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Plachetka

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(54) **PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS**

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(52) **U.S. Cl.** **424/472**; 424/457; 424/463; 424/468; 424/474; 424/480; 424/482

(58) **Field of Search** 424/457, 463, 424/468, 472, 474, 480, 482, 464, 451

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,255,431 A	3/1981	Junggren et al.	.....	424/263
4,508,905 A	4/1985	Junggren et al.	.....	546/271
4,554,276 A	11/1985	LaMattina	.....	514/272

(Continued)

FOREIGN PATENT DOCUMENTS

DE	198 01 811 A1	1/1998	..... A61K/9/50
EP	0 320 550 A1	6/1989	..... A61K/33/08
EP	0 426 479 B1	5/1991	..... A61K/31/415

(Continued)

OTHER PUBLICATIONS

Howden, "Clinical Pharmacology of Omeprazole," *Clin. Pharmacokinet. 20(1)*:38–49 (1991) abstract.

Pilbrant, et al., "Development of an Oral Formulation of Omeprazole," *Scand. J. Gastroenterol. 20(Suppl. 108)*:113–120 (1985).

Sharma, "Comparison of 24–Hour Intragastric pH Using Four Liquid Formulations of Lansoprazole and Omeprazole," *Am. J. Health–Syst. Pharm. 56(Supp. 4)*:S18–S21 (1999).

(Continued)

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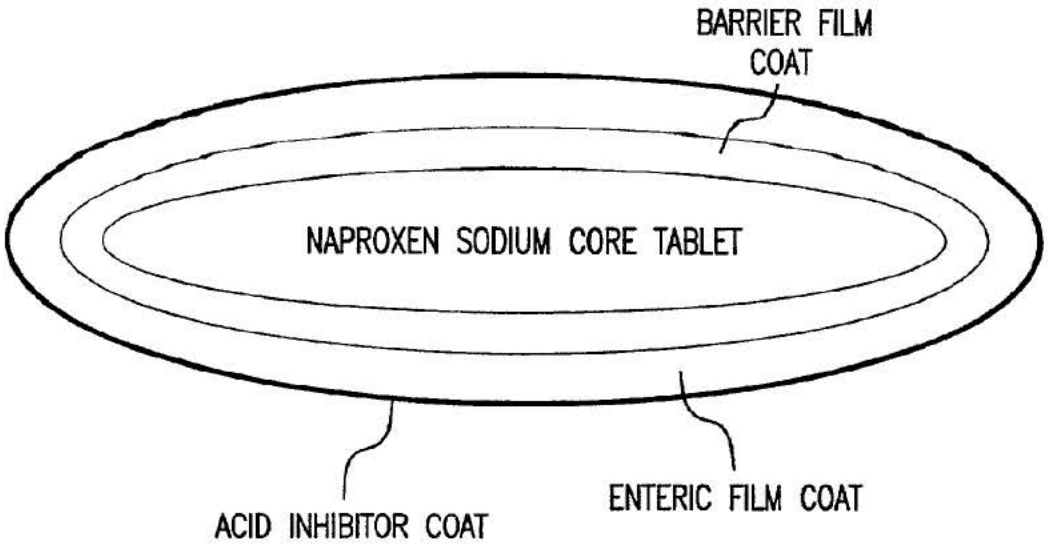
(57) **ABSTRACT**

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

55 Claims, 2 Drawing Sheets



U.S. PATENT DOCUMENTS

4,562,261	A	12/1985	Hirata et al.	548/184
4,619,934	A	10/1986	Sunshine et al.	514/277
4,676,984	A	6/1987	Wu et al.	424/157
4,704,278	A	11/1987	Wu et al.	424/157
4,757,060	A	7/1988	Lukacsko et al.	514/160
4,766,117	A	8/1988	Crawford et al.	514/219
4,786,505	A	11/1988	Lovgren et al.	424/468
4,965,065	A	10/1990	Lukacsko et al.	424/10
5,037,815	A	8/1991	Lukacsko et al.	514/162
5,043,358	A	8/1991	Lukacsko et al.	514/653
5,204,118	A	4/1993	Goldman et al.	424/489
5,260,333	A	11/1993	Lukacsko et al.	514/471
5,364,616	A	11/1994	Singer et al.	424/52
5,373,022	A	12/1994	Fawzi et al.	514/570
5,417,980	A	5/1995	Goldman et al.	424/464
5,466,436	A	11/1995	Stables	514/161
5,514,663	A	5/1996	Mandel	514/33
5,631,022	A	5/1997	Mandel et al.	424/456
5,643,960	A	7/1997	Breitner et al.	514/570
5,686,105	A	11/1997	Kelm et al.	424/452
5,716,648	A	2/1998	Halskov et al.	424/682
5,955,451	A	9/1999	Lichtenberger et al.	514/78
6,013,281	A	1/2000	Lundberg et al.	424/468
6,025,395	A	2/2000	Breitner et al.	514/570
6,160,020	A	12/2000	Ohannesian et al.	514/629
6,162,816	A	12/2000	Bohlin et al.	514/338
6,207,188	B1	3/2001	Gustavsson et al.	424/464
6,365,184	B1	4/2002	Depui et al.	424/469
6,395,298	B1	5/2002	Flanagan et al.	424/479
6,485,747	B1	11/2002	Flanagan et al.	424/479
6,544,556	B1	4/2003	Chen et al.	424/469
2001/0025107	A1	9/2001	Barberich et al.	546/273.7
2001/0036473	A1	11/2001	Scott et al.	424/463
2001/0044410	A1	11/2001	Gelber et al.	514/27
2002/0012676	A1	1/2002	Lundeberg et al.	424/400
2002/0042433	A1	4/2002	Yelle et al.	514/338
2002/0044962	A1	4/2002	Cherukuri et al.	424/459
2002/0045184	A1	4/2002	Chen	435/6
2002/0086029	A1	7/2002	Lundberg et al.	424/184.1
2002/0111370	A1	8/2002	Bergman et al.	514/338
2002/0155153	A1	10/2002	Depui et al.	424/452
2003/0008903	A1	1/2003	Barberich et al.	514/338
2003/0113375	A1	6/2003	Lundberg et al.	424/474
2003/0129235	A1	7/2003	Chen et al.	424/470

FOREIGN PATENT DOCUMENTS

EP	0 426 479 A1	5/1991	A61K/31/415
EP	0 550 083 B1	7/1993	A61K/31/34
GB	2 105 193	3/1983	A61K/31/34
WO	WO 85/03443	8/1985	A61K/45/06
WO	WO 93/12817	7/1993	A61K/45/06
WO	WO 94/07541	4/1994	A61K/49/00
WO	WO 98/22117	5/1998	A61K/33/24
WO	WO 99/00380	1/1999	C07D/401/12
WO	WO 99/12524	3/1999	A61K/9/20
WO	WO 00/71122	11/2000	A61K/31/44
WO	WO 00/72838 A1	12/2000	A61K/31/04
WO	WO 03/017980 A1	3/2003	A61K/9/16

OTHER PUBLICATIONS

Bigard, et al., "Complete Prevention by Omeprazole of Aspirin Induced Gastric Lesions in Healthy Subjects," *GUT 29*(5):A712, T49 (1988).

Bombardier, et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," *N. Engl. J. Med. 343*:1520–1528 (2000).

Brown, et al., "Prevention of the Gastrointestinal Adverse Effects of Nonsteroidal Anti–Inflammatory Drugs," *Pract. Drug Safety 21*:503–512 (1999).

Cullen, et al., "Primary Gastroduodenal Prophylaxis with Hawkey, "Progress in Prophylaxis Against Nonsteroidal Anti–Inflammatory Drug–Associated Ulcers and Erosions," *Am. J. Med. 104*:67S–74S (1998).

Hawkey, et al., "Omeprazole Compared with Misoprostol for Ulcers Associated with Nonsteroidal Anti–Inflammatory Drugs," *N. Engl. J. Med. 338*:727–734 (1998).

Katz, et al., "Gastric Acidity and Acid Breakthrough with Twice–Daily Omeprazole or Iansoprazole," *Aliment. Pharmacol. Ther 14*:709–714 (2000).

Kephart, et al., "Coprescribing of Nonsteroidal Anti–Inflammatory Drugs and Cytoprotective and Antiulcer Drugs in Nova Scotia's Senior Population," *Clin. Ther. 17*:1159–1173 (1995).

Lad, et al., "Management of Nonsteroidal Anti–Inflammatory Drug–Induced Gastroduodenal Disease by Acid Suppression," *Can. J. Gastroenterol 13*:135–142 (1999).

Mattsson, et al., "Omeprazole Provides Protection Against Experimentally Induced Gastric Mucosal Lesions," *Eur. J. Pharmacol. 91*:111–114 (1983).

Oddsson, et al., "Endoscopic Findings in the Stomach and Duodenum after Treatment with Enteric–Coated and Plain Naproxen Tablets in Healthy Subjects," *Scand. J. Gastroenterol. 25*:231–234 (1990).

Scheiman, "NSAID–Induced Peptic Ulcer Disease: A Critical Rview of Pathogenesis and Management," *Dig. Dis. 12*:210–222 (1994).

Selway, "Potential Hazards of Long–Term Acid Suppression," *Scand. J. Gasatroenterol. 25*(*Supp. 178*):85–92 (1990).

Silverstein, et al., "Gastrointestinal Toxicity with Celecoxib vs. Nonsteroidal Anti–Inflammatory Drugs for Osteoarthritis and Rheumatoid Arthritis; The CLASS Study: A Randomized Controlled Trial," *JAMA 284*:1247–1255 (2000).

Tronstad, et al., "Gastroscopic Findings after Treatment with Enteric–Coated and Plain Naproxen Tablets in Healthy Subjects," *Scand. J. Gastroenterol. 20*:239–242 (1985).

Wolfe, et al., "Gastrointestinal Toxicity of Nonsteroidal Anti–Inflammatory Drugs," *N. Engl. J. Med. 340*:1888–1899 (1999).

Yeomans, et al., "A Comparison of Omeprazole with Ranitidine for Ulcers Associated with Nonsteroidal Anti–Inflammatory Drugs," *N. Engl. J. Med. 338*:719–726 (1998).

Yeomans, et al., "New Data on Healing of Nonsteroidal Anti–Inflammatory Drug–Associated Ulcers and Erosions," *Am. J. Med. 104*:56S–61S (1998).

English language abstract for DE 198 01 811, Reference B13 above.

Dent, "Why Proton Pump Inhibition Should Heal and Protect Against Nonsteroidal Anti–Inflammatory Drug Ulcers," *Am. J. Med. 104*:52S–55S (1998).

Kimmey, et al., "Role of H_2–Receptor Blockers in the Prevention of Gastric Injury Resulting from Nonsteroidal Anti–inflammatory Agents," *Am. J. Med. 84*:49–52 (1988).

Lee, et al., "Omeprazole Prevents Indomethacin–Induced Gastric Ulcers in Rabbits," *Aliment. Pharmacol. Ther. 10*:571–576 (1996).

Lichtenbergetr, et al., "Nonsteroidal Anti–inflammatory Drug and Phospholipid Prodrugs: Combination Therapy with Antisecretory Agents in Rats," *Gastroenterology 111*:990–995 (1996).

Savarino, et al., "Effect of One–Month Treatment with Nonsteroidal Antiinflammatory Drugs (NSAIDs) on Gastric pH of Rheumatoid Arthritis Patients," *Digestive Diseases and Sciences 43*:459–463 (1998).

Wagner, et al., "Effects of Nonsteroidal Antiinflammatory Drugs on Ulcerogenesis and Gastric Secretion in Pylorus-

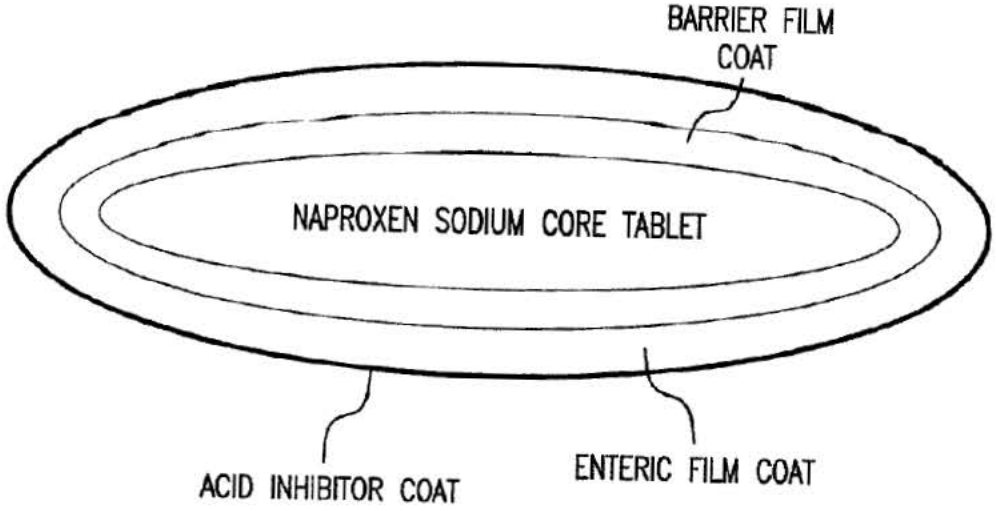


FIG.1

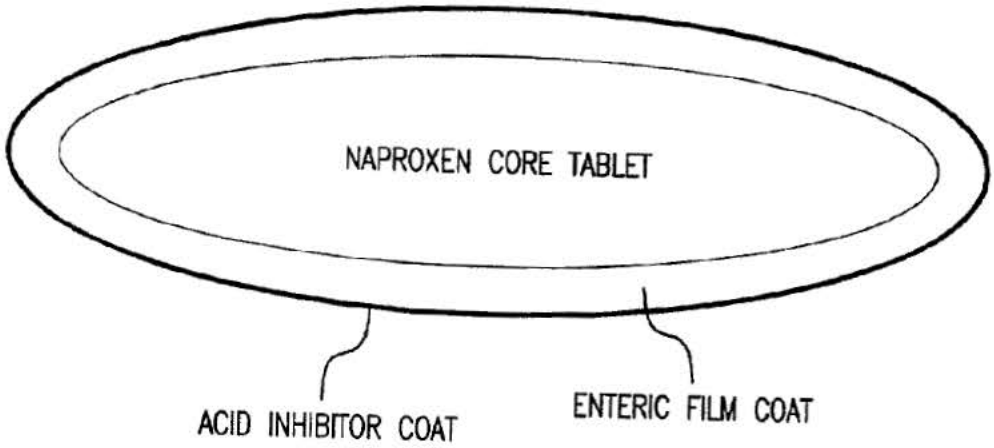


FIG.2

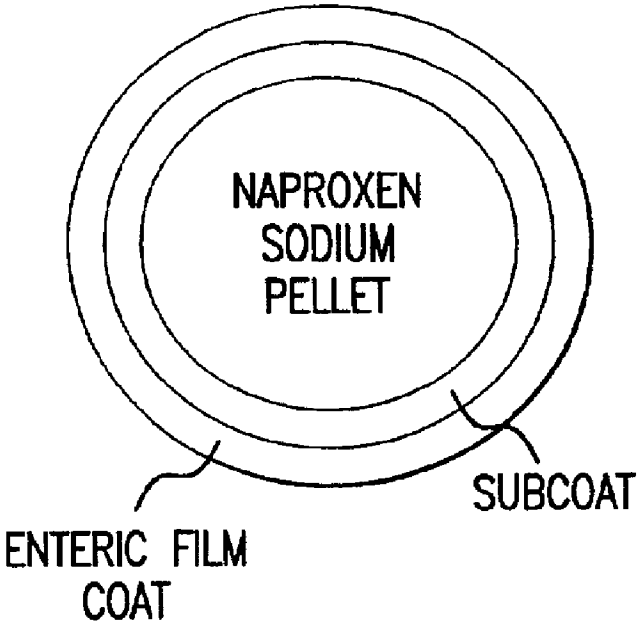


FIG.3

PHARMACEUTICAL COMPOSITIONS FOR THE COORDINATED DELIVERY OF NSAIDS

CROSS REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. provisional application No. 60/294,588, filed on Jun. 1, 2001.

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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

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

Although longer lasting agents, such as proton pump inhibitors (PPIs), usually maintain a consistently higher gastroduodenal pH throughout the day, after several days dosing, their antisecretory effect may be delayed for several hours and may not take full effect for several days (*Clin. Pharmacokinet.* 20:38–49 (1991)). Their effect may be diminished toward the end of the usual dosing interval.

coated to avoid destruction by stomach acid. As a result, absorption is delayed for several hours. Even then, some patients fail to respond consistently to drugs of this type and suffer from "acid breakthrough" which again leaves them vulnerable to NSAID-associated gastroduodenaldamage (*Aliment. Pharmacol. Ther.* 14:709–714 (2000)). Despite a significant reduction in gastroduodenal lesions with the concomitant administration of a proton pump inhibitor during six months of NSAID therapy, up to 16% of patients still develop ulcers, indicating that there remains substantial room for improvement (*N. Eng. J. Med.* 338:727–734 (1998)). Thus, the addition of a pH sensitive enteric coating to an NSAID could provide additional protection against gastroduodenal damage not provided by the H2 blocker or PPI alone. In addition, although long acting acid inhibitors may reduce the risk of GI lesions in chronic NSAID users, there are questions about the safety of maintaining an abnormally elevated pH in a patient's GI tract for a prolonged period of time (*Scand. J. Gastroenterol. Suppl.* 178:85–92 (1990)).

Recognizing the potential benefits of PPIs for the prevention of NSAID-induced gastroduodenal damage, others have disclosed strategies for combining the two active agents for therapeutic purposes. However, these suggestions do not provide for coordinated drug release or for reducing intragastric acid levels to a non-toxic level prior to the release of NSAID (U.S. Pat. Nos. 5,204,118; 5,417,980; 5,466,436; and 5,037,815). In certain cases, suggested means of delivery would expose the gastrointestinal tract to NSAIDs prior to onset of PPI activity (U.S. Pat. No. 6,365,184).

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

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

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

Overall, it may be concluded that the risk of inducing GI ulcers is a recognized problem associated with the admin-

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