

## Pharmaceutical Compositions for the Coordinated Delivery of NSAIDs

### Cross Reference to Related Applications

5           The present application is a continuation-in-part of U.S. application no. 10/158,216, filed on May 31, 2002. The '216 application claims the benefit of U.S. provisional application no. 60/294,588, filed on June 1, 2001.

### Field of the Invention

10           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.

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### 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.

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          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<sub>2</sub> receptor antagonists (H<sub>2</sub> blockers) (*N. Eng. J. Med.* 338:719-726 (1998); *Am. J. Med.* 104(3A):56S-61S (1998)). The most likely

5 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.

10 Although longer lasting agents, such as proton pump inhibitors (PPIs), usually maintain a consistently higher gastroduodenal pH throughout the day, 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. Intra-gastric pH rises particularly slowly with the first dose in a course  
15 of treatment since this class of drugs is enteric coated to avoid destruction by stomach acid. As a result, absorption is delayed for several hours. Even then, some patients fail to respond consistently to drugs of this type and suffer from “acid breakthrough” which again leaves them vulnerable to NSAID-associated gastroduodenal damage (*Aliment. Pharmacol. Ther.* 14:709-714 (2000)). Despite a significant reduction in gastroduodenal lesions with the  
20 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 H<sub>2</sub> blocker or PPI alone. In addition, although  
25 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)).

30 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 intra-gastric acid levels to a non-toxic level prior to the release of NSAID (U.S. 5,204,118; U.S. 5,417,980; U.S. 5,466,436; and U.S. 5,037,815). In certain

cases, suggested means of delivery would expose the gastrointestinal tract to NSAIDs prior to onset of PPI activity (U.S. 6,365,184).

5 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  
10 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)).

15 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 misoprostol (a cytoprotective prostaglandin) and the NSAID diclofenac. Although patients administered Arthrotec™ do have a lower risk of developing  
20 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  
25 studies (*Scand. J. Gastroenterol.* 20: 239–242 (1985) and *Scand. J. Gastroenterol.* 25:231–234 (1990)), there is no consistent evidence of a long term benefit during chronic treatment.

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

**Summary of the Invention**

The present invention is based upon the discovery of a new method for reducing the

level of prostaglandin synthase activity in the gastrointestinal tract of patients taking NSAIDs. Such patients include those with

conditions, particularly during chronic treatment. The method involves the administration of

5 a single coordinated unit dose product that combines a) an agent that actively raises

inhibitor has been developed which competes with potassium at the acid pump. The compounds in this class have been referred to as “reversible proton pump inhibitors” or “acid pump antagonists” and may also be used in the present invention. Examples include AZD-0865, AR-H047108, CS-526, pumaprazole, revaprazan and soraprazan (see  
5 WO9605177 and WO9605199). Other compounds in this group are H-335/25 (AstraZeneca, Dialog file 128, accession number 020806); Sch-28080 (Schering Plough, Dialog file 128, accession number 009663); Sch-32651 (Schering Plough, Dialog file 128, accession number 006883) and SK&F-96067 (CAS Registry no. 115607-61-9).

10 The pharmaceutical composition also contains a non-steroidal anti-inflammatory drug in an amount effective to reduce or eliminate pain or inflammation. The NSAID may be celecoxib, rofecoxib, lumiracoxib, valdecoxib, parecoxib, etoricoxib, CS-502, JTE-522, L-745,337, NS398, aspirin, acetaminophen (considered to be an NSAID for the purposes of the present invention), ibuprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin, etodolac,  
15 indomethacin, ketorolac, lornoxicam, meloxicam, piroxicam, droxicam, tenoxicam, nabumetone, diclofenac, meclofenamate, mefenamic acid, diflunisal, sulindac, tolmetin, fenoprofen, suprofen, benoxaprofen, aceclofenac, tolfenamic acid, oxyphenbutazone, azapropazone, and phenylbutazone. The most preferred NSAID is naproxen in an amount of between 50 mg and 1500 mg, and more preferably, in an amount of between 200 mg and  
20 600 mg. It will be understood that, for the purposes of the present invention, reference to an acid inhibitor, NSAID, or analgesic agent will include all of the common forms of these compounds and, in particular, their pharmaceutically acceptable salts. The amounts of NSAIDs which are therapeutically effective may be lower in the current invention than otherwise found in practice due to potential positive kinetic interaction and NSAID  
25 absorption in the presence of an acid inhibitor.

Preferably, the pharmaceutical composition of the present invention is in the form of a tablet or capsule that has: (a) the acid inhibitor present in an amount effective to raise the gastric pH of a patient to at least 3.5 upon the administration of one or more unit dosage  
30 forms; and (b) the non-steroidal anti-inflammatory drug (NSAID) present in an amount effective to reduce or eliminate pain or inflammation in a patient upon administration of one or more of said unit dosage forms. The NSAID in the dosage form should be in a core, preferably a single core when tablets are used, that is surrounded by a coating that does not

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