	

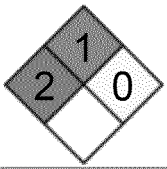
technique, which is still the major industrial route to citric acid used today, cultures of *A. niger* are fed on a sucrose or glucose-containing medium to produce citric acid. The source of sugar is corn steep liquor, molasses, hydrolyzed corn starch or other inexpensive sugary solutions.[10] After the mold is filtered out of the resulting solution, citric acid is isolated by precipitating it with calcium hydroxide to yield calcium citrate salt, from which citric acid is regenerated by treatment with sulfuric acid, as in the direct extraction from citrus fruit juice.

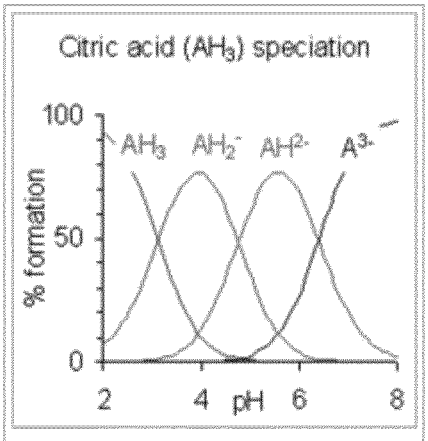
In 1977, a patent was granted to Lever Brothers for the chemical synthesis of citric acid starting either from aconitic or isocitrate/alloisocitrate calcium salts under high pressure conditions. This produced citric acid in near quantitative conversion under what appeared to be a reverse non-enzymatic Krebs cycle reaction.[11]

In 2007, worldwide annual production stood at approximately 1,600,000 tons.[12] More than 50% of this volume was produced in China. More than 50% was used as acidity regulator in beverages, some 20% in other food applications, 20% for detergent applications and 10% for related applications other than food, such as cosmetics, pharmaceutics and in the chemical industry.

Chemical characteristics

Citric acid was first isolated in 1784 by the chemist Carl Wilhelm Scheele, who crystallized it from lemon juice.[9][13] It can exist either in an anhydrous (water-free) form or as a monohydrate. The anhydrous form crystallizes from hot water, while the monohydrate forms when citric acid is crystallized from cold water. The monohydrate can be converted to the anhydrous form at about 78 °C. Citric acid also dissolves in absolute (anhydrous) ethanol (76 parts of citric acid per 100 parts of ethanol) at 15 °C. It decomposes with loss of carbon dioxide above about 175 °C.

Specific heat capacity (*C*)	226.51 J/(mol·K) (26.85 °C)[6]
Std molar entropy (S°_{298})	252.1 J/(mol·K)[6]
Std enthalpy of formation ($\Delta_f H^{\circ}_{298}$)	−1548.8 kJ/mol[2]
Std enthalpy of combustion ($\Delta_c H^{\circ}_{298}$)	−1960.6 kJ/mol[6] −1972.34 kJ/mol (monohydrate)[2]
Pharmacology	
ATC code	A09AB04 (WHO (https://www.whocc.no/atc_ddd_index/?code=A09AB04))
Hazards	
Main hazards	skin and eye irritant
Safety data sheet	HMDB (http://www.hmdb.ca/system/metabolites/msds/000/000/065/original/HMDB00094.pdf?1358893891)
GHS pictograms	 [3]
GHS signal word	Warning
GHS hazard statements	H319[3]
GHS precautionary statements	P305+351+338[3]
NFPA 704	
Flash point	155 °C (311 °F; 428 K)
Autoignition temperature	345 °C (653 °F; 618 K)
Explosive limits	8%[3]
Lethal dose or concentration (*LD*, *LC*):	
LD_{50} (median dose)	3000 mg/kg (rats, oral)
Except where otherwise noted, data are given for materials in their standard state (at 25 °C [77 °F], 100 kPa). ✘ verify (what is ✓✘ ?) Infobox references	



Speciation diagram for a 10-millimolar solution of citric acid

Citric acid is normally considered to be a tribasic acid, with pK_a values, extrapolated to zero ionic strength, of 5.21, 4.28 and 2.92 at 25 °C.[14] The pKa of the hydroxyl group has been found, by means of ^{13}C NMR spectroscopy, to be 14.4.[15] The speciation diagram shows that solutions of citric acid are buffer solutions between about pH 2 and pH 8. In biological systems around pH 7, the two species present are the citrate ion and mono-hydrogen citrate ion. The SSC 20X hybridization buffer (http://openwetware.org/wiki/SSC) is an example in common use.[16] Tables compiled for biochemical studies[17] are available.

On the other hand, the pH of a 1 mM solution of citric acid will be about 3.2. The pH of fruit juices from citrus fruits like oranges and lemons depends on the citric acid concentration, being lower for higher acid concentration and conversely.

Acid salts of citric acid can be prepared by careful adjustment of the pH before crystallizing the compound. See, for example, sodium citrate.

The citrate ion forms complexes with metallic cations. The stability constants for the formation of these complexes are quite large because of the chelate effect. Consequently, it forms complexes even with alkali metal cations. However, when a chelate complex is formed using all three carboxylate groups, the chelate rings have 7 and 8 members, which are generally less stable thermodynamically than smaller chelate rings. In consequence, the hydroxyl group can be deprotonated, forming part of a more stable 5-membered ring, as in ammonium ferric citrate, $(NH_4)_5Fe(C_6H_4O_7)_2 \cdot 2H_2O$.[18]

Esters such as triethyl citrate can be made.

Biochemistry

Citric acid cycle

Citrate is an intermediate in the TCA cycle (*aka* **Tri**C**a**rboxylic **A**cid cycle, Krebs cycle, Szent-Györgyi — Krebs cycle), a central metabolic pathway for animals, plants and bacteria. Citrate synthase catalyzes the condensation of oxaloacetate with acetyl CoA to form citrate. Citrate then acts as the substrate for aconitase and is converted into aconitic acid. The cycle ends with regeneration of oxaloacetate. This series of chemical reactions is the source of two-thirds of the food-derived energy in higher organisms. Hans Adolf Krebs received the 1953 Nobel Prize in Physiology or Medicine for the discovery.

Some bacteria, notably *E. coli*, can produce and consume citrate internally as part of their TCA cycle, but are unable to use it as food because they lack the enzymes required to import it into the cell. After tens of thousand of evolution in a minimal glucose medium that also contains citrate during Richard Lenski's Long-Term Evolution Experiment, a variant *E. coli* evolved with the ability to grow aerobically on citrate. Zachary Blount, a student of Lenski's, and colleagues studied these "Cit^+" *E. coli*[19][20] as a model for how novel traits evolve. They found evidence that in this case the innovation was immediately caused by a rare duplication mutation that was effective in causing the trait due to the accumulation of several prior "potentiating" mutations, the identity and effects of which are still under study. The evolution of the Cit^+ trait has been considered a notable example of the role of historical contingency in evolution.

Other biological roles

Citrate can be transported out of the mitochondria and into the cytoplasm, then broken down into acetyl-CoA for fatty acid synthesis and into oxaloacetate. Citrate is a positive modulator of this conversion,

and allosterically regulates the enzyme acetyl-CoA carboxylase, which is the regulating enzyme in the conversion of acetyl-CoA into malonyl-CoA (the commitment step in fatty acid synthesis). In short, citrate is transported to the cytoplasm, converted to acetyl CoA, which is converted into malonyl CoA by the acetyl CoA carboxylase, which is allosterically modulated by citrate.

High concentrations of cytosolic citrate can inhibit phosphofructokinase, the catalyst of one of the rate-limiting steps of glycolysis. This effect is advantageous: high concentrations of citrate indicate that there is a large supply of biosynthetic precursor molecules, so there is no need for phosphofructokinase to continue to send molecules of its substrate, fructose 6-phosphate, into glycolysis. Citrate acts by augmenting the inhibitory effect of high concentrations of ATP, another sign that there is no need to carry out glycolysis.[21]

Citrate is a vital component of bone, helping to regulate the size of apatite crystals.[22]

Applications

Food and drink

Because it is one of the stronger edible acids, the dominant use of citric acid is used as a flavoring and preservative in food and beverages, especially soft drinks.[9] Within the European Union it is denoted by E number **E330**. Citrate salts of various metals are used to deliver those minerals in a biologically available form in many dietary supplements. The buffering properties of citrates are used to control pH in household cleaners and pharmaceuticals. In the United States the purity requirements for citric acid as a food additive are defined by the Food Chemicals Codex, which is published by the United States Pharmacopoeia (USP).

Powdered citric acid being used to prepare lemon pepper seasoning

Citric acid can be added to ice cream as an emulsifying agent to keep fats from separating, to caramel to prevent sucrose crystallization, or in recipes in place of fresh lemon juice. Citric acid is used with sodium bicarbonate in a wide range of effervescent formulae, both for ingestion (e.g., powders and tablets) and for personal care (*e.g.*, bath salts, bath bombs, and cleaning of grease). Citric acid sold in a dry powdered form is commonly sold in markets and groceries as "sour salt", due to its physical resemblance to table salt. It has use in culinary applications, as an alternative to vinegar or lemon juice, where a pure acid is needed.

Citric acid can be used in food coloring to balance the pH level of a normally basic dye.

Cleaning and chelating agent

Citric acid is an excellent chelating agent, binding metals by making them soluble. It is used to remove and discourage the buildup of limescale from boilers and evaporators.[9] It can be used to treat water, which makes it useful in improving the effectiveness of soaps and laundry detergents. By chelating the metals in hard water, it lets these cleaners produce foam and work better without need for water softening. Citric acid is the active ingredient in some bathroom and kitchen cleaning solutions. A solution with a six percent concentration of citric acid will remove hard water stains from glass without scrubbing. In industry, it is used to dissolve rust from steel. Citric acid can be used in shampoo to wash out wax and coloring from the hair.

Illustrative of its chelating abilities, citric acid was the first successful eluant used for total ion-exchange separation of the lanthanides, during the Manhattan Project in the 1940s. In the 1950s, it was replaced by the far more efficient EDTA.

Cosmetics, pharmaceuticals, dietary supplements, and foods

Citric acid is widely used as an acidulent in creams, gels, and liquids of all kinds. In its use in foods and dietary supplements, it may be classified as a processing aid if the purpose it was added was for a technical or functional effect (e.g. acidulent, chelator, viscosifier, etc...) for a process. If it is still present in insignificant amounts, and the technical or functional effect is no longer present, it may be exempted from labeling <21 CFR §101.100(c)>.

Citric acid is an alpha hydroxy acid and used as an active ingredient in chemical peels.

Citric acid is commonly used as a buffer to increase the solubility of brown heroin. Single-use citric acid sachets have been used as an inducement to get heroin users to exchange their dirty needles for clean needles in an attempt to decrease the spread of HIV and hepatitis.[23] Other acidifiers used for brown heroin are ascorbic acid, acetic acid, and lactic acid; in their absence, a drug user will often substitute lemon juice or vinegar.

Citric acid is used as one of the active ingredients in the production of antiviral tissues.[24]

Other uses

Citric acid is used as an odorless alternative to white vinegar for home dyeing with acid dyes.

Sodium citrate is a component of Benedict's reagent, used for identification both qualitatively and quantitatively, of reducing sugars.

Citric acid can be used as an alternative to nitric acid in passivation of stainless steel.[25]

Citric acid can be used as a lower-odor stop bath as part of the process for developing photographic film. Photographic developers are alkaline, so a mild acid is used to neutralize and stop their action quickly, but commonly used acetic acid leaves a strong vinegar odor in the darkroom.[26]

Citric acid/potassium-sodium citrate can be used as a blood acid regulator.

Synthesize solid materials from small molecules

In materials science, the Citrate-gel method is a process similar to the sol-gel method, which is a method for producing solid materials from small molecules. During the synthetic process, metal salts or alkoxides are introduced into a citric acid solution. The formation of citric complexes is believed to balance the difference in individual behaviour of ions in solution, which results in a better distribution of ions and prevents the separation of components at later process stages. The polycondensation of ethylene glycol and citric acid starts above 100°C, resulting in polymer citrate gel formation.

Safety

Although a weak acid, exposure to pure citric acid can cause adverse effects. Inhalation may cause cough, shortness of breath, or sore throat. Over-ingestion may cause abdominal pain and sore throat. Exposure of concentrated solutions to skin and eyes can cause redness and pain.[27] Long-term or repeated consumption may cause erosion of tooth enamel.[27][28][29]

Compendial status

- British Pharmacopoeia[30]
- Japanese Pharmacopoeia[31]

See also

- The closely related acids isocitric acid, aconitic acid, and propane-1,2,3-tricarboxylic acid (tricarballylic acid, carballylic acid)
- Acids in wine

Wikimedia Commons has media related to ***Citric acid***.

Wikisource has the text of the 1911 *Encyclopædia Britannica* article ***Citric Acid***.

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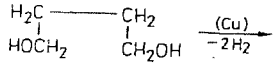
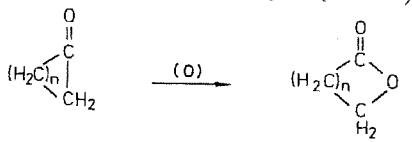
a. This still does not make the lemon particularly strongly acidic. This is because, as a weak acid, most of the acid molecules are not dissociated so not contributing to acidity inside the lemon or its juice.

: *γ-Butyrolacton* entsteht durch Dehydrierung von 1,4-Butandiol am Kupfer-
t bei 200 °C (475 K) (*Reppe*):

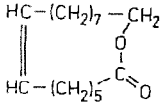


1,4-Butandiol

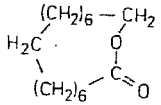
Höhergliedrige Lactone sind durch Oxid Per-
vefelsäure (*Caro*sche Säure), H_2SO_5, zugänglich (*Ruzicka*):



ıaften. Die Lactone sieden niedriger als die zugehörigen Hydroxysäuren. Sie
einen starken, meist angenehmen Geruch auf, vor allem die höhergliedrigen
17 Ringgliedern, zu denen z. B. *Ambrettolid*, der Duftstoff z. B. des Moschus-
s, sowie das Lacton des Angelicawurzelöls, das unter dem Namen *Exaltolid*
ch hergestellt wird, zählen:



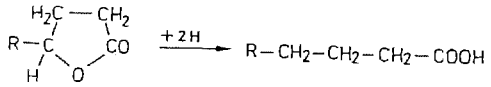
Ambrettolid



Exaltolid

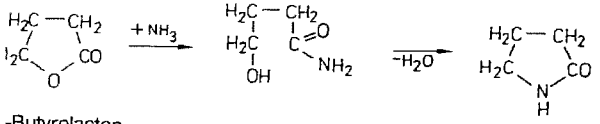
, die bis zu 7 Glieder haben, liegt die Lactongruppe in der (*E*)-Konfiguration vor; bei
0 Ringgliedern bevorzugt sie die (*Z*)-Konfiguration (vgl. S. 69).

ctivität der Lactone ist vornehmlich auf die *Lactongruppierung* beschränkt. Bei
duktion mit Natriumamalgam in saurem Medium entstehen die betreffenden
iuren:



ührt die gleiche Reaktion bei Polyhydroxylactonen in schwach saurer Lösung zu den

spaltung der Lactonbindung unter Bildung der entsprechend substituierten
uren tritt mit konzentrierten Halogenwasserstoffsäuren, Alkalicyanid oder
ıydrogensulfit ein; mit Ammoniak entstehen Hydroxycarbonsäureamide, die
sserabspaltung leicht in *Lactame* übergehen, z. B.

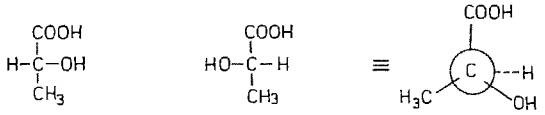


-Butyrolacton

2-Pyrrolidon, 4-Butanlactam

2.29.6.1 Glykolsäure (Hydroxy-essigsäure), $HOCH_2-COOH$, Schmp. 79 °C (352 K), kommt im Pflanzenreich vor, z. B. in unreifen Weintrauben und im Zuckerrohr.

2.29.6.2 DL-Milchsäure (α-Hydroxypropionsäure, engl. Lactic acid: Lac), $H_3C-CH(OH)-COOH$, wurde von *Scheele* (1780) in der sauren Milch entdeckt, und zwar entsteht sie durch Vergärung der Lactose (Milchzucker) mittels *Streptococcus lactis* bzw. *Lactobacillus lactis*. Außerdem tritt sie im Magensaft und in sauren Gurken auf.
Die *optisch aktiven* Milchsäuren besitzen folgende Konfigurationen:



D(−)-Milchsäure L(+)-Milchsäure (*S*)-Form

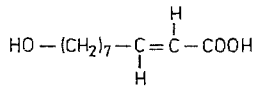
L(+)-Milchsäure findet sich in verschiedenen tierischen Organen sowie im Muskelsaft und wird daher auch *Fleischmilchsäure* (*Berzelius*, 1808) genannt. Sie weist die gleiche sterische Anordnung wie die α-Aminosäuren im Eiweiß auf. Diese ist im *CIP*-System die (*S*)-Form.
Reine DL-Milchsäure ist eine sirupöse Flüssigkeit, die bei 18 °C (291 K) erstarrt; die D- und L-Milchsäure schmelzen bei 25 °C (298 K) ($pK_a = 3{,}86$). Ihre Salze heißen *Lactate*.

2.29.6.3 Milchsäuregärung. Technisch gewinnt man Milchsäure *durch enzymatische Verzuckerung von Kohlenhydraten* (meist Kartoffel- oder Getreidestärke) mittels *Diastase* zu Maltose, die bei 35 bis 45 °C (310–320 K) in Gegenwart von *Lactobacillus delbrueckii* über Glucose zu Milchsäure vergoren wird:

$$C_6H_{12}O_6 \rightarrow 2\,H_3C-CH(OH)-COOH$$

Da die Vergärung der Zucker an einen bestimmten pH-Bereich gebunden ist, fängt man die entstehende Milchsäure durch Zugabe von Calciumcarbonat als *Calciumlactat* ab. Aus diesem läßt sie sich mit Schwefelsäure in Freiheit setzen. Zum *Mechanismus* der Milchsäuregärung s. S. 901.
Meist erhält man die DL-Milchsäure (Gärungsmilchsäure), jedoch mit spezifisch wirkenden Bakterien auch überwiegend D(−)- bzw. L(+)-Milchsäure. Wirtschaftliche Bedeutung kommt diesem Gärprozeß bei der *Futtersilierung* (Rübenblätter, Grünfutter) zu.

Verwendung. Die Milchsäure wird zum Entkalken von Fellen in der Gerberei, als Reduktionsmittel in der Chrombeizenfärberei und wegen ihrer leichten Verdaulichkeit als Zusatz für alkoholfreie Getränke verwendet.
Zur Aufzucht einer Bienenkönigin dient ein als Gelée royale (Weiselfuttersaft) bezeichnetes Substanzgemisch aus Proteinen, Kohlenhydraten und Lipiden, das eine Anzahl von C_{10} Carbonsäuren enthält, hauptsächlich (*E*)-10-Hydroxy-2-decensäure:



D5

ANNEX A

Experiments to Test the Stability of Compositions of the Invention Against Formation of PEG Esters

PRODUCTION OF CAPSULES IN ACCORDANCE WITH THE INVENTION

Active Ingredients

Ingredient	Amount per Capsule
naproxen sodium	220mg

Fill Excipients

Ingredient	Amount (mg) per Capsule
Lactic Acid	44.0
Propylene Glycol	17.7
Povidone K-30	17.7
Polyethylene Glycol 600	580.6

Gelain Shell Excipients

Ingredient
Gelatin
Glycerin
Sorbital Special
Purified Water
ED&C Yellow # 6
FD&C Blue # 1

Using these ingredients capsules were produced using a method as described in the Examples of European Patent Application No. 06737018.9.

PACKAGING OF THE CAPSULES

The capsules were either packaged 15 to a bottle or 200 to a bottle or in a bulk carton. The bottles containing 15 capsules were 45 cc, round, opaque white HDPE bottles with child resistant caps.

The bottles containing 200 capsules were 400 cc, round, opaque, white, HDPE bottles with child resistant caps.

STUDY DESIGN

Bottles containing 15 capsules and bottles containing 200 capsules were stored at 25°C and a relative humidity of 60% and at 30°C and a relative humidity of 65%. A carton containing the capsules stored in bulk was stored at 25°C and 60% relative humidity.

The percentage of PEG esters in the capsules, as a percentage of the drug (naproxen sodium), was determined using HPLC, before storage and after storage for 3 months, 6 months, 9 months and 12 months.

THE RESULTS

TEST WITH BOTTLES CONTAINING 15 CAPSULES

Storage at 25°C/60% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.10%	0.17%	0.25%	0.32%
	None	0.10%	0.17%	0.25%	0.33%
	None	0.10%	0.15%	0.25%	0.32%

Storage at 30°C/65% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.15%	0.28%	0.30%	0.57%
	None	0.15%	0.29%	0.44%	0.58%
	None	0.15%	0.29%	0.44%	0.59%

TEST WITH BOTTLES CONTAINING 200 CAPSULES

Storage at 25°C/60% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.10%	0.17%	0.25%	0.31%
	None	0.11%	0.17%	0.25%	0.32%
	None	0.10%	0.17%	0.24%	0.32%

Storage at 30°C/65% Relative Humidity

	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.16%	0.29%	0.41%	0.57%
	None	0.15%	0.29%	0.45%	0.59%
	None	0.15%	0.28%	0.44%	0.58%

TEST OF BULK PACK CAPSULES

Storage at 25°c/60% Relative Humidity

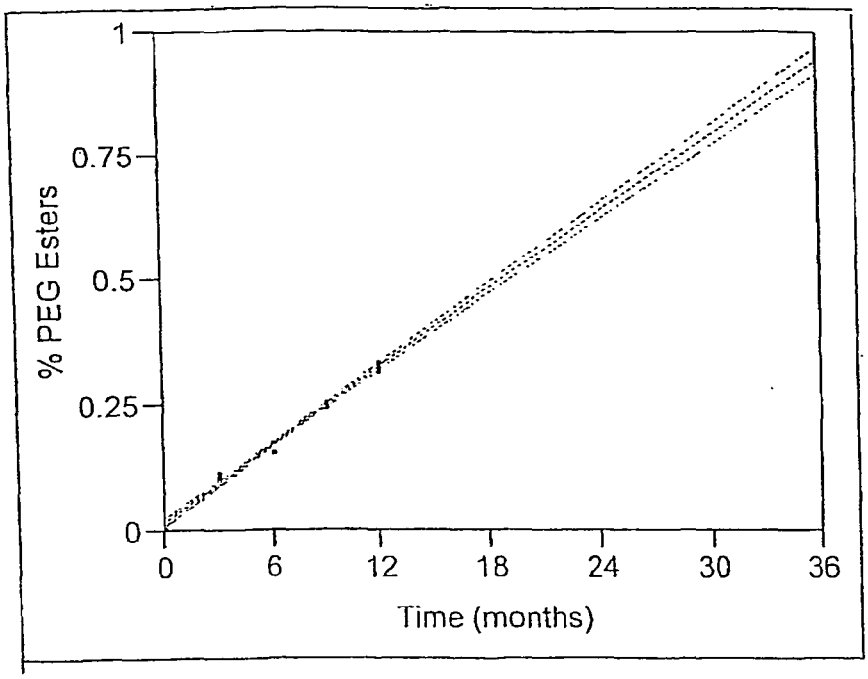
	No. Of Months				
	0	3	6	9	12
% PEG-esters	None	0.10%	0.17%	0.25%	0.32%
	None	0.10%	0.16%	0.26%	0.32%
	None	0.09%	0.17%	0.22%	0.32%

These results show that initially the capsules of the invention contained no PEG esters and that even after storage for up to one year under a variety of storage conditions the capsules of the invention contained very low levels of PEG esters. In every case, significantly less than 1% of the drug had formed PEG esters even after storage for a year. Less than 1% PEG ester formation was considered to represent a low level of PEG ester formation which did not cause significant loss of activity and therefore compositions with less than 1% PEG ester were considered to be stable. All of the capsules tested passed this test.

EVALUATION OF PEG ESTER RESULTS

The percent PEG esters was plotted versus time (see graph on page 5). In addition, the 95% confidence bounds were added to the plot. Both the fitted least-squares line and the 95% upper confidence bound were extrapolated through 36 months to examine product expiration. According to the extrapolated data points for the upper 95% confidence bound, the percent PEG esters at 24 months should be 0.65 and according to the fitted least-squares line, the percent PEG esters should be 0.63. This means that even after three years the predicted values from both the upper 95% confidence and the least-squares line did not exceed the upper acceptable specification limit of not more than 1.0% PEG esters. In other words, compositions of the invention are not predicted to lose activity through PEG ester formation after 3 years and to therefore have a shelf life of at least three years.

Naproxen Sodium 220 mg SGC 25°C/60% RH
(% PEG esters vs. Time)



D6

European Patent Application No.06737018.9
Banner Pharmacaps, Inc
PC Ref: PABCX/P38814EP

ANNEX TO GROUNDS OF APPEAL

REPORT OF COMPARATIVE STUDIES CONDUCTED TO COMPARE THE PROPERTIES OF COMPOSITIONS OBTAINED IN ACCORDANCE WITH THE INVENTION AND THE COMPOSITIONS DESCRIBED IN US 5,360,615

1.0 INTRODUCTION

European patent application no. 06737018.9 is directed to a method of preparing a pharmaceutical composition. This method comprises mixing (i) naproxen sodium, (ii) polyethylene glycol, (iii) hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid, or lactic acid. Component (iii) is used in an amount of from 0.2 to 1.0 mole equivalents per mole of naproxen sodium.

An advantage of the present invention is that it provides a reduction in the production of undesired degradation products such as polyethylene glycol (PEG) esters compared with the prior art.

The applicant company conducted experiments to demonstrate that preparing a pharmaceutical composition in accordance with the present invention results in reduced formation of polyethylene glycol (PEG) esters compared to producing a composition in accordance with the teaching of D1.

Accordingly, the study was designed based on the information provided in D1 and the teaching of European patent application no. 06737018.9. The compositions tested are summarized in Tables 1, 2 and 3 below.

Table 1: Study of compositions prepared in accordance with the present invention

Naproxen Form	Naproxen amount	Acid	Approximate mole equivalent level (amount of acid)		
Naproxen Sodium	285 mg	HCl	0.2	0.6	1.0
	220 mg	HCl	0.2	0.6	1.0
Naproxen Sodium	285 mg	Lactic acid	0.2	0.6	1.0
	220 mg	Lactic acid	0.2	0.6	1.0
Naproxen Sodium	285 mg	Citric acid	0.2		1.0
	220 mg	Citric acid	0.2		

285 mg of Naproxen Sodium is equivalent to 260 mg of the free acid.

220 mg of Naproxen Sodium is equivalent to 200 mg of the free acid.

Table 2: Study based on the teaching of D1

Naproxen Form	Naproxen amount	Base	Approximate mole equivalent level (amount of base)		
Naproxen free acid	260 mg	KOH	0.2	0.6	1.0
	200 mg	KOH	0.2	0.6	1.0

All the experiments were performed using PEG 600. This is a representative example of a PEG that can be used in the present invention and was used in some of the Examples of the application as filed and was also used in Example IV of D1.

Table 3: Study based of compositions containing water

Naproxen Form	Naproxen Amount	Acid/Base	Water	Approximate mole equivalent level (amount of acid/base)		
Naproxen Sodium	285 mg	Lactic acid	8.5%	0.2	0.6	1.0
	220 mg	Lactic acid	8.5%	0.2	0.6	1.0
Naproxen free acid	260 mg	KOH	8.5%	0.2	0.6	1.0
	200 mg	KOH	8.5%	0.2	0.6	1.0

2.0 MATERIALS

Material	Lot #	Supplier
6N Hydrochloric Acid	E05P01	J.T. Baker
PEG-600	100009129	Banner
Lactic Acid	20010740	Banner
Citric Acid	08-0091	Banner
Potassium Hydroxide	E17K52	J.T. Baker
Naproxen Sodium	SO60103	RoChemical International
Naproxen	081M1091V	Sigma-Aldrich

3.0 PROCEDURE

Naproxen sodium or free acid was added to PEG 600 followed by addition of molar equivalent of the appropriate acid or based in accordance with the method of the present invention and the teaching of D1, respectively.

The compositions produced in this manner were subjected to an accelerated stability study. In this study the compositions were heated to 60°C for 1 week and analyzed for the amount of PEG esters initially and at the end of the accelerated stability study.

The following formulations were prepared:

- Two series of formulations identical to that described in D1 and in the present application.
- Two series of modified formulations prepared using:

  (1) 220 mg Naproxen Sodium and PEG 600, PG and Povidone were replaced with PEG 600. Three mole ratios of acid or base such as 0.2, 0.6 and 1 were used as illustrative of the range specified in the claims of the present application.

(2) Formulations based on the teaching of D1 comprising Naproxen free acid in an amount equivalent to the molar amount used in the formulations representative of the invention, with the same amount of PEG 600 and with KOH.

Samples were analyzed by HPLC:

Agilent 1100 Series HPLC System

Column: DeactiSil ODS-3 5u 100A, 25cm X 4.6mm (ES Industries)

Column Oven Temperature: ambient

Flow Rate: 1.5 mL/min

Injection Volume: 25 uL

UV Detector at 272 nm

Run Time: 60 minutes

Mobile Phase A:

Phosphate Buffer:Acetonitrile (3:2 ratio)

Mobile Phase B:

Phosphate Buffer:Acetonitrile (1:3 ratio)

Limit of quantitation was approximated to be 0.00011 mg/mL

Banner's Formulations

Sample #	Name	Naproxen Na (g)	6N HCl (mL)	PEG-600 (g)
1	NS 285-0.2 HCl	7.128	0.95	16.950
2	NS 285-0.6 HCl	7.120	2.80	15.024
3	NS 285-1.0 HCl	7.152	4.70	13.514
4	NS 220-0.2 HCl	5.512	0.70	18.790
5	NS 220-0.6 HCl	5.521	2.15	17.413
6	NS 220-1.0 HCl	5.548	3.60	15.891

		Naproxen Na (g)	Lactic Acid (g)	DI H20 (g)	PEG-600 (g)
7	NS 285-0.2 lactic	7.133	0.513	0.434	16.947
8	NS 285-0.6 Lactic	7.150	1.528	1.295	15.053
9	NS 285-1.0 Lactic	7.132	2.544	2.167	13.188
10	NS 220-0.2 Lactic	5.559	0.388	0.460	18.789
11	NS 220-0.6 Lactic	5.518	1.186	1.030	17.339
12	NS 220-1.0 Lactic	5.523	1.972	1.660	15.899

		Naproxen Na (g)	Citric Acid (g)	DI H20 (g)	PEG-600 (g)
13	NS 285-0.2 Citric	7.129	1.020	0.439	16.364
14	NS 285-1.0 Citric	7.128	5.436	2.519	10.350
15	NS 220-0.2 Citric	5.012	0.865	0.364	18.355

Yu's Formulations

	Naproxen API	Naproxen (g)	50% KOH (9)	PEG-GOO (g)
16	Yu 260-0.2 KOH	6.499	0.330	17.892
17	Yu 260-0.6 KOH	6.497	0.957	16.681
18	Yu 260-1.0 KOH	6.510	1.594	15.357
19	Yu 200-0.2 KOH	5.027	0.286	19.555
20	Yu 200-0.6 KOH	5.100	0.757	18.580
21	Yu 200-1.0 KOH	5.134	1.230	17.540

In the tables above, "Banner's formulations" refers to formulations prepared using the method of the present invention and "Yu's formulations" refers to formulations that are representative of the teaching of D1.

4.0 RESULTS

The results are summarized in the Table below.

Banner's Formulations		Room Temperature		Stress at 60C for 7-Days		Physical Observations of Formulations	
Sample #	Name	Peaks RT	% Area	Peaks RT	% Area	Room Temp	Stress at 60C 7-Days
1	NS 285-0.2 HCl	*10.78 **14.347	0.0084% 99.9916%	14.36	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
2	NS 285-0.6 HCl	10.787 14.34	0.0101% 99.9899%	10.78 14.38	0.0030% 99.9970%	Phase Separate, precipitate	Phase Separate, precipitate
3	NS 285-1.0 HCl	10.753 14.36	0.0076% 99.9924%	10.8 14.4	0.0069% 99.9931%	Phase Separate, precipitate	Phase Separate, precipitate
4	NS 220-0.2 HCl	10.773 14.347	0.0076% 99.9924%	14.4	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
5	NS 220-0.6 HCl	14.36	100.0000%	14.427	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
6	NS 220-1.0 HCl	10.773 14.36	0.0082% 99.9918%	10.793 14.413	0.0048% 99.9952%	Phase Separate, precipitate	Phase Separate, precipitate
7	NS 285-0.2 Lactic	10.78 14.293	0.0075% 99.9925%	14.36	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
8	NS 285-0.6 Lactic	10.773 14.287	0.0072% 99.9928%	14.38	100.0000%	Clear Solution, crystallize at bottom	Clear Solution
9	NS 285-1.0 Lactic	10.767 14.327	0.0073% 99.9927%	14.413	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate

10	NS 220-0.2 Lactic	10.767 14.327	0.0069% 99.9931%	14.42	100.0000%	Phase Separate, precipitate	Phase Separate, precipitate
11	NS 220-0.6 Lactic	10.773 14.347	0.0067% 99.9933%	14.407	100.0000%	Clear solution	Clear solution
12	NS 220-1.0 Lactic	10.773 14.367	0.0064% 99.9936%	14.393	100.0000%	White semi-solid crystallized	Phase Separate, precipitate
13	NS 285-0.2 Citric	10.747 14.327	0.0087% 99.9913%	10.76 14.38	0.0038% 99.9962%	White semi-solid crystallized	Phase Separate, precipitate
14	NS 285-1.0 Citric	10.78 14.32	0.0021% 30.4552%	10.78 14.373	0.0107% 99.9893%	White semi-solid paste	White semi-solid paste
15	NS 220-0.2 Citric	10.787 14.353	0.0061% 99.9939%	14.393	100.0000%	Opaque solution fill, viscuous	Phase Separate, precipitate

Yu's Formulations		Room Temperature		Stress at 60C for 7-Days		Physical Observations of Formulations	
Sample #	**Name**	**Peaks RT**	**% Area**	**Peaks RT**	**% Area**	**Room Temp**	**Stress at 60C 7-Days**
16	Yu 260-0.2 KOH	*10.773 **14.333	0.0178% 99.8580%	10.793 14.387	0.0132% 99.8658%	Phase Separate, precipitate	Clear solution
17	Yu 260-0.6 KOH	10.767 14.367	0.0154% 99.8745%	10.807 14.387	0.0133% 99.8689%	Clear solution	Clear solution
18	Yu 260-1.0 KOH	10.793 14.36	0.0160% 99.8751%	10.813 14.373	0.0140% 99.8647%	Clear solution	Clear solution
19	Yu 200-0.2 KOH	10.793 14.393	0.0144% 99.8879%	10.8 14.413	0.0093% 99.8861%	Clear solution	Clear solution
20	Yu 200-0.6 KOH	10.787 14.387	0.0146% 99.8797%	10.793 14.4	0.0128% 99.8784%	Clear solution	Clear solution
21	Yu 200-1.0 KOH	10.787 14.38	0.0148% 99.8835%	10.807 14.387	0.0135% 99.8750%	Clear solution	Clear solution

* PEG ester peak retention time.

** Naproxen peak retention time.

In general, the amount of PEG ester in the formulations prepared in accordance with the teaching of D1 when subjected to stressed conditions varied from 0.0093 to 0.014. The compositions prepared by the method of the present invention exhibited lower levels of PEG esters at room temperature and after the stress study.

5.0 CONCLUSION

The results of these experiments show that formulations prepared in accordance with the teaching of the present invention surprisingly contain lower amounts of PEG esters that formulations prepared following the teaching of D1.

Technical Data Sheet

D7

CARBOWAX™ Polyethylene Glycol (PEG) 600

Product CAS # 25322-68-3
Description CHEMICAL FAMILY – Oxyalkylene Polymer
CFTA NOMENCLATURE – PEG-12

Typical Physical Properties – CARBOWAX™ PEG 600 [1]

Range of Avg. Molecular Weight	570 - 630
Range of Average Hydroxyl Number, mg KOH/g	178 - 197
Density, g/cm^3 @ 20°C	1.1258
Melting or Freezing Range, C	15 - 25
Solubility in Water at 20°C, % by wt	Complete
Viscosity at 100°C, cSt	10.8
Average Number of Repeating Oxyethylene Units	13.2
Avg. Liquid Specific Heat, cal/g/°C	0.51
Heat of Fusion, Cal/g	35
pH at 25°C, 5% Aqueous Solution	4.5 - 7.5
Flash Point, Pensky Martens Closed Cup, C	238
Flash Point, Cleveland Open Cup, °C	274
Physical Form	Liquid
Weight per gallon, lbs/gal @ 20°C	9.39

1. Typical properties, not to be construed as specifications

Typical Known Applications for Polyethylene Glycols*

- Adhesives
- Ceramic Glaze
- Chemical Intermediates
- Food Packaging
- Inks
- Lubricants
- Mold Release Agent
- Plasticizer
- Wood Treatment

*Refer to the CARBOWAX™ Polyethylene Glycols and Methoxypolyethylene Glycols brochure (Form No. 118-01789-1011) for more specific application information

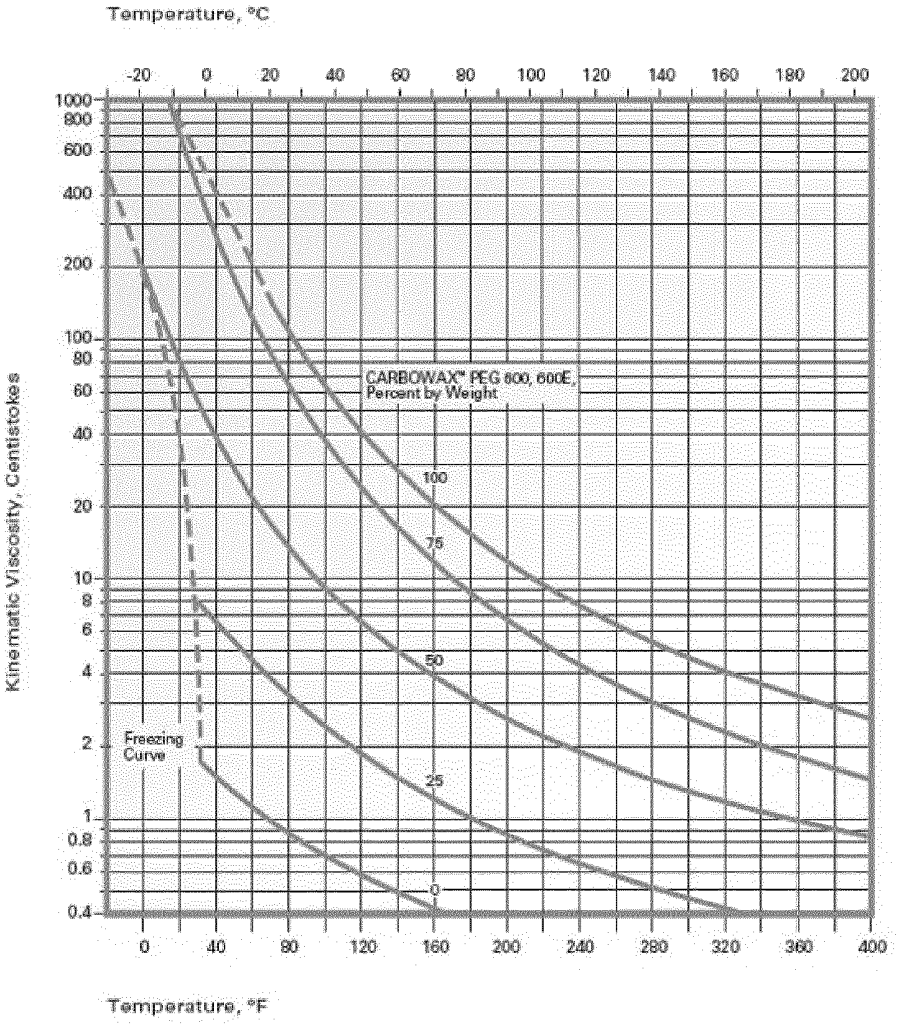
FDA Status CARBOWAX™ Polyethylene Glycols are produced to meet the requirements for use under Food Additive Regulations for indirect use as components of articles intended for use in contact with food. It is the responsibility of the user of CARBOWAX™ PEGs and MPEGs to read and understand all current applicable FDA and EPA regulations, as well as any other applicable regulations.

Product Stewardship Dow encourages its customers and potential users to review their applications from the standpoint of human health and environmental aspects. To help ensure that Dow products are not used in ways for which they are not intended or tested, Dow personnel will assist customers in dealing with environmental and product safety considerations. Dow literature, including material Safety Data Sheets, should be consulted prior to the use.

Form No. 118-01800-1211

Technical Data Sheet

Kinematic Viscosity of A ueous Solutions of CARBOWAX™ Polyethylene Glycol 600



For further information, call...

In the United States and Canada: 1-800-447-4369 • FAX: 1-989-832-1465

In Europe: +800 3 694 6367 • FAX: +31 11567 4704

In the Asia Pacific: +800 7776 7776 • FAX: +800 7779 7779

In Latin America: +55 11 5188 9000 • FAX: +55 11 5184 8790

www.carbowax.com

Published December 2011

Form No. 118-01800-1211

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact

Potter Clarkson LLP
The Belgrave Centre
Talbot Street
Nottingham NG1 5GG
ROYAUME UNI

Date
20.07.2017

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 1466 / 1863458
Applicant/Proprietor	
Banner Life Sciences, LLC	

Communication of notices of opposition (R. 79(1) EPC)

Notice of opposition has been filed within the opposition period by:

01.
Dieckhoff, Beate
Dünnwalder Grenzweg 20
51375 Leverkusen
ALLEMAGNE

The notice of opposition indicated above has already been communicated to you.

You are requested to file your observations within a period of **four months** from notification of this communication.

You may also file amendments, where appropriate, to the description, claims and drawings within the period specified. One set of these documents is to be filed.

If you introduced documents which have not yet been mentioned during the proceedings, your attention is drawn to Rule 83 EPC.

Enclosures:

For the Opposition Division

Europäisches Patentamt • European Patent Office • Office européen des brevets •

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact

Lohmanns, Bernard
Benrather Schlossallee 49-53
40597 Düsseldorf
ALLEMAGNE

Date
20.07.2017

Reference	Application No./Patent No.
BD.01.17.EIN OPPO 01	06737018.9 - 1466 / 1863458
Applicant/Proprietor	
Banner Life Sciences, LLC	

Communication of further notices of opposition pursuant to Rule 79(2) EPC

No further opposition has been filed.

If oral proceedings are to take place, parties are advised to check the electronic file via the European Patent Register at **www.epo.org/register** in advance of the hearing to ensure that they are in possession of all relevant documents. (OJ EPO 2009, 434)

A copy of the communication pursuant to Rule 79(1) EPC sent to the proprietor of the patent is enclosed for your information.

The observations of the patent proprietor on the notice of opposition will be communicated to the opponent without delay. A time limit for reply will be fixed if the Opposition Division considers this expedient.

If no reply to a communication is received within the time limit set, the proceedings will be continued. Your attention is drawn to Article 114(2) EPC.

For the Opposition Division

Europäisches Patentamt • European Patent Office • Office européen des brevets •

Enclosures: copy of the communication pursuant to Rule 79(1) EPC (Form 2317A)

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact

Potter Clarkson LLP
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ROYAUME UNI

Date: 20.07.2017

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 1466 / 1863458
Applicant/Proprietor: Banner Life Sciences, LLC	

Communication of notices of opposition (R. 79(1) EPC)

Notice of opposition has been filed within the opposition period by:

01.
Dieckhoff, Beate
Dünnwalder Grenzweg 20
51375 Leverkusen
ALLEMAGNE

The notice of opposition indicated above has already been communicated to you.

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If you introduced documents which have not yet been mentioned during the proceedings, your attention is drawn to Rule 83 EPC.

Enclosures:

For the Opposition Division

Europäisches Patentamt • European Patent Office • Office européen des brevets

Europäisches Patentamt
European Patent Office
Office européen des brevets

Letter accompanying subsequently filed items

Representative:

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The document(s) listed below is (are) subsequently filed documents pertaining to the following application:

Application number and/or EP publication number	EP06737018.9 - EP1863458
Reference	BRICX/P38814EP
Procedural phase	All procedures
Name of represented party	Banner Life Sciences, LLC

	Description of document	Original file name	Assigned file name
1	Request for assignment	24OCT17-EPO (M20616).pdf	APPRASSI-1.pdf
2	Request for assignment	Assignment.pdf	APPRASSI-2.pdf

	Fees	Factor applied	Fee schedule	Amount to be paid
15-1	022 Registering of transfer	1	100.00	100.00
	Total:		**EUR**	**100.00**

	Payment	
1	Mode of payment	Debit from deposit account
	Currency:	EUR
	The European Patent Office is hereby authorised, to debit from the deposit account with the EPO any fees and costs indicated on the fees page.	
	Deposit account number:	28050040
	Account holder:	Potter Clarkson LLP
2	Refund/Reimburserment	
	Reimbursement (if any) to be made to EPO deposit account:	28050040
	Account holder:	Potter Clarkson LLP

Signature 1

Place: **Nottingham, United Kingdom**

Date: **24 October 2017**

Signed by: **/Caroline Marshall/**

Association:	**Potter Clarkson LLP**
Capacity:	**Representative 1**

Smart card certificate 1

Common name:	**Lindsey Pengelly 25038**
EPO ID:	**25038**
Issued by:	**European Patent Office CA G2**

POTTER CLARKSON

European Patent Office
80298 München
GERMANY

24 October 2017

Dear Sirs

Recordal of Transfer – EP Application No. 06737018.9
From: Banner Life Sciences LLC
To: Patheon Softgels Inc.
Our ref: BRICX/P38814EP

There has been an assignment from Banner Life Sciences LLC to Patheon Softgels Inc. in respect of European patent application no. 06737018.9.

We enclose a copy of the assignment by way of evidence.

Please record the transfer such that EP application no. 06737018.9 stands in the name of Patheon Softgels Inc..

We are making arrangements for our Accounts Department to pay the transfer fee from our Deposit Account.

We look forward to receiving confirmation of recordal.

Yours faithfully

Caroline Marshall
For and on behalf of Potter Clarkson LLP

lp

Enc: Copy of assignment.

cc: BRIAS/M20616

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W:www.potterclarkson.com

ASSIGNMENT

THIS ASSIGNMENT is made the 14th day of May, two thousand seventeen (14-MAY-2017)

BETWEEN:-

(1) Banner Life Sciences LLC of 4125 Premier Drive, High Point, NC 27265, USA ("the Assignor"); and

(2) Patheon Softgels Inc. of 4125 Premier Drive, High Point, NC 27265, USA ("the Assignee").

BACKGROUND:-

(A) The Assignor is the beneficial owner of the Patents and Patent Applications identified in the schedule to this Assignment (the "Patent Matters").

(B) The parties have agreed that the Assignor's rights in the Patent Matters should be transferred by the Assignor to the Assignee on the terms set out below.

IT IS AGREED that:

1 In consideration of the sum of £100 now paid by the Assignee to the Assignor (the receipt of which is acknowledged) the Assignor ASSIGNS with full title guarantee absolutely and free from any licences, charges or other encumbrances:-

a. all right, title and interest in and to the Patent Matters (including any and all divisions, reissues, continuations and extensions of or from the Patent Matters) to the intent that any patents granted pursuant to the Patent Matters shall be in the name of and shall vest in the Assignee TOGETHER WITH all the rights and powers arising or accrued from the Patent Matters including the right to sue for damages and other remedies in respect of any infringement of such rights or other rights within the scope of the claims of any published specifications accompanying the Patent Matters prior to the date of this Assignment; and

b. the right to apply for, prosecute and obtain patent or similar protection throughout the world in respect of the inventions (the "Inventions") claimed in the Patent Matters including the right to obtain priority from the Patent Matters to the intent that the resulting grant of any patents or similar protection shall be in the name of and vest in the Assignee.

2 The Assignor agrees that at the request of the Assignee it will

a. execute all such deeds and documents and do all such acts as may be necessary or desirable to secure the vesting in the Assignee of all rights assigned by clause 1 and to secure the registration of this Assignment at the European Patent Office and relevant national Patent Offices and to assist in the resolution of any question concerning the Patent Matters; and

b. render all such assistance of which it is capable as may reasonably be required by the Assignee in connection with bringing or defending any proceedings relating to any of the rights assigned by clause 1, prosecuting the Patent Matters to grant and obtaining patents in respect of the Inventions.

3 All sums payable to the Assignor under this Assignment are exclusive of value added tax which shall where applicable be paid in addition at the rate in force at the due time for payment subject to the Assignor supplying a valid VAT invoice to the Assignee.

4 This Assignment and any dispute or claim arising out of or in connection with it shall be governed by and construed in accordance with English law and the parties submit to the exclusive jurisdiction of the English Courts.

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SCHEDULE A-1. PATENTS AND PATENT APPLICATIONS
A. PLATFORM PROPERTIES
1. SHELL TECHNOLOGIES

SPREADER BOX AND MULTI-LAYERED SOFTGEL (Expires 7/15/2018)

JURISDICT.	TITLE	APP. NO.	FILING DATE	PATENT NO.	ISSUE DATE	STATUS
Netherlands	MULTIPLE, ADJUSTABLE GATE GELATIN SPREADER BOX AND MULTIPLE LAYER SOFTGEL	1009107	5/8/1998	1009107	6/15/1999	Granted

NON-GELATIN SOFT CAPSULES (Expires 8/25/2018)

JURISDICT.	TITLE	APP. NO.	FILING DATE	PATENT NO.	ISSUE DATE	STATUS
International	NON-GELATIN SUBSTITUTES FOR ORAL DELIVERY CAPSULES, THEIR COMPOSITION AND PROCESS OF MANUFACTURE	99/19,570	8/24/1999	Expired		Expired
Germany	NON-GELATIN SUBSTITUTES FOR ORAL DELIVERY CAPSULES, THEIR COMPOSITION AND PROCESS OF MANUFACTURE	99946656.8	8/24/1999	1 105 108	1/3/2007	Lapsed
Europe	NON-GELATIN SUBSTITUTES FOR ORAL DELIVERY CAPSULES, THEIR COMPOSITION AND PROCESS OF MANUFACTURE	99946656.8	8/24/1999	1 105 108	1/3/2007	Lapsed
France	NON-GELATIN SUBSTITUTES FOR ORAL DELIVERY CAPSULES, THEIR COMPOSITION AND PROCESS OF MANUFACTURE	99946656.8	8/24/1999	1 105 108	1/3/2007	Lapsed
Great Britain	NON-GELATIN SUBSTITUTES FOR ORAL DELIVERY CAPSULES, THEIR COMPOSITION AND PROCESS OF MANUFACTURE	99946656.8	8/24/1999	1 105 108	1/3/2007	Lapsed
Italy	NON-GELATIN SUBSTITUTES FOR ORAL DELIVERY CAPSULES, THEIR COMPOSITION AND PROCESS OF MANUFACTURE	68799BE/2007	8/24/1999	1 105 108	1/3/2007	Lapsed
Netherlands	NON-GELATIN SUBSTITUTES FOR ORAL DELIVERY CAPSULES, THEIR COMPOSITION AND PROCESS OF MANUFACTURE	99946656.8	8/24/1999	1 105 108	1/3/2007	Lapsed

COLORED SOFTGELS (Expires 10/24/2020)

JURISDICT.	TITLE	APP. NO.	FILING DATE	PATENT NO.	ISSUE DATE	STATUS
International	COLORED GELATIN-BASED FORMULATIONS AND METHOD	PCT/US2001/05 0714	5/24/2002	Expired		Expired
Europe	COLORED GELATIN-BASED FORMULATIONS AND METHOD	1988580.5	10/24/2001	Abandoned		Abandoned

ECOCAPS® CARRAGEENAN SOFTGELS (Expires 1/18/2022)

JURISDICT.	TITLE	APP. NO.	FILING DATE	PATENT NO.	ISSUE DATE	STATUS
Europe	NON-GELATIN FILM AND METHOD AND APPARATUS FOR PRODUCING SAME	4755975.2	1/30/2006	Lapsed		Lapsed
International	NON-GELATIN FILM AND METHOD AND APPARATUS FOR PRODUCING SAME	PCT/US04/20187	2/28/2005	Expired		Expired
Germany	NON-GELATIN CAPSULE SHELL FORMULATION COMPRISING IOTA-CARRAGEENAN AND KAPPA-CARRAGEENAN	3731918.3	1/15/2003	60331524.0-08	3/3/2010	Granted
Europe	NON-GELATIN CAPSULE SHELL FORMULATION COMPRISING IOTA-CARRAGEENAN AND KAPPA-CARRAGEENAN	3731918.3	1/15/2003	1 474 115	3/3/2010	Granted
International	NON-GELATIN CAPSULE SHELL FORMULATION COMPRISING IOTA-CARRAGEENAN AND KAPPA-CARRAGEENAN	PCT/US03/01134	8/15/2003	Expired		Expired

CHEWELS (Expires 10/31/2023)

JURISDICT.	TITLE	APP. NO.	FILING DATE	PATENT NO.	ISSUE DATE	STATUS
International	CHEWABLE SOFT CAPSULE	PCT/US2003/012983	10/31/2003			Expired
Germany	CHEWABLE SOFT CAPSULE	3724255.9	4/24/2003	60319355.2-08	2/27/2008	Granted
Europe	CHEWABLE SOFT CAPSULE	3724255.9	4/24/2003	1 496 873	2/27/2008	Granted
Spain	CHEWABLE SOFT CAPSULE	3724255.9	4/24/2003	1 496 873	2/27/2008	Granted
France	CHEWABLE SOFT CAPSULE	3724255.9	4/24/2003	1 496 873	2/27/2008	Granted
Great Britain	CHEWABLE SOFT CAPSULE	3724255.9	4/24/2003	1 496 873	2/27/2008	Granted
Italy	CHEWABLE SOFT CAPSULE	3724255.9	4/24/2003	69509BE/2008	2/27/2008	Granted
Netherlands	CHEWABLE SOFT CAPSULE	3724255.9	4/24/2003	1 496 873	2/27/2008	Granted

ENTERICARE (Methylmethacrylate) (Expires 6/27/2023) *US 8685445 expires 11/14/2030 because of PTA

JURISDICT.	TITLE	APP. NO.	FILING DATE	PATENT NO.	ISSUE DATE	STATUS
International	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	PCT/US2003/020579	6/27/2003	Expired		Expired
AT	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
Belgium	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
BG	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted

CH	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
CY	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
CZ	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
Germany	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	60346485.8	7/16/2014	Granted
DK	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
EE	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
Europe	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
Europe	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	14170492.4	5/29/2014	2 772 250	9/28/2016	Granted
ES	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
FI	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
France	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
Great Britain	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
GR	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	3083994	7/16/2014	Granted
HU	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
IE	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
Italy	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
LU	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
MC	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
Netherlands	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
PT	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
RO	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
SE	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
SI	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted

SK	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted
TR	ENTERIC COMPOSITION FOR THE MANUFACTURE OF SOFT CAPSULE WALL	3742336.5	6/27/2003	1545475	7/16/2014	Granted

ENTERICARE (Pectin) (Expires 12/18/2026)

JURISDICT.	TITLE	APP. NO.	FILING DATE	PATENT NO.	ISSUE DATE	STATUS
International	GASTRIX REFLUX RESISTANT DOSAGE FORMS	PCT/US2006/048029	12/18/2006	Expired		Expired
Europe	GASTRIC REFLUX RESISTANT DOSAGE FORMS	06845613.6	12/18/2006	1973533	7/29/2015	Granted
Germany	GASTRIX REFLUX RESISTANT DOSAGE FORMS	06845613.6	12/18/2006	1973533		Granted
ES	GASTRIX REFLUX RESISTANT DOSAGE FORMS	06845613.6	12/18/2006	1973533		Granted
France	GASTRIX REFLUX RESISTANT DOSAGE FORMS	06845613.6	12/18/2006	1973533		Granted
Great Britain	GASTRIX REFLUX RESISTANT DOSAGE FORMS	06845613.6	12/18/2006	1973533		Granted
Italy	GASTRIX REFLUX RESISTANT DOSAGE FORMS	06845613.6	12/18/2006	1973533		Granted
Netherlands	GASTRIX REFLUX RESISTANT DOSAGE FORMS	06845613.6	12/18/2006	1973533		Granted
Europe	GASTRIC REFLUX RESISTANT DOSAGE FORMS	14150121.3	12/18/2006	2716283	4/16/2015	Granted
Germany	GASTRIC REFLUX RESISTANT DOSAGE FORMS	14150121.3	12/18/2006	2716283		Granted
Spain	GASTRIC REFLUX RESISTANT DOSAGE FORMS	14150121.3	12/18/2006	2716283		Granted
France	GASTRIX REFLUX RESISTANT DOSAGE FORMS	14150121.3	12/18/2006	2716283		Granted
Great Britain	GASTRIC REFLUX RESISTANT DOSAGE FORMS	14150121.3	12/18/2006	2716283		Granted
Italy	GASTRIC REFLUX RESISTANT DOSAGE FORMS	14150121.3	12/18/2006	2716283		Granted
Netherlands	GASTRIX REFLUX RESISTANT DOSAGE FORMS	14150121.3	12/18/2006	2716283		Granted
Europe	GASTRIX REFLUX RESISTANT DOSAGE FORMS	15163491.2	12/18/2006	Pending		Pending

LIQUISOFT (Will expire 3/25/2036 upon grant)

JURISDICT.	TITLE	APP. NO.	FILING DATE	PATENT NO.	ISSUE DATE	STATUS
International	LIQUISOFT CAPSULES	PCT/US2016/24127	3/25/2016	Pending		Pending

2. FILL TECHNOLOGIES

VERSATROL (Expires 7/13/2023)

VERSATROL						
JURISDICT.	**TITLE**	**APP. NO.**	**FILING DATE**	**PATENT NO.**	**ISSUE DATE**	**STATUS**
Europe	CONTROLLED RELEASE PREPARATION	4778128.1	2/15/2006	Abandoned		Abandoned
Europe	CONTROLLED RELEASE PREPARATION	10075739.2	11/17/2010	2 279 729	8/17/2016	Granted
International	CONTROLLED RELEASE PREPARATION	PCT/US2004/022456	2/16/2005	Expired		Expired

VERSATROL 2.0 (Expires 10/26/2026)

JURISDICT.	TITLE	APP. NO.	FILING DATE	PATENT NO.	ISSUE DATE	STATUS
International	HYDROPHILIC VEHICLE-BASED DUAL CONTROLLED RELEASE MATRIX SYSTEM	PCT/US2006/042177	10/26/2006	Expired		Expired
Europe	HYDROPHILIC VEHICLE-BASED DUAL CONTROLLED RELEASE MATRIX SYSTEM	06826983.6	10/26/2006	Abandoned		Abandoned
International	LIPOPHILIC VEHICLE-BASED DUAL CONTROLLED RELEASE MATRIX SYSTEM	PCT/US2006/041722	10/26/2006	Expired		Expired
Europe	LIPOPHILIC VEHICLE-BASED DUAL CONTROLLED RELEASE MATRIX SYSTEM	06826700.4	10/26/2006	Abandoned		Abandoned

SOLVATROL (Naproxen Sodium) (Expires 3/6/2026)

JURISDICT.	TITLE	APP. NO.	FILING DATE	PATENT NO.	ISSUE DATE	STATUS
International	SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS	PCT/US2006/007788	3/6/2006	Expired		Expired
Europe	SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS	06737018.9	3/6/2006	EP1863458	11/18/2015	Granted
Europe	SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS	16163757.4	4/4/2016	EP3061447 A1 (Publication)		Pending

B. PRODUCT-SPECIFIC PROPERTIES

ENTERIC FISH OIL (Will expire 10/29/2034 upon grant)

JURISDICT.	TITLE	APP. NO.	FILING DATE	PATENT NO.	ISSUE DATE	STATUS
International	ENTERIC SOFT CAPSULES COMPRISING POLYUNSATURATED FATTY ACIDS	PCT/US2014/062892	10/29/2014	Expired		Expired LICENSED TO BIONPHARMA
Europe	ENTERIC SOFT CAPSULES COMPRISING POLYUNSATURATED FATTY ACIDS	14859007.8	5/9/2016	Pending		Pending

IN WITNESS of these matters this document has been executed by the parties on the date set out at the beginning of this Assignment

Signed by Claudia A. Garcia

for and on behalf of

Claudia A. Garcia, Asst. Secretary

Banner Life Sciences LLC

In the presence of:-

Name of witness: Michelle Spedden

Address: 4125 Premier Dr.
High Point, NC 27265

Signature

In the presence of:-

Name of witness: Peter Pawlik

Address: 415 Premier Dr,
High Point, NC 27265

Signature

Signed by Jason B. Conner

for and on behalf of

Jason B. Conner - Secretary

Patheon Softgels Inc.

In the presence of:-

Name of witness: PETER N. EFREMENKO

Address: 4815 EMPEROR BLVD.
DURHAM, NC 27703

Signature

In the presence of:-

Name of witness: Manda Miller

Address:
4815 Emperor Blvd.
Durham, NC 27703

Signature

Europäisches Patentamt
European Patent Office
Office européen des brevets

Acknowledgement of receipt

We hereby acknowledge receipt of the following subsequently filed document(s):

Submission number	5729087	
Application number	EP06737018.9	
Date of receipt	24 October 2017	
Filing Office	European Patent Office, The Hague	
Procedural phase	All procedures	
Your reference	BRICX/P38814EP	
Documents submitted	package-data.xml ep-cms-sfd-request.pdf (2 p.) APPRASSI-2.pdf\Assignment.pdf (9 p.)	ep-cms-sfd-request.xml APPRASSI-1.pdf\24OCT17-EPO (M20616).pdf (1 p.)
Submitted by	CN=secure.epoline.org,OU=PDIS,O=European Patent Office,C=NL	
Method of submission	Online	
Date and time receipt generated	24 October 2017, 16:46 (CEST)	
Message Digest	B1:91:42:66:12:53:B7:C0:C6:D3:0B:9D:E0:2E:64:56:24:8E:EF:4E	

/European Patent Office/

Europäisches Patentamt
European Patent Office
Office européen des brevets

European Patent Office
80298 MUNICH
GERMANY

Questions about this communication ?
Contact Customer Services at www.epo.org/contact

Potter Clarkson LLP
The Belgrave Centre
Talbot Street
Nottingham NG1 5GG
ROYAUME UNI

Date
08.11.17

Reference	Application No./Patent No.
PABCA/P38814EP	06737018.9 - 1466 / 1863458
Applicant/Proprietor	
Patheon Softgels Inc.	

C o m m u n i c a t i o n

concerning the registration of amendments relating to

☑ a transfer (R. 22 and 85 EPC)

☐ entries pertaining to the applicant / the proprietor (R. 143(1)(f) EPC)

As requested, the entries pertaining to the applicant of the above-mentioned European patent application / to the proprietor of the above-mentioned European patent have been amended to the following:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI SK TR
Patheon Softgels Inc.
4125 Premier Drive
High Point, NC 27265/US

The registration of the changes has taken effect on 24.10.17.

In the case of a published application / a patent, the change will be recorded in the Register of European Patents and published in the European Patent Bulletin (Section I.12 / II.12).

Your attention is drawn to the fact that, in the case of the registration of a transfer, any automatic debit order only ceases to be effective from the date of its express revocation (cf. point 14(c) of the Arrangements for the automatic debiting procedure, supplementary publication 3 - OJ EPO 2015).

Receiving Section / For the Examining Division / For the Opposition Division / For the Legal Division *)

Europäisches Patentamt • European Patent Office • Office européen des brevets

*) See note.

Note
This communication is issued by/for the department with whom responsibility lies. The Legal Division is responsible for the registration of transfers, changes of name (Articles 71, 72 and 74 EPC and Rules 22 and 85 EPC) as well as for the rectification of the designation of the inventor (Rule 21 EPC) (see Decision of the President of the EPO, OJ EPO 2013, 600). In all other cases, the Receiving Section, the Examining Division or the Opposition Division is responsible, depending on the stage in proceedings.

POTTER CLARKSON

EPO - Munich
100
08 Nov. 2017

European Patent Office
80298 München
GERMANY

3 November 2017

Dear Sirs

Recordal of Transfer of
European Patent Applications Nos. 06737018.9, 16163757.4, 14859007.8 and 15163491.2
From: Banner Life Sciences LLC
To: Patheon Softgels inc.
Our refs: BRICX/P38814EP; BRICX/P38814EPdiv1; BRICX/P60681EP; and BRIAS/M20616

We write in response to the communication dated 5 October 2017

We enclose herewith a Limited Liability Company Annual Report in respect of the Assignee, Banner Life Sciences LLC, which shows that Claudia A Garcia (Assistant Secretary) is authorised to sign legally binding documents on behalf the Assignee.

We also enclose herewith a Business Corporation Annual Report in respect of the Assignor, Patheon Softgels Inc., which shows that Jason B Conner (Secretary) is authorised to sign legally binding documents on behalf of the Assignor.

We look forward to receiving confirmation of the recordals in respect of European patent applications nos. 06737018.9, 16163757.4, 14859007.8 and 15163491.2.

Yours faithfully

Caroline Marshall
For and on behalf of Potter Clarkson LLP

lp

Enc: Limited Liability Company Annual Report
Business Corporation Annual Report

Potter Clarkson LLP
The Belgrave Centre
Talbot Street
Nottingham NG1 5GG

T:+44 (0)115 955 2211
F:+44 (0)115 955 2201
E:info@potterclarkson.com
W:www.potterclarkson.com

LIMITED LIABILITY COMPANY ANNUAL REPORT

NAME OF LIMITED LIABILITY COMPANY: Banner Life Sciences LLC

SECRETARY OF STATE ID NUMBER: 1408880 STATE OF FORMATION: DE

REPORT FOR THE YEAR: 2017

Filing Office Use Only
E-Filed Annual Report
1408880
CA201707904850
3/20/2017 04:01
☐ Changes

SECTION A: REGISTERED AGENT'S INFORMATION

1. NAME OF REGISTERED AGENT: CT Corporation System

2. SIGNATURE OF THE NEW REGISTERED AGENT: _____

SIGNATURE CONSTITUTES CONSENT TO THE APPOINTMENT

3. REGISTERED OFFICE STREET ADDRESS & COUNTY

160 Mine Lake Ct Ste 200
Raleigh, NC 27615-6417 Wake County

4. REGISTERED OFFICE MAILING ADDRESS

160 Mine Lake Ct Ste 200
Raleigh, NC 27615-6417

SECTION B: PRINCIPAL OFFICE INFORMATION

1. DESCRIPTION OF NATURE OF BUSINESS: Pharmaceuticals manufacturing

2. PRINCIPAL OFFICE PHONE NUMBER: 3368128700

3. PRINCIPAL OFFICE EMAIL: Privacy Redaction

4. PRINCIPAL OFFICE STREET ADDRESS & COUNTY

4125 Premier Drive
High Point, NC 27265-8144

5. PRINCIPAL OFFICE MAILING ADDRESS

4125 Premier Drive
High Point, NC 27265-8144

SECTION C: COMPANY OFFICIALS (Enter additional Company Officials in Section E.)

NAME: Jason B Conner	NAME: Claudia A Garcia	NAME:
TITLE: Secretary	TITLE: Assistant Secretary	TITLE:
ADDRESS: 4815 Emperor Boulevard Durham, NC 27703	ADDRESS: 4125 Premier Drive High Point, NC 27265	ADDRESS:

SECTION D: CERTIFICATION OF ANNUAL REPORT. Section D must be completed in its entirety by a person/business entity.

Jason B Conner
SIGNATURE
Form must be signed by a Company Official listed under Section C of this form.

3/20/2017
DATE

Jason B Conner
Print or Type Name of Company Official

Secretary
Print or Type The Title of the Company Official

This Annual Report has been filed electronically.
MAIL TO: Secretary of State, Corporations Division, Post Office Box 29525, Raleigh, NC 27626-0525

BUSINESS CORPORATION ANNUAL REPORT

NAME OF BUSINESS CORPORATION: Patheon Softgels Inc.

SECRETARY OF STATE ID NUMBER: 0375488 STATE OF FORMATION: DE

REPORT FOR THE FISCAL YEAR END: 10/31/2016

Filing Office Use Only
E-Filed Annual Report
0375488
CA201702700663
1/27/2017 01:28
☐ Changes

SECTION A: REGISTERED AGENT'S INFORMATION

1. NAME OF REGISTERED AGENT: CT Corporation System

2. SIGNATURE OF THE NEW REGISTERED AGENT: _____
SIGNATURE CONSTITUTES CONSENT TO THE APPOINTMENT

3. REGISTERED OFFICE STREET ADDRESS & COUNTY
160 Mine Lake Ct Ste 200
Raleigh, NC 27615-6417 Wake County

4. REGISTERED OFFICE MAILING ADDRESS
160 Mine Lake Ct Ste 200
Raleigh, NC 27615-6417

SECTION B: PRINCIPAL OFFICE INFORMATION

1. **DESCRIPTION OF NATURE OF BUSINESS:** Pharmaceuticals manufacturer

2. **PRINCIPAL OFFICE PHONE NUMBER:** 3368127000

3. **PRINCIPAL OFFICE EMAIL:** Privacy Redaction

4. PRINCIPAL OFFICE STREET ADDRESS & COUNTY
4125 Premier Drive
High Point, NC 27265-8144

5. PRINCIPAL OFFICE MAILING ADDRESS
4125 Premier Drive
High Point, NC 27265-8144

SECTION C: OFFICERS (Enter additional officers in Section E.)

NAME: Jason Conner
TITLE: Secretary
ADDRESS:
4125 Premier Drive
High Point, NC 27265

NAME: Francisco R Negron
TITLE: President
ADDRESS: 111 Speen Street
Suite 550
Framingham, MA 01701

NAME: Jason Mieding
TITLE: Executive Director
ADDRESS:
4125 Premier Drive
High Point, NC 27265

SECTION D: CERTIFICATION OF ANNUAL REPORT. Section D must be completed in its entirety by a person/business entity.

Jason Conner
SIGNATURE
Form must be signed by an officer listed under Section C of this form.

1/27/2017
DATE

Jason Conner
Print or Type Name of Officer

Secretary
Print or Type Title of Officer

MAIL TO: Secretary of State, Corporations Division, Post Office Box 29525, Raleigh, NC 27626-0525

SECTION E: ADDITIONAL OFFICERS

NAME: Dean F Wilson
TITLE: Treasurer
ADDRESS: 4815 Emperor Boulevar
Suite 300
Durham, NC 27703

NAME:
TITLE:
ADDRESS:

NAME:
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Europäisches Patentamt
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Office européen des brevets

1 General authorisation

667310.7 General authorisation No. (For official use only)

Please forward the original direct to the EPO, Legal Division (Dir. 5.2.4) in Munich.
Please read the attached notes before completing the form.

2 I (We)

Patheon Softgels Inc.
4125 Premier Drive
High Point
North Carolina 27265
United States of America

Full name and address of authorisor(s)

3 do hereby authorise

Potter Clarkson LLP
(Association 414)

And legal practitioners
O A Laing N D McDonald H S L Mitchell R A Roberts

The Belgrave Centre
Talbot Street
Nottingham
NG1 5GG
United Kingdom

Full name and address of association of representatives.

4 to represent me (us) in all proceedings established by the European Patent Convention and to act for me (us) in all patent transactions.

[X] This authorisation includes the power to receive payments on my (our) behalf.

[X] This authorisation shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty.

5 [X] Sub-authorisation may be given.

[ ] Additional representatives indicated on supplementary sheet.

6 [X] Please return a copy, supplemented by the general authorisation number, to the authorisor.

Durham, NC, USA	Place	Jason B. Conner	Name (printed)
15 SEPTEMBER 2017	Date	Secretary, Patheon Softgels Inc.	Position within the company (where relevant)
			Signature*

7 *The form must bear the personal signature(s) of the authorisor(s). In the case of legal persons, the signature must be that of the person empowered to sign on behalf of the company. If possible, please sign in blue.

EPO 1004 12.07 1

Europäisches Patentamt
European Patent Office
Office européen des brevets

Submission in opposition proceedings

Representative:

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414
The Belgrave Centre
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NL-2280 HV Rijswijk
Netherlands
Tel. +31(0)70 340-2040 | Fax -3016

10958 Berlin
Germany
Tel. +49(0)30 25901-0 | Fax -840

- representing the proprietor(s):	Patheon Softgels Inc.
Proprietor/representative's reference	BRICX/M20527EP

The information given below is pertaining to the following patent in opposition proceedings:

Patent No.	EP1863458
Application No.	EP06737018.9
Date of mention of the grant in the European Patent Bulletin (Art. 97(3), Art. 99(1) EPC)	14 September 2016
Title of the invention	Solvent system for enhancing the solubility of pharmaceutical agents

Documents attached:

	Description of document	Original file name	Assigned file name
1	Reply of the patent proprietor to the notice(s) of opposition	M20527EP- Response to opposition.pdf	OBSO3.pdf
2	General authorisation	M20527EP General Authorisation.pdf	GENAUTH-1.pdf
3	Any annexes (other than citation) to an opposition letter - Covering letter	28Nov17-EPO (M20527EP).pdf	OTHER-1.pdf

Evidence filed subsequently:

D14	Other evidence	Cited document original file name: M20527EP D14.pdf attached as: Other-evidence-1.pdf

Signatures

Place:	**Nottingham, United Kingdom**
Date:	**28 November 2017**
Signed by:	**/Charlotte Crowhurst PhD/**
Association:	**Potter Clarkson LLP**
Representative name:	**Charlotte Crowhurst PhD**
Capacity:	**(Representative)**

Response to Opposition

European Patent No. 1863458
(European Patent Application No. 06737018.9)

Patentee: Patheon Softgels Inc.

Opposition by Beate Dieckhhoff

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28 November 2017

CONTENTS

1. ***REQUESTS***

We request that the opposition is rejected and that European patent no. 1863458 B1 (referred to herein as the opposed patent or as the patent) is maintained as granted.

In the alternative, we request maintenance of the patent on the basis of any of the auxiliary claim requests filed subsequently.

Oral proceedings are requested in the event that the Opposition Division (OD) does not intend to reject the opposition and maintain the patent as granted.

2. ***THE PATENTEE***

European patent no. 1863458 was granted in the name of Banner Life Sciences, LLC but is now owned by Patheon Softgels Inc. The steps to record the change of ownership have been taken and the European Patent Office Register has been updated to reflect this change.

A General Authorisation (Reference No. 667310.7) signed on behalf of the new patentee, authorising Potter Clarkson LLP to act on behalf of the new patentee is attached.

3. ***THE CITED DOCUMENTS***

The following documents were cited by the Opponent:

D1: US 5,360,615

D2: WO 2006/096580 (application of the patent as originally filed)

D3: US 2001/007668

D4: US 5,541,210

D5: Experiments filed by the Patentee on 16 September 2011 during examination procedure

D6: Experiments filed by the Patentee on 26 March 2012 with the substantiation of the appeal

D7: Technical data sheet for PEG-600

D8: Beyer, Walter – Lehrbuch der organischen Chemie, 21. Edition, Stuttgart, Hirzel, 1988, page 280

D9: Excerpt from the German Wikipedia webpage on Milchsäure (lactic acid)

D10: Beyer, Walter – Lehrbuch der organischen Chemie, 21. Edition, Stuttgart, Hirzel, 1988, page 260

D11: Excerpt from the U.S. webpage pharmacopeia on PEG (lactic acid)

D12: Excerpt from the English Wikipedia webpage on citric acid

D13: Beyer, Walter, Lehrbuch der organischen Chemie, 21. Edition, Stuttgart, Hirzel, 1988, page 283

4. ***ATTACHED DOCUMENTS***

We attach the following document:

D14: Sevelius et al, Bioavailability of Naproxen Sodium and its relationship to clinical analgesic effects, Br. J. clin. Pharmac. (1980), 10, 259-263.

5. ***THE INVENTION***

The opposed patent contains 13 claims. Claim 1 reads as follows:

1. A softgel capsule comprising a fill material wherein the fill material comprises
   (a) naproxen sodium;
   (b) fumaric acid, maleic acid, tartaric acid, citric acid, malic acid, acetic acid, proprionic acid, pyruvic acid, butanoic acid or lactic acid in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium;
   (c) polyethylene glycol;
   (d) water; and
   (e) a solubilizer selected from the group consisting of glycerin, polyvinylpyrrolidone, propylene glycol and combinations thereof.

Claims 2 to 10 are dependent on claim 1, claims 11 and 12 relate to a method of manufacturing the capsule of claim 1 and claim 13 relates to the use of ingredients that correspond to those listed in claim 1 in the manufacture of a medicament.

6. ***THE GROUNDS OF OPPOSITION***

The patent has been opposed on the grounds of Articles 100(a) (lack of novelty and lack of inventive step), (b) and (c) EPC.

7. ***THE SUBJECT MATTER OF THE PATENT DOES NOT EXTEND BEYOND THE CONTENT OF THE APPLICATION AS FILED – ARTICLES 100(C) AND 123(2) EPC***

The Opponent is of the opinion that claims 11 and 12 as granted contain subject matter that was not present in the application as filed. We disagree.

The Opponent is correct that the text at page 8, line 25 to page 9, line 2 of the application as originally filed describes a method of making a capsule of the invention. This is not the only disclosure in the application as filed of a method for making the capsule. Such a method is also the subject of claims 14 to 17 of the application as filed. Claims 14, 15 and 16 do not specify the temperature at which the method is conducted or the amounts of any of the ingredients. The Opponent's assertion that the only disclosure in the application as filed of the method for making the capsule of the invention includes details of the temperature and the amount of the ingredients is incorrect and there is basis in the application as filed for the wording of claims 11 and 12 as granted.

It is also noted that during prosecution the Board of Appeal stated that the claims as granted were supported by the original disclosure.

There is no added subject matter.

8. ***THE DISCLOSURE OF THE INVENTION IS SUFFICIENTLY CLEAR AND COMPLETE – ARTICLES 100(B) AND 83 EPC***

The Opponent is of the opinion that the opposed patent does not disclose the invention in a sufficiently clear and complete manner for it to be carried out by the person skilled in the art.

The Opponent is incorrect.

At the outset, it is noted that it is well established that an objection of lack of sufficiency can only be considered convincing if it is based on serious doubts that are substantiated by verifiable facts. The Opponent has not provided any such facts. For this reason alone, the Opponent's objection fails.

The Opponent's objection under Article 100(B) EPC relates to claim 7 only. By focusing on a dependent claim in this manner, he has inherently acknowledged that he considers there to be no lack of sufficiency in relation to the invention as defined by claim 1.

As stated in the Guidelines for Examination in the European Patent Office, Part F, Chapter III, to satisfy the requirement for sufficiency of disclosure, it is only necessary to describe at least one way of carrying out the invention. The Opponent's comments do not suggest that he has any doubt that this has been done.

Turning to the Opponent's objection, he has suggested that the use of the terms "crystallisation inhibitors", "bulk filing agents" and "bioavailability enhancers" in claim 7 leads to a lack of sufficiency. We do not agree. It must be remembered that a patent specification is addressed to the person of skill in the art. The skilled reader would readily understand what is meant by these terms and would be able to select ingredients that could be used in the capsules of the invention to provide the required effect.

The skilled reader would readily be able to determine which excipients can be used and the patent satisfies the requirements of Article 83 EPC.

9. ***THE CLAIMED INVENTION IS NOVEL***

The Opponent has alleged that the subject matter of claims 1, 2, 4 to 10 and 13 lacks novelty over the disclosure of D4.

As claims 2 and 4 to 10 are dependent on claim 1 and claim 13 contains the same limitations as claim 1, our comments will focus on claim 1, but also apply to the other claims.

The Opponent alleges that the softgel capsule of claim 1 lacks novelty in view of the disclosure of Example R of D4 (columns 28 and 29). The text of Example R of D4 is repeated below:

> ***"Example R***
>
> *For the relief of minor aches, pains, headache, muscular aches, sore throat pain, and fever associated with a cold or flu. Relieves nasal congestion, cough due to minor throat and bronchial irritations, runny nose, and sneezing associated with the common cold. Adults 12 and over take one fluid ounce every six hours.*

		mg/fl oz
naproxen sodium anhydrous, USP		*220 mg*
doxylamine succinate, USP		*12.5*
dextromethorphan hydrobromide, USP		*30*
Subject Compound 1		*6*
Dow XYS-40010.00 resin		*3*
high fructose corn syrup		*16000*
polyethylene glycol, NF		*3000*
propylene glycol, USP		*3000*
alcohol, USP		*2500*
sodium citrate dihydrate, USP		*150*
citric acid, anhydrous, USP		*50*
saccharin sodium, USP		*20*
flavor		*3.5*
purified water, USP		*3800*
	total	*28795 mg"*

There is nothing in this Example to suggest that the composition described is or even could be formulated into softgel capsules. In fact, it is quite clear from the information provided in Example R of D4 that the composition produced in this Example is not intended to be provided in softgel capsules. The large quantity of water (3.8 mL) and ethanol (~2.5 mL) present in this formulation would significantly weaken and potentially dissolve the soft shell of a capsule if the formulation were encapsulated. Rather, it appears that the composition of Example R must administered as a liquid by the spoonful or drunk.

It is stated in the text above the table in Example R that adults 12 and over take one fluid ounce every six hours. One fluid ounce equates to 28.4 mL. This is a relatively large volume of medicament to administer, even by the spoonful, and is completely unsuitable for formulation into softgel capsules.

Typically, the volume of liquid in a softgel capsule ranges from 0.1 ml to 1.5 mL, and most often less than 0.5 mL, roughly 50-fold less volume than the suggested dose for Example R.

In addition, the inclusion of certain ingredients in the composition of Example R make it clear that this composition is not intended to be contained within a softgel capsules. When administered, softgel capsules are usually swallowed so the capsule fill is not tasted by the patient. Thus, it is not usually necessary to include ingredients that mask taste or provide a sweet taste in the fill composition. On the other hand, the composition of Example R contains

a large amount of high fructose corn syrup and saccharin sodium. Both of which would make the composition more palatable to a patient who will taste it. Further, the inclusion of Dow XYS-40010.00 resin (a taste masking agent) would be expected to make the composition unsuitable for encapsulation methods widely used in the industry. For example, resin containing compositions can be unsuitable for rotary die encapsulation because they can settle and potentially clog the injection apparatus.

In summary, Example R of D4 does not describe a softgel capsule and the composition that is the subject of Example R is not suitable for formulation into a softgel capsule. As all of claims 1, 2 and 4 to 10 are directed to a softgel capsule and claim 13 relates to the manufacture of a capsule, the disclosure of Example R of D4 is not novelty destroying.

The subject matter of the claims satisfies the requirements of Article 54 EPC.

10. ***THE CLAIMED INVENTION IS INVENTIVE***

As described in paragraphs [0009] and [0010] of the patent, the problem solved by the invention is the provision of a stable solvent system for naproxen sodium which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG-esters is minimized.

The invention solves this problem in a manner that could not have been predicted from the prior art.

10.1 ***THE EXPERIMENTAL DATA FILED DURING PROSECUTION***

The Opponent has alleged that the experimental data filed during prosecution does not support the conclusion that the claimed subject matter is inventive. We disagree.

We would like to draw the Opposition Division's attention to the comments on the data made by the Board of Appeal during prosecution. The following is an extract from the Decision of the Board of Appeal:

"Problem solved

5. According to the appellant, the problem to be solved is the provision of a stable solvent system for naproxen sodium which is suitable for encapsulation in a softgel capsule, wherein the formation of PEG esters is minimized.

5.1 As a solution to this problem, the appellant proposes a softgel capsule according to claim 1 of the main request comprising inter alia naproxen sodium and an organic

acid chosen from a list in an amount of from 0.2 to 1.0 mole equivalents per mole of the naproxen sodium.

5.2 The experimental tests provided by the appellant as D7 compare the production of undesired PEG esters in samples 16-21 prepared according to D1 with samples 1-15 according to the application. Samples 7-15 correspond to compositions prepared in accordance with claim 1 of the main request with the exception that component (e) thereof is missing, while samples 1-6 employ HC1, an acid which does not fall under the alternatives listed in claim 1, part (b). After being subjected to accelerated stability testing at 60 °C for 7 days, no PEG ester formation was detected in samples 7-12 and 15, while minor amounts were observed in samples 13 and 14. In the solutions of samples 16-21, PEG ester formation was detected (D7, table on pages 6and 7).

5 2.1 While samples 8 and 11 were physically characterised as clear solutions after the stability tests, samples 7, 9, 10 and 12-15, despite displaying no detectable PEG ester formation, were all physically characterised by either a phase separated precipitate or a semi-solid paste, physical states unfavourable for encapsulation into softgel capsules. The explanation provided by the appellant that the tests of D7 were carried out specifically for the purpose of demonstrating the reduction in PEG ester formation vis a vis the compositions prepared according to D1, rather than necessarily to produce clear solutions suitable for incorporation into a softgel capsule, is plausible. Addition of the solubilizer required by claim 1, step(e) to said samples would indeed be expected to provide the desired clear solutions.

5.2.2 It is also plausible that the effect of a reduction in PEG ester formation displayed by samples 7, 9, 10 and 12-15 would remain had the required solubilizer of claim 1, component (e) been included therein, thus producing a clear solution. Furthermore, said effect is credible not only for softgel capsule fill material prepared using lactic acid or citric acid according to comparative samples 7-15, but also for fill materials prepared using the alternative closely related organic acids listed in claim 1, component (b). The effect of a reduction in PEG ester formation is consequently recognised in respect of the whole scope of claim 1.

5.3 On the basis of the effect, the problem has been credibly solved by the subject-matter of claim 1."

In other words, the Board of Appeal was of the opinion that the Experimental Data filed on 26 March 2017 (D7 in the Appeal Proceedings and D6 in the numbering used by the Opponent) illustrated that the claimed invention solves the stated technical problem. This data should not be dismissed in the manner suggested by the Opponent.

10.2 *EXAMPLE R OF D4 AS THE CLOSEST PRIOR ART*

As discussed above, the subject matter of the claims as granted is novel in view of the disclosure of Example R of D4. The subject matter claimed is also inventive in view of this disclosure.

It is highly unlikely that the person of ordinary skill in the art seeking to address the problem addressed by the present invention would have even considered the teaching of D4.

D4 is concerned with providing compounds of the formula specified under the heading "Summary of the Invention" in column 2 of D4. These compounds may be formulated with additional pharmaceutically active compounds and naproxen sodium is an example of one such *additional* pharmaceutically active compounds. In other words, the use of naproxen sodium in some of the formulations of D4, such as Example R, is incidental to the main technical focus of D4, and D4 is not concerned with improving the formulation of naproxen sodium. D4 certainly does not address issues associated with provision of a stable solvent system for naproxen sodium which is suitable for encapsulation in a softgel capsule.

For these reasons, the skilled person seeking to solve the problem of the present invention would not have considered the teaching of D4.

Even in the unlikely event that he had considered D4, he would not have been provided with information that would have lead him to the invention as defined in the patent as granted.

As explained in relation to novelty, Example R of D4 relates to a composition that is intended to be administered in a relatively large volume and is entirely unsuitable for inclusion in softgel capsules. It would not have been an obvious or straight forward matter to adapt the composition of Example R of D4 to provide a composition suitable for use as the fill in a softgel capsule.

Numerous changes would have been required to the composition of Example R and D4 does not provide any teaching about the changes that could be made nor motivation as to which changes might assist the skilled person to solve the problem addressed by the invention.

There is most certainly nothing in D4 to suggest that the technical problem addressed by the present invention could be solved in the manner that the inventors have used.

The subject matter of all of the claims is inventive in view of the disclosure of D4.

We are not individually addressing the Opponent's comments on the inventive step of claims 3, 11 and 12 in view of Example R of D4. This is not necessary. The subject matter of claim 1 is inventive in view of this Example. This means that dependent claim 3 must also be inventive. It is a well-established principle that a process for producing a novel and inventive product is itself novel and inventive. Thus, the subject matter of claims 11 and 12 is novel and inventive.

10.3 *D1 AS THE CLOSEST PRIOR ART*

D1 was considered to be the closest prior art during prosecution of the application and has already be considered by a Board of Appeal. In paragraph 6.3 of the Decision of the Board of Appeal it was acknowledged that the subject matter of claim 1 as now granted is inventive in view of the disclosure of D1. The Opponent's arguments do not cast doubt on the conclusions of the Board of Appeal.

D1 suggests the preparation of aqueous compositions comprising naproxen, hydroxide ions and polyethylene glycol. However, we note that the sections of D1 to which the Opponent has referred in paragraph 101 of the Opposition do not actually describe a combination of naproxen, sodium hydroxide, PEG and solubilizers in an aqueous environment. The Opponent has referred to the combination of claims 4, 6 and 8. The subject matter of these claims cannot be combined, as each claim is dependent on claim 1 only.

The teaching of D1 is very clear; an acid drug (which may be naproxen or another acid drug) is used in combination with a hydroxide species. The skilled person reading D1 would not have considered using a salt form of the drug in combination with a hydrogen ion species. This would have gone directly against the teaching of D1 and would also have been counter-intuitive.

Combining naproxen with an alkali metal hydroxide such as sodium or potassium hydroxide would produce the alkali metal salt of naproxen, such as naproxen sodium or naproxen potassium. This is desirable when developing a pharmaceutical composition because the naproxen salt has improved bioavailability compared to the naproxen free acid. *See* Sevelius et al., "Bioavailability of Naproxen Sodium and its Relationship to Clinical Analgesic Effects,"

Br. J. Clin. Pharmacol. 10:259-263 (1980) which shows that naproxen sodium is more bioavailable than the free acid.

On the other hand, it is counter-intuitive to start with a naproxen salt and then add a weak acid to convert a fraction of the salt form to the less bioavailable naproxen free acid form. This would be expected to reduce the bioavailability of a portion of the drug. Not a desirable aim.

There is absolutely no reason why the skilled person starting from D1 would have done the complete opposite to what is taught be D1, by partially converting some of the naproxen salt to the free acid form, and this would have also required them to go completely against their own scientific understanding regarding improved bioavailability of the naproxen salt. In other words, adding acid would defeat the intent of D1 which is to produce the salt form to improve bioavailability and solubility. The present inventors have surprisingly found that by going completely against D1, by reducing the amount of salt, reduced ester formation can be achieved while providing the required therapeutic effect. This was not suggested by D1 in any manner.

The Opponent's comment in paragraph 107 of the Opposition that it would have been obvious starting from D1 to add an acid cannot be followed. It is an essential feature of the invention of D1 to use a source of hydroxide ions such as sodium hydroxide to neutralize the free acid form of a drug. Adding an acid to a composition as described in D1 would simply neutralise the hydroxide ions, and regenerate the free acid form of the drug, thus defeating the object of D1.

For at least these reasons, it would not have been obvious to the skilled person starting from D1 to produce a composition as defined in claim 1.

The subject matter claimed is inventive in view of the disclosure of D1.

The patent as granted satisfies the requirements of Article 56 EPC.

11. ***CLAIMS 2 TO 13***

The subject matter of Claims 2 to 13 is patentable for at least the reasons discussed above.

Signature of representative: ……..
Dr Charlotte Crowhurst
For and on behalf of Potter Clarkson LLP

Date: 28 November 2017

POTTER CLARKSON

European Patent Office
80298 München
GERMANY

28 November 2017

Electronically filed

Dear Sirs

European Patent No. 1863458
European Patent Application No. 06737018.9
SOLVENT SYSTEM FOR ENHANCING THE SOLUBILITY OF PHARMACEUTICAL AGENTS
PROPRIETOR: PATHEON SOFTGELS INC.
Our ref: BRICX/M20527EP

We refer to the communication of 20 July 2017 and are now providing the patentee's response to the opposition.

We request that the patent is maintained as granted. If the Opposition Division is considering any other outcome, we request oral proceedings.

Yours faithfully

Charlotte Crowhurst PhD
For and on behalf of Potter Clarkson LLP

lw

Enc: Response to opposition

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D14

Br. J. clin. Pharmac. (1980), **10**, 259–263

BIOAVAILABILITY OF NAPROXEN SODIUM AND ITS RELATIONSHIP TO CLINICAL ANALGESIC EFFECTS

H. SEVELIUS, R. RUNKEL, E. SEGRE & S.S. BLOOMFIELD

The Institutes of Clinical Medicine and Pharmacology and Metabolism, Syntex Research, Palo Alto, California and Division of Clinical Pharmacology, University of Cincinnati Medical Center, Cincinnati, Ohio, USA

1 In the first of a series of trials with naproxen sodium it was shown that patients achieved significantly earlier and higher plasma levels of naproxen when naproxen sodium was administered.

2 In a second study comparing naproxen with naproxen sodium in patients with post-partum pain, pain intensity was consistently lower for the group receiving naproxen sodium. However, statistically significant differences were not seen until 4 or 5 h after medication.

3 A final study documented that a more frequent dosage schedule of every 6 h led to clearly higher plasma levels than those achieved with an every 8 h regimen; plasma levels did not plateau. Doses up to 1,375 mg/day were well tolerated.

4 In conclusion, naproxen sodium appears to be an improved form of naproxen for use as an analgesic agent.

Introduction

Naproxen is a nonsteroidal agent with demonstrated anti-inflammatory, analgesic and antipyretic properties (Roszkowski, Rooks, Tomolonis, Miller & Pelczarska, 1973). Studies with single 200 to 600 mg doses of naproxen have shown it to be at least as effective as single standard doses of aspirin or other standard reference analgesics in patients with moderate or severe postoperative pain resulting from orthopaedic (Ruedy & McCullough, 1973), dental (Ruedy, 1973), and other surgical procedures (Mahler, Forrest, Brown, Shroff, Gordon, Brown & James, 1976; Stetson, Robinson, Wardell & Lasagna, 1973). The need for an analgesic agent with an even faster onset of action than naproxen, however, has led to an investigation of methods to increase the speed of absorption of naproxen.

If it is true that a certain minimum effective plasma concentration is necessary for analgesic activity, then it follows that a more rapidly absorbed dosage form should provide a more rapid onset of activity (Swarbrick, 1973). Alkali metal salts of weak organic acids are known to dissolve more rapidly in aqueous solutions than the corresponding weak acid itself (Wagner, 1975). The rate at which a drug dissolves in the gastrointestinal tract often partially or completely controls the rate at which the drug appears in the blood (Levy, 1961). Accordingly, since naproxen is a weak acid (pKa = 4.15), the sodium salt of naproxen was developed since it logically represented one of the best means of providing more rapid absorption of naproxen and, thereby, an earlier effect. A series of studies was then designed to evaluate the bioavailability and efficacy of naproxen sodium.

First the pharmacokinetics of naproxen and naproxen sodium were compared to determine whether the sodium salt was more rapidly absorbed. Then an analgesic study was conducted to determine whether any such differences in absorption rates were clinically significant (Bloomfield, Barden & Mitchell, 1978). While the rate of absorption may affect the onset of analgesic activity, continued plasma levels of the drug are likely to be important in maintaining analgesia. Therefore, the steady state plasma levels of naproxen sodium associated with two different dosage regimens were measured in a third study.

Methods

Bioavailability (*naproxen* v *naproxen sodium*)

Twelve healthy male volunteers participated in this study. All study subjects were within 10% of the average weight for their age, sex and height as determined by the Metropolitan Life Insurance Company weight tables. At the beginning and end of the study, each volunteer underwent a complete physical examination including routine blood

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chemistry determinations. During the study, any adverse effects reported by the subjects were recorded. Hypnotics, sedatives, antihistamines or other enzyme inducing drugs were not permitted for 1 month prior to the study, and no other drugs or alcohol were permitted 72 h prior to the start of the study and throughout the study period. Excessive smoking was discouraged during the trial.

At 08.30 h of the test day, following an overnight fast, subjects ingested either a tablet of 500 mg of naproxen or the equimolar 550 mg of naproxen sodium with 100 ml of water (drug was assigned randomly). Blood (10 ml) was obtained from each subject at basline and 10, 20, 40, 60 min, 2, 4, 6, 8 and 24 h after ingestion of the drug. Plasma was separated and frozen for later naproxen plasma level determinations by gas chromatography (Runkel Chaplin, Sevelius, Ortega & Segre, 1976). The subjects remained fasting until after the fourth hour blood sample. After a 1 week interval, they repeated the same procedure with the second drug in a crossover design.

Time course of analgesia (naproxen v *naproxen sodium)*

Sixty postpartum women with moderate or severe uterine cramping during the 48 h after an uncomplicated delivery participated in this study. This single-dose, double-blind parallel study evaluated the comparative analgesia of naproxen and its sodium salt. No other analgesic, sedative or psychotropic medications were permitted during the 6 h preceding the study. None of the patients was breast feeding her infant.

On demand, patients randomly received either 500 mg naproxen or 550 mg naproxen sodium tablets with a glass of water. The two treatment groups were comparable in terms of demographic characteristics and degree of cramping. Each patient evaluated pain intensity at baseline (immediately before drug administration) and 15, 30, 60 min, 2, 3, 4, 5 and 6 h after ingestion of the drug. Pain intensity was rated on a scale of 0 to 3 (0=no pain, 1=mild pain, 2=moderate pain, 3=severe pain) and then Pain Intensity Differences (PID) were calculated by finding the arithmetic difference between the patient's baseline score and each periodic post-treatment score. These periodic PID scores were used to compute the degree of pain relief (SPID—sum of pain intensity differences), and, together with pain intensity scores, were used to measure onset, peak, and duration of pain relief. SPID scores have been shown to be an appropriate and valid technique to evaluate analgesics (Bellville, Forrest & Brown, 1968; Houde, Wallenstein & Rogers, 1960).

Any adverse effects reported during the study period were recorded.

Steady state plasma levels (two dosage regimens of naproxen sodium)

Sixteen healthy volunteers (8 males and 8 females) participated in this study. None received any enzyme inducing drugs during the month prior to the study. Subjects did not alter their daily activities or dietary habits. All volunteers were within 10% of average weight for their age, sex and height.

Each subject received a loading dose of naproxen sodium (550 mg) at 09.00 h on the test day. Thereafter, subjects ingested 275 mg naproxen sodium either every 6 h or every 8 h, for a total of 3 consecutive days (drug regimen was assigned randomly). Ten millilitres of blood was obtained at baseline and 4, 8, 24, 32, 48, 52, 56 and 72 h after ingestion of the drug. Plasma was separated and frozen for later naproxen plasma level determinations by gas chromatography. After a 10-day interval, subjects repeated the same procedure with the second dosage regimen.

Routine blood chemistry determinations were performed on all subjects before and after the study, and any adverse effects reported during the study period were recorded.

Results

Bioavailability

Two variables were of primary interest in this study: the rate of absorption of the drug, measured by the upslope of the drug concentration over time curve, and the total absorption, as characterized by the area under that curve. For a drug such as naproxen sodium which is primarily intended as an analgesic, the rate of absorption is particularly important.

Naproxen sodium resulted in significantly earlier and higher plasma levels for the first 2 h. At 20 and 40 min after administration, the plasma concentrations of naproxen sodium were approximately twice as high as those of naproxen (Figure 1). These differences were statistically significant ($P < 0.005$ and $P < 0.01$, respectively). One hour after adminstration the plasma level of naproxen sodium was still approximately 39% higher than the plasma level of naproxen ($P < 0.01$). As can be seen in Figure 1, the mean time to peak plasma level was 1 h for naproxen sodium and 2 h for naproxen, with the sodium salt achieving a significantly higher peak ($P < 0.01$). After 2 h, the plasma levels for the two drugs were approximately equal.

The area under the plasma curve was significantly larger for naproxen sodium during early time periods, i.e., 33% larger during the 0 to 2 h time period ($P < 0.01$). The total absorption of naproxen and

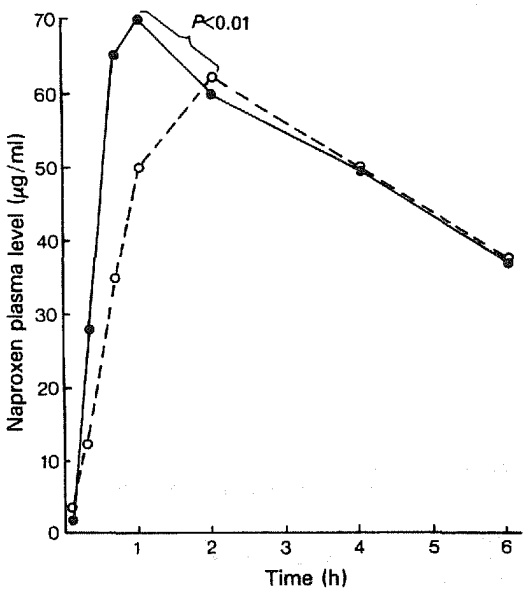

Figure 1 Naproxen plasma levels after administration of 500 mg naproxen (○) or the equimolar 550 mg naproxen sodium (●) to 12 healthy men in a crossover study. Significantly earlier and higher naproxen levels were achieved after naproxen sodium.

naproxen sodium, as indicated by the total areas under the curve, was equal.

No clinically significant adverse effects were noted during the study.

Time course of analgesia

There were no differences between the 30 patients who received naproxen and the 30 who received naproxen sodium with respect to age distribution, type of labor and delivery, premedication, initial severity of pain or any other baseline parameter measured.

Mean pain intensity scores during the study are illustrated in Figure 2. On the average, patients in both groups obtained greater than a 50% reduction in initial pain (24 of 30 in the naproxen sodium group and 25 of 30 in the naproxen group). However, naproxen sodium resulted in consistently lower mean pain intensity scores than did naproxen.

Figure 3 illustrates the mean pain intensity differences (PID) for the two groups. At all time points, except 1 h, the PID scores were higher for the naproxen sodium group (i.e., greater pain relief) than for the naproxen group. However, these differences between the naproxen and naproxen sodium groups became statistically significant only 4 and 5 h after administration of medication. The

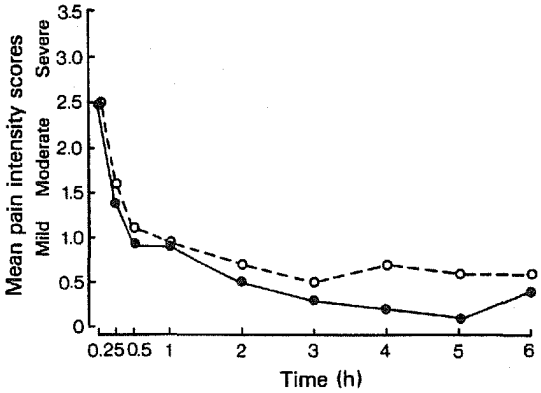

Figure 2 Mean pain intensity scores before and after administration of 500 mg naproxen (○) or the equimolar 550 mg naproxen sodium (●) to 30 postpartum women with moderate or severe uterine cramps. Scores were consistently lower for those patients receiving naproxen sodium.

naproxen sodium group achieved a peak PID score of 2.37 in the fifth hour, while the naproxen group achieved a lower peak PID score (2.00) in the third hour. The sum of pain intensity differences (SPID) was also greater for the naproxen sodium group than for the naproxen group. These data suggest that naproxen sodium resulted in better analgesia than naproxen in this clinical setting.

No clinically significant side effects were noted during the study.

Steady state plasma levels

More frequent dosing (i.e., larger total dose of drug ingested) was reflected in higher mean plasma levels of naproxen. Those patients on the every 6 h regimen achieved mean naproxen plasma levels approximately 20 μg/ml higher than those on every 8 h regimen (Figure 4). Differences between the two regimens at 24, 48 and 72 h were highly statistically significant ($P < 0.001$).

No clinically significant adverse effects were noted during the study.

Discussion

The results of the first study document the theoretical advantages of utilizing the sodium salt of naproxen to achieve more rapid absorption of the drug. Patients achieved significantly earlier and higher plasma levels of naproxen with naproxen sodium.

This improved bioavailability was not immediately evident, however, in a clinical setting. Both those

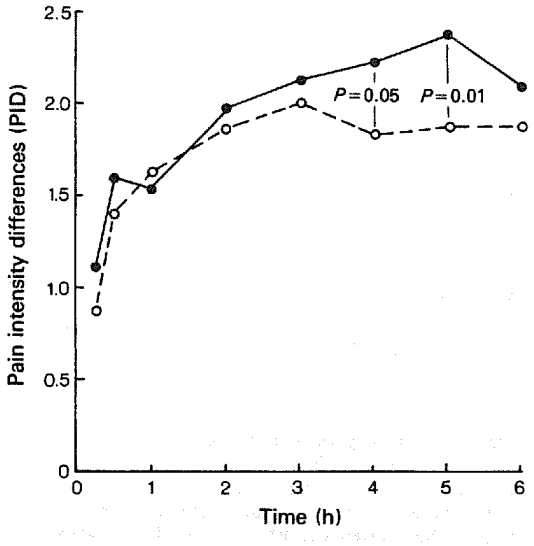

Figure 3 Mean pain intensity differences (PID; arithmetic differences between baseline and each post-treatment score) after administration of 500 mg naproxen (○) or 550 mg naproxen sodium (●) to 30 postpartum women with moderate to severe uterine cramps.

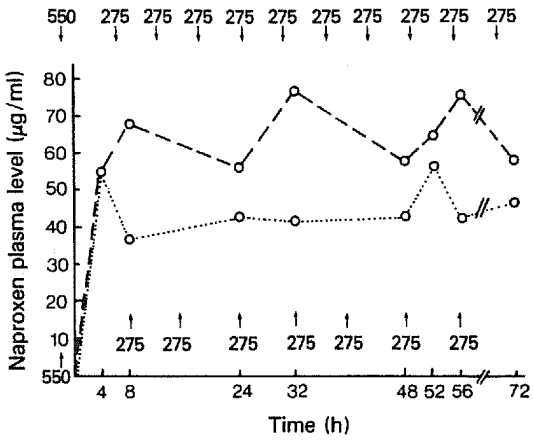

Figure 4 Comparison of the mean naproxen plasma levels between naproxen sodium administered every 6 h (○----○) or every 8 h (○····○) to 16 healthy men and women in a crossover study. The every 6 h regimen produced average naproxen plasma levels approximately 20 μg/ml higher than the every 8 h regimen.

patients who received naproxen and those who received naproxen sodium noted a rapid reduction in pain. The early differences between the two groups were small, and statistically significant differences in analgesic response were not seen until 4 and 5 h after medication. However, pain is a very subjective variable, and statistically significant differences are notoriously difficult to achieve between two active analgesic agents. Nonetheless, pain intensity was consistently lower for the group receiving naproxen sodium, even 15 min after administration. It may be that much larger numbers of patients are necessary to demonstrate statistically significant differences, particularly during the first hours of study. This remains to be resolved by future studies.

In two earlier studies of analgesics in patients with postpartum pain (one comparing naproxen to placebo and codeine and the other comparing naproxen sodium to placebo and aspirin), statistically significant differences between naproxen or naproxen sodium and placebo were seen only 2 to 3 h after medication (Bloomfield, Barden & Mitchell, 1977). The dose of naproxen was 300 or 600 mg and the dose of naproxen sodium was 275 mg (half the recommended therapeutic dose). However, in a separate study using the full therapeutic dose of naproxen sodium (550 mg), patients with pain of varying origin (musculoskeletal, dental, headache, etc.) found naproxen sodium significantly superior to both placebo and aspirin 1 hour after dosing (Sevelius, Segre & Bursick, 1980).

Whether naproxen or naproxen sodium is administered, the circulating moiety is the same, and the two drugs thus share the same long biological half-life (13-14 h). This long half-life is particularly useful when naproxen is used for chronic anti-inflammatory therapy, since the drug can be administered on a twice daily regimen and still reach adequate steady-state plasma levels to maintain therapeutic efficacy. In addition, using a single dose of naproxen sodium, a previous study demonstrated a sustained duration of analgesic effect for up to 7 h (entire length of follow-up period in study) (Bloomfield *et al.*, 1977).

For analgesia, it may be desirable to reach quickly and maintain high plasma levels in order to obtain fast and continuous maximum therapeutic benefits. The more rapid bioavailability of the sodium salt of naproxen was shown in the first study. The final study documented that a more frequent dosage schedule of every 6 h led to clearly higher plasma levels than those achieved with an every 8 h regimen. This study did not evaluate the potential therapeutic benefits of more frequent dosing. It did demonstrate, however, that when more drug was ingested plasma levels increased. While many patients may receive rapid and good pain relief with an every 8 h regimen, others may receive added benefit from the higher plasma levels achieved with an every 6 h regimen. Individual patient variations in response to pain and initial level of pain make it difficult to draw any conclusions for

even the 'average' patient. However, further studies may help clarify this question.

Including the loading dose of 550 mg, the total daily dosage in the final study was 1,375 mg/day and 1,100 mg/day for the every 6 and every 8 h regimens, respectively. The ability to tolerate doses in this range was evaluated in an earlier study with naproxen during which single doses of 1, 2, 3 or 4 g were administered to 16 healthy volunteers (Runkel *et al.*, 1976). Aside from 1 person who reported mild epigastric pain after receiving 3 g of naproxen, no other subjects reported any side effects. In addition, there were no abnormal findings on physical examination nor were there any clinically meaningful changes in blood chemistry values. These high doses of naproxen were quickly cleared by the kidney without saturating any of the body's eliminating mechanisms. In another study, healthy subjects received 1,800 mg/day of naproxen for 30 days without significant side effects or changes in laboratory values (unpublished data, Syntex Corporation). In contrast, studies have shown that doses of 1 g or more of aspirin result in salicylate accumulation and a threat of salicylate intoxication (Levy, 1965; Wagner, 1971).

Thus, the regimens employed in our study (550 mg naproxen sodium as a loading dose, followed by 275 mg every 6 or 8 h appear to fall within a range which is well tolerated in man. It has the advantage of allowing one rapidly to achieve and then maintain therapeutic plasma levels of the drug thereby minimizing fluctuations which might lead to some loss of analgesic effect.

In conclusion, naproxen sodium appears to be an improved form of naproxen for use as an analgesic agent. It is more rapidly available to the body and appears to provide greater pain relief than naproxen. Earlier studies suggested that, at the doses employed in this study, naproxen sodium is well tolerated. The analgesic efficacy of naproxen sodium in single doses as low as 275 mg has been demonstrated previously. This, coupled with the long duration of efficacy for the recommended 550 mg dose and wide safety margin, should provide good flexibility in dosing for patients with pain of various origins. In addition, since many causes of pain are frequently accompanied by inflammation, the use of an analgesic which is also an anti-inflammatory agent may provide added benefit.

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Patent number	EP1863458
Date of receipt	28 November 2017
Your reference	BRICX/M20527EP
Proprietor	Patheon Softgels Inc.
Title	Solvent system for enhancing the solubility of pharmaceutical agents

Documents submitted	package-data.xml ep-oppo.pdf (2 p.) GENAUTH-1.pdf\M20527EP General Authorisation.pdf (1 p.) Other-evidence-1.pdf\M20527EP D14.pdf (5 p.)	ep-opposition-data.xml OBSO3.pdf\M20527EP- Response to opposition.pdf (13 p.) OTHER-1.pdf\28Nov17-EPO (M20527EP).pdf (1 p.)

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