the processing of the ingredients to obtain the first fraction (cf. Danish Patent Application filed on 10 September 1998 in the name of Nycomed Danmark). In those cases, where a coating is present on the units of the first fraction, the coating may of course also contribute to the control of the release of the active drug substance from the first fraction. In the second fraction, the release rate is primarily governed by the constitution and thickness of a controlled release membrane which are applied on pellet cores (also denoted "pellets").

The delayed and extended fraction is based on the application of a release controlling membrane. The release is being controlled by the membrane which makes the formulation much more robust and easier to manipulate and manufacture. Ideally there is no release controlling effect from the uncoated units of the second fraction, i.e. the uncoated multiple-units of the second fraction do not significantly contribute to any control of the extended release of the active drug substance but the uncoated multiple-units merely release the active drug substance freely without any significant retardation.

The modified release multiple-units dosage forms of the present invention achieve and maintain therapeutic levels and, at the same time, reduces the risks for any side effect, which are believed to be associated with high blood levels of NSAID substances. Furthermore, the delayed or extended release properties of the coating applied on the second fraction of the multiple-units dosage forms of the present invention are unaffected by the pH in the gastro-intestinal tract.

The first fraction of the multiple-units dosage form of the invention may also be in the form of coated multiple-units provided that the release rate of such a fraction is so fast in the dissolution medium employed in dissolution method II described herein that at least 50% w/w of the total dose of the first fraction is released within the first 20 min.

When a coating is present on the multiple-units of the first fraction then it could advantageous be of the same kind as an outer coating on the multiple-units of the second fraction. The employment of the same kind of coating for each fraction may be performed with substantially identical procedures and materials and the production cost can be kept at a low level.

DETAILED DISCLOSURE OF THE INVENTION

Accordingly, the present invention relates to an oral pharmaceutical modified release multiple-units composition in unit dosage form for administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance (an NSAID substance), a unit dosage form comprising two NSAID-containing fractions,

i) a first NSAID-containing fraction of multiple-units for quick release of the NSAID substance, and

ii) a second NSAID-containing fraction of multiple-units for extended release of the NSAID substance,

the first fraction which - when subjected to dissolution method II as defined herein employing 0.07 N HCl as dissolution medium - releases at least 50% w/w of the NSAID substance present in the fraction within the first 20 min of the test,

the second fraction being in the form of coated delayed release multiple units for extended release of the NSAID substance.

As discussed above it is very important to secure that the release pattern of the active drug substance contained in the composition is suitable for a composition for administration once or twice daily. The employment of at least two different fractions of multiple-units gives very flexible formulation parameters. Thus, it is possible to vary i) the percentage of the total dose of the NSAID substance contained in each fraction and ii) the weight ratio between the different fractions. The system (i.e. formulation concept) is therefore very suitable to not only one specific drug substance but can within certain limits be applied on a class or many classes of active drug substances once the target release profile has been determined. Of course, a change from one active drug substance to another active drug substance may give rise to certain adjustments of the constitution of the individual fractions to the specific substance. In the following is given a discussion of how to determine a target profile for an active drug substance and the release requirements generally applicable for the group of active drug substances belonging to the non-steroid anti-inflammatory drug substances.

Dissolution requirements

As described in the following, a target release profile can be designed for any NSAID substance. In the following the target release profile for a selected NSAID substance is described, namely lornoxicam.

Based on the knowledge of the pharmacokinetics of lornoxicam and a study performed by us employing a plain tablet and a solution (Hitzenberger G, Radhofer-Welte S, Takacs F, Rosenow D.: Pharmacokinetics of lornoxicam in man, Postgrad. Med. J. 1990, 66, pp S22-S26), a target in vivo profile for a once daily product has been estimated (Figure 1).

The presumptions made in estimating this target profile were:

i) a double peak and an effective concentration for 24 hours are desired from a therapeutic point of view (i.e. plasma lornoxicam concentrations at 24 hours should be similar to the plasma concentration obtained 8-12 hours after administration of half the dose in the form of a plain tablet),

ii) that the first fraction of the composition should have an absorption rate similar to or faster than that of plain tablets

iii) that the peak concentration should not be higher than the peak concentration observed after administration of half the dose in the form of a plain tablet, and

iv) that the second peak should appear about 5-6 hours after dosing.

A person skilled in the art is capable of determining the actual values with respect to the above-mentioned provisions and based on such values perform any necessary correction to the estimated profile (target profile).

The estimated target plasma profile as well as the profile from plain tablets have been deconvoluted with plasma concentrations from an oral solution to give an estimated *in vivo* dissolution profile (Figure 2). All data were normalised to a dose of 16 mg. In the deconvolution a time interval of 0.5 hours was employed (cf. Langenbucher F., and H.

Möller: Correlation of *in vitro* drug release with in vivo response kinetics. Part I: Mathematical treatment of time functions. Pharm. Ind. 1983, 45, pp 623-8 and Langenbucher F. and H. Möller: Correlation of in vitro drug release with in vivo response kinetics. Part II: Use of function parameters. Pharm. Ind. 1983, 45, pp 629-33).

The presumptions in making this deconvolution were that the daily dose of lornoxicam is the same irrespective of whether a once daily composition or a plain tablet or a solution were administered,

The estimated *in vivo* dissolution profile for a once daily product can be used as the target *in vitro* profile for the combination of a fast or quick release fraction (i.e. the first fraction) and an extended or slow release fraction (i.e. the second fraction, coated pellets). The estimated *in vivo* dissolution profile for the once daily composition can be used as the target *in vitro* profile, when performing the dissolution tests *in vitro* with 1 hour in 0.1 N HCl and then shift to phosphate buffer pH 7.3 or 7.4 (dissolution methods III or IV described herein). This knowledge has been utilized in order to arrive at the dissolution requirements described in the following.

The presumptions made in using the estimated *in vivo* profile as target for *in vitro* profile were:

i) that a plain tablet will remain in the stomach for about 1 hour before a passage into the intestine takes place (estimated from the difference in T_{max} between the solution (0.5 hours) and the plain tablet (1.5 hour),

ii) that the correlation between the *in vitro* dissolution and the *in vivo* dissolution is a 1:1 correlation, and

iii) that lornoxicam is absorbed through the whole gastrointestinal tract (including colon) in order not to loose any amount of active drug substance ready for absorption into the circulatory system.

Before going into detail with respect to the release requirement to the first fraction, the second fraction and the composition in its final form, in the following is given details

with respect to the target release profile for a once daily lornoxicam composition. The target profile has been estimated as described above.

Target release *in vivo* profile (corresponds to target release profile *in vitro* employing dissolution methods III or IV as described herein):

Time (hours)	% w/w released lornoxicam
0.5	21 (range: 10-25%)
1	29 (range: 15-35%)
2	37 (range: 25-45%)
3	42 (range: 30-55%)
4	52 (range: 40-65%)
5	62 (range: 45-70%)
6	69 (range: 50-75%)
7	75 (range: 55-80%)
8	79 (range: 60-85%)
9	83 (range: 60-90%)
10	86 (range: 60-95%)
12	89 (range: 65-99%)
16	94 (range: at least about 85%)
20	97 (range: at least about 90%)
24	100 (range: at least about 90%)

As apparent from the above, the first fraction must release the active drug substance very quickly in 0.1 N HCl or in the dissolution medium employed in dissolution method II described herein, i.e. under conditions simulating the conditions in the stomach and under these conditions the second fraction does not release any significant amount of the active drug substance. In this connection it is important to note that even if the second fractions does not release any significant amount of the active substance within the first 20 min or 1 hours under acidic conditions, then the controlled release coating is not necessarily designed as an enteric coating, i.e. a coating which is insoluble at acidic pH and soluble at neutral/basic pH. The compositions according to the invention exemplified in the experimental section are examples on compositions wherein the controlled release coating of the second fractions is not an enteric coating. Furthermore, application of an enteric coating on e.g. pellets would not lead to an extended release of

an active drug substance. The release will of course be delayed (no release under acidic conditions) but as the pH becomes neutral and alkaline, then the enteric coating dissolves, i.e. there is no membrane left to control the release.

Notably, the release of the active drug substance from the first fraction is at least 55% w/w such as, e.g., at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w or at least about 80% w/w of the total NSAID substance present in the first fraction within the first 20 min of the test, i.e. the dissolution method II (pH corresponding to 0.07 N HCl) as defined in the experimental section.

In one embodiment the composition may comprise modified release multiple units wherein the *in vitro* dissolution characteristics of the first fraction of quick release multiple-units within 0.5 hour provides a release as defined by the dissolution methods II as described herein of at least about 50% w/w, at least about 60% w/w, at least about 70% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w calculated on the total amount of active drug substance contained in the first fraction.

In addition, the composition may comprise modified release multiple units wherein the *in vitro* dissolution characteristics of the first fraction of quick release multiple units within 1 hour provides a release as defined by the dissolution methods II described herein of at least about 50% w/w, such as, e.g., at least about 60% w/w, at least about 70% w/w, at least about 80% w/w, at least about 85%, at least about 90% w/w or at least about 95% w/w calculated on the total amount of active drug substance in the first fraction.

As apparent from the discussion above, the overall release characteristics with respect to release of the active drug substance from the final composition are composed of the release characteristics of the first and the second fraction of multiple-units, respectively. With regard to compositions containing an NSAID substance intended for administration once or twice daily, the present inventors have found that the release characteristics of the second fractions most suitably should have the following order of magnitude provided that the release characteristics of the first fraction are as discussed above.

Accordingly, the *in vitro* dissolution characteristics of the second fraction of extended release multiple units may in one embodiment within 1 hour provide a release as defined by the dissolution method III described herein in the range of 0%- about 30% w/w, such as, e.g., in the range of 0%- about 20% w/w, in the range of 0%-about 10%w/w such as about 5% w/w calculated on the total amount of active drug substance in the second fraction.

Furthermore, the *in vitro* dissolution characteristics of the second fraction of extended release multiple units may within 3 hours provide a release as defined by the dissolution method III described herein in the range of about 10%-70% w/w, such as, e.g., in the range of about 10%-60% w/w, in the range of about 12%-50% w/w, in the range of 14%-45% w/w, in the range of about 15%-30% w/w, in the range of about 15%-20% w/w such as, e.g., about 17% w/w of the NSAID substance.

Within 6 hours, the *in vitro* dissolution characteristics of the second fraction of extended release multiple units may provide a release as defined by the dissolution method III described herein in the range of about 35%-95% w/w, such as, e.g., in the range of about 50%-90% w/w, in the range of about 50%-80% w/w, in the range of 50%-75% w/w, in the range of about 50%-60% w/w, in the range of about 53%-59% w/w such as, e.g. about 56% w/w of the NSAID substance.

In addition, within 9 hours the *in vitro* dissolution characteristics of the second fraction of extended release multiple units may provide a release as defined by the dissolution method III described herein in the range of about 50%-100% w/w, such as, e.g., in the range of about 60%-98% w/w, in the range of about 65%-95% w/w, in the range of about 70%-90% w/w, in the range of about 70%-80% w/w such as, e.g., about 76% w/w of the NSAID substance.

To ensure that the final composition has a proper constitution with respect to the weight amount of first fraction relative to the amount of second fraction, the *in vitro* dissolution characteristics of the first and second fractions are in one embodiment adapted so that the first fraction is substantially released when the release from the second fraction is initiated, corresponding to at least 50% w/w release of the first fraction at the time at the most about 15% w/w such as, e.g., at the most about 10% or at the most about 5% w/w of the second fraction is released, as measured by

the dissolution method III described herein. In addition, the *in vitro* dissolution characteristics of the first and second fractions in the same or a second embodiment as mentioned above are adapted so that the first fraction is substantially released when the release from the second fraction is initiated, corresponding to at least 70% w/w release of the first fraction at the time at the most about 20% w/w such as, e.g., at the most 15% w/w or at the most about 10% w/w of the second fraction is released, as measured by the dissolution method III described herein.

Apart from the requirements to the individual fractions contained in the composition it is of course of utmost importance to ensure that the composition in its final form has *in vitro* dissolution characteristics which give evidence for a suitable *in vivo* behaviour, i.e. a fast onset of the effect together with an extended release of the active drug substance to ensure a therapeutic and/or prophylactic effect upon administration once or twice daily.

The two fractions of multiple units may be selected, with respect to the release from each fraction and the ratio between the two fractions, so that the *in vitro* dissolution characteristics of the composition within 1 hour provide a release of the NSAID substance in the first and second fractions in the range of from about 5% w/w to about 50% w/w, such as, e.g., in the range of from about 5% w/w to about 45% w/w, in the range of from about 15% w/w to about 40% w/w, in the range of from about 20% w/w to about 35% w/w such as about 29% w/w, as defined by the dissolution method III described herein.

In addition, the two fractions of multiple units may be selected, with respect to the release from each fraction and the ratio between the two fractions, so that the *in vitro* dissolution characteristics of the composition within 3 hours provide a release as defined by the dissolution method III described herein in the range of from about 20% w/w to about 80% w/w, such as, e.g., in the range of from about 25% w/w to about 70% w/w, the range of from about 30% w/w to about 60% w/w, in the range of from 35% w/w to about 55% w/w such as about 42% w/w.

In an additional aspect, the two fractions of multiple units may be selected, with respect to the release from each fraction and the ratio between the two fractions, so that the *in vitro* dissolution characteristics of the composition within 6 hours provide a release as

defined by the dissolution method III described herein in the range of from about 40% w/w to about 98% w/w, such as, e.g., in the range of from about 50% w/w to about 95% w/w, in the range of from about 60% w/w to about 90% w/w, in the range of from about 60% w/w to about 85% w/w, in the range of from about 60% to about 83% such as about 69-70% w/w.

Furthermore, the two fractions of multiple units may be selected, with respect to the release from each fraction and the ratio between the two fractions, so that the *in vitro* dissolution characteristics of the composition within 9 hours provide a release as defined by the dissolution method III described herein in the range of from about 50% w/w to about 100% w/w, such as, e.g., in the range of from about 60% w/w to about 99% w/w, in the range of from about 70% w/w to about 98% w/w, in the range of from about 70% w/w to about 97% w/w, in the range of from about 75% w/w to about 96% w/w, such as in the range of from about 80% w/w to about 96%, such as about 80-85% w/w.

In a preferred embodiment, the composition fulfils the above criteria with respect to the dissolution characteristics of the composition in the full time span mentioned.

The percentage of NSAID substance in the first fraction is in the range of about 5%-50% w/w such as, e.g., in the range of about 10%-45% w/w, in the range of about 15%-45% w/w, in the range of about 20%-40% w/w, in the range of about 25%-40% w/w, in the range of about 25%-35% w/w such as, e.g., about 30% w/w, calculated on the total amount of NSAID substance in the composition.

The percentage of NSAID substance in the second fraction is in the range of about 30%-99% w/w such as, e.g. in the range of about 40%-98% w/w, in the range of about 45%-95% w/w, in the range of about 50%-95% w/w, in the range of about 55%-85% w/w, in the range of about 60%-80% w/w, in the range of about 60%-75% w/w, in the range of abut 65%-75% w/w such as, e.g., about 70% w/w, calculated on the total amount of NSAID substance in the composition.

In a preferred embodiment, the multiple units of the second and, when appropriate, the first fraction are coated, cross-sectionally substantially homogeneous pellets.

It is preferred that the multiple units of the first fraction result in a peak plasma concentration of the NSAID substance which is substantially the same as the peak concentration resulting from the second fraction. As the peak plasma concentration of the second fraction is adapted so that plasma concentration has a prolonged character due to the dissolution characteristics of the fraction described herein, the peak of this second fraction should preferably substantially represent the upper level of the therapeutic plasma concentration. In a preferred embodiment, the plasma concentration level is of such a size that no NSAID substance is in excess.

Since the total amount of NSAID substance contained in the first fraction is balanced compared to the total amount of NSAID substance in the composition, a peak plasma concentration of NSAID substance derived from the first fraction which is higher than the peak concentration resulting from the second fraction does not necessarily represent a substantial waste of the NSAID substance.

However, unless the patient suffers from heavy breakthrough symptoms wherein a higher plasma concentration than the plasma concentration for maintaining symptom alleviation often seems to be needed, the concentrations obtained from the first fraction should not exceed the peak from the second fraction.

Even in the circumstances wherein the peak of the first fraction is preferably higher than the peak from the second fraction, unsuitable high plasma concentrations (within the toxic level) derived from the first fraction may easily be avoided by adjusting the amount of active drug substance contained in the first fraction.

In another embodiment, e.g. in the circumstances wherein the patient is well treated by administration once or twice a day with a composition according to the invention, the first fraction may be adapted so that it results in a peak plasma concentration of the NSAID substance which is lower than the peak concentration resulting from the second fraction. This would not necessarily result in breakthrough symptoms as the NSAID substance remaining in the plasma from the previous dosage administered may contribute to maintaining the plasma concentration sufficiently high until the second fraction of the composition is released. In other cases, the daily dosage may be administered at a suitable time of the day when the patient has experienced less need for the NSAID, e.g. before bedtime.

Accordingly, an important aspect of the invention is an embodiment wherein the first fraction results in a therapeutically active plasma concentration of the NSAID substance until the delayed release of an NSAID substance from the second fraction of modified release multiple units contributes to the maintenance of a therapeutically active plasma concentration of the NSAID substance.

As discussed above, the multiple-units of the first fraction may be in the form of uncoated pellet cores, coated pellet cores, granules, a granulate or small plain tablets provided that the requirements with respect to release of active drug substance in 0.1 N HCl and under conditions as those described under dissolution method II herein are fulfilled. In those cases, where the first fraction is in the form of coated pellets, the time lag of the release from the second fraction relative to the first fraction may be obtained by a modified release coating of the second fraction which is present in a range of about 2%-80% such as, e.g., about 2%-70%, about 2-60%, about 3-50%, about 3-40%, about 4-30%, about 5-20% or about 2-5%, relative to the uncoated unit.

It is also preferred that the modified release coating of the fraction(s) is substantially water-insoluble, but water-diffusible and substantially pH-independent which will facilitate an absorption independent of the presence of food in the stomach.

Dosage

In general, the dosage of the active drug substance present in a composition according to the invention depends *inter alia* on the specific drug substance, the age and condition of the patient and of the disease to be treated.

Compositions according to the invention intended for once daily administration will generally contain a daily dose of the active drug substance whereas compositions according to the invention intended for twice daily administrations will generally contain half the daily dose of the active drug substance. However, the daily dose may be divided into several dosage forms.

In the following is listed the recommended daily doses for selected NSAID substances.

Aceclofenac: 200 mg

Diclofenac: 100 mg

Etodolac: 400 mg

Fenbufen: 900 mg

Fenoprofen: 1.5 g

Flurbiprofen: 200 mg

Ibuprofen: 1.6 g

Indometacin: 100 mg

Ketoprofen: 200 mg

Meloxicam: 15 mg

Nabumeton: 1 g

Naproxen: 750 mg

Piroxicam: 20 mg

Sulindac: 300 mg

Tenoxicam: 20 mg

Tiaprofenic acid: 600 mg

Tolfenamic acid: 400 mg

Tolmetin: 800 mg

The amount of an NSAID substance of the modified release multiple-units composition according to the invention may be selected so that is corresponds to about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 8 mg, 10 mg, 12 mg, 16 mg, 20 mg, 24 mg, 25 mg, 30 mg, 32 mg, 50 mg, 60 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1 g, 1.1 g, 1.2 g, 1.3 g or 1.6 g of NSAID substance which are dosages generally known in the art. However, the composition according to the invention preferably comprises an amount of an NSAID substance which is a daily therapeutically effective amount of the NSAID substance.

Generally, with conventional dosage forms such as plain tablets comprising an NSAID substance, it is not always possible to obtain identical release profiles when different dosages are administered together as the load of active ingredient may differ depending on the size of the tablet. The release profile for 100 mg given in a single dosage may thus differ from 100 mg given as 5 dosages comprising 20 mg each. Not even with the commercially available modified release dosage forms, a substantially identical release profile within the different dosages is always observed.

With a composition according to the present invention, it is now possible to administer different dosages with identical release profiles (cf. results reported in the experimental section). For example, if each modified release multiple-units composition according to the invention is prepared with the same type of multiple units of the first and second fractions and in the same ratios, each of the dosage forms may be administered together to obtain any desired total dosage without altering the overall release profile from the total dosage. Accordingly, reliable and predictable plasma concentrations during the complete time span between administration may be obtained independently of the total dosage.

Therefore, a further advantage of the composition according to the invention is that the composition may be produced in different series of dosage forms of e.g. 4 mg, 8 mg, 12 mg, 16 mg, 24 mg, 32 mg etc., each of the series having individual properties resulting from the design of modified release of the first and second fractions as well as from the ratio between the fractions. Any desired total dosage can then be selected from the relevant dosage forms within each of the series.

The preferred dosage form according to the invention is in the form of a capsule, tablet, sachet etc. The size of the dosage form is adapted to the amount of the NSAID substance of the composition.

The above suggested dosage amounts should not be regarded as a limitation of the scope of the invention as it is obvious for the skilled person that any desired amount of the NSAID substance may be applied and is only limited by the size of the composition and the type of the NSAID substance.

The overall goal of the present invention is to provide a composition in unit dosage form for the administration of a therapeutically effective amount of an NSAID substance once a day. However, as some patients may still need to, or prefer to, receive administration twice a day, the invention should not be limited to a once-a-day composition as long as each of the unit dosage forms fulfils the criteria with respect to the dissolution mentioned above.

In a further aspect, the invention relates to a process for the preparation of an oral pharmaceutical modified release composition, the process comprising incorporating into the unit dosage at least two fractions as follows:

a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically or prophylactically active plasma concentration within a relatively short period of time, and a second fraction of coated extended release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically active plasma concentration in order to enable dosing once or twice daily,

the formulation of the first and the second fractions, with respect to release therefrom and with respect to the ratio between the first and the second fraction in the unit dosage, being adapted so as to obtain:

a relative quick *in vitro* release of the NSAID substance from the first fraction of quick release multiple-units, as measured by the dissolution method II defined herein,

an extended *in vitro* release of the NSAID substance from the second fraction of extended release multiple-units relative to the *in vitro* release of the first fraction of the NSAID substance, as measured by the dissolution method III as defined herein, the quick release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least about 50% w/w release of the NSAID substance contained in the first fraction at the time when about 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III as defined herein.

Definitions of selected terms used herein

The term "modified release multiple-units composition" used in the present context is defined as the release of the drug differs from that of a traditional composition. The release rate is in other words controlled and it is possible to manipulate the release rate by means of e.g. changing the formulation parameters. The rate is often controlled in such a manner that the plasma concentration levels are maintained for the longest

possible period above the therapeutic (the therapeutically active) level, but below the toxic level. However, the term "modified" is not restricted to an extended or prolonged effect, the term "modified" may as well cover the situation where the release rate is manipulated in such a manner that a quicker release than normally expected is obtained. Thus, in the present context the terms "quick" , "fast" and "enhanced" release as well as "controlled", "delayed", "sustained", prolonged", "extended" and other synonyms well known to a person skilled in the art are covered by the term "modified".

The term modified release in the present context refers to a composition which can be coated or uncoated and prepared by using pharmaceutically acceptable excipients and/or specific procedures which separately or together are designed to modify the rate or the place at which the active ingredient or ingredients are released (Ph. Eur. 97).

The term "extended release" in the present context refers to a modified release composition of which the release of the active ingredient and its subsequent absorption are prolonged in comparison with a conventional non-modified form (Commision of the European Communities).

The terms "quick release", "fast release" or "enhanced release" in the present context refer to a modified release composition of which the release of the active ingredient and its subsequent absorption are fast. More specifically, the terms "quick release", "fast release" or "enhanced release" mean that for a composition – when subjected to a dissolution method II described herein – at least about 50% w/w of the active substance is dissolved within the first 20 min of the test.

The term "fraction" of multiple units in the present context refers to a part of the multiple units of a dosage unit. One fraction will generally differ from another fraction of multiple units of the dosage unit. Even though only two fractions have been defined, it is within the scope of the invention to have more than two fractions in one dosage unit. Accordingly, the dosage unit according to the invention comprises at least two fractions.

The term "dosage unit" in the present context refers to one single unit, e.g. a capsule, tablet, a sachet or any other relevant dosage form known within the art. A dosage unit

represents a plurality of individual units which in accordance with the general state of the art may be in the form of a capsule, a tablet, a sachet, etc.

The term "bioavailability" designates the rate and extent to which the drug is absorbed from the modified multiple-units composition.

In the present context the term "therapeutically active plasma concentration which enables dosing once or twice daily" includes the situation wherein the NSAID substance administered has been metabolised to active metabolites resulting in a therapeutic effect for the stated period. It also includes the situation wherein the NSAID substance administered is present in a periferal compartment resulting in a therapeutic effect for the stated period.

The terms "NSAIDs" or "NSAID substances" are used herein to designate a group of drugs that belongs to non-steroid anti-inflammatory drug substances and pharmaceutically acceptable salts, prodrugs and/or complexes thereof as well as mixtures thereof.

The therapeutic classes mentioned herein are in accordance with the ATC (Anatomical Therapeutic Chemical) classification system.

Active drug substances

In the following are given examples of active drug substances which may be incorporated in a composition according to the invention. A majority of the active drug substances mentioned are weak acids, i.e. substances which have a pK_a value below about 5.5 such as, e.g., in a range of from about 3.0 to about 5.5 or in a range of from about 4.0 to about 5.0. In this connection it can be mentioned that the pK_a value for lornoxicam is about 4.7, for naproxen about 4.2, for indometacin about 4.5 and for acetylsalicylic acid about 3.5. When such substances which have a pK_a value of between about 3.0 to about 5.5 is employed in the composition, the present inventors have found that the first fraction should be in the form of uncoated multiple-units as the coating or the manufacture of the units to a form suitable for application of a coating seem to have a retarding effect on the release rate of the active drug substance from the first fraction (see the experimental section). Moreover, active drug substances like

those mentioned above (i.e. weak acids having a pK_a value of at the most about 5.5 or about 5.0) generally have a poor solubility in media having a pH below the pK_a value; as an example the solubility of lornoxicam at a pH corresponding to 0.1 N HCl is less than about 1 mg/100 ml at room temperature and active drug substances like acetylsalicylic acid, indometacin and naproxen are regarded as substances which are practically insoluble in water and 0.1 N HCl at room temperature. From the discussion relating to solubility and availability of the active drug substance in order to get access to the circulatory system it is should be appreciated that the release (dissolution) of the active drug substance from the first fraction should be quick under acidic conditions, e.g., in 0.1 N HCl even if the active drug substance has a very low solubility in this medium. First fractions containing such active drug substances are generally not in the form of coated multiple-units in compositions according to the invention (cf. the discussion above).

However, when the active drug substance incorporated in a composition according to the invention has a pK_a value of at least about 5.0 such as at least about 5.5 the multiple-units of the invention may as well be in the form of coated multiple-units such as, e.g., coated pellet cores.

The first fraction is normally uncoated when the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at the most about 0.5% w/v such as, e.g. at the most about 0.1% w/v, at the most about 0.05% w/v, at the most about 0.03% w/v, at the most about 0.01% w/w, at the most about 0.007% w/v, at the most about 0.005% w/v, at the most about 0.003% w/v, at the most about 0.002% w/v or at the most about 0.001% w/v.

The first fraction may be coated when the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at least about 0.1% w/v such as e.g. at least about 0.5% w/v or at least about 1% w/v.

Relevant examples of NSAID substances suitable for use in compositions according to the invention are:

- aminoarylcarboxylic acid derivatives like e. g. enfenamic acid, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, morniflumate, niflumic acid, and tolfenamic acid,
- arylacetic acid derivatives like e.g. aceclofenac, acemetacin, amfenac, bromfenac, cimmetacin, diclofenac, etodolac, fentiazac, glucametacin, indomethacin, lonazolac, metiavinic acid, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, and zomepirac,
- arylcarboxylic acids like e.g. ketorolac and tinoridine,
- arylpropionic acid derivatives like e. g. alminoprofen, bermoprofen, carprofen, dexibuprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, ketoprofen, loxoprofen, naproxen, oxaprozin, pranoprofen, protizinic acid, and tiaprofenic acid,
- pyrazoles like e.g. epirizole,
- pyrazolones like e.g. benzpiperylon, mofebutazone, oxyphenbutazone, phenylbutazone, and ramifenazone,
- salicylic acid derivatives like e.g. acetaminosalol, acetylsalicylic acid, benorylate, eterisalate, fendosal, imidazole salicylate, lysine acetylsalicylate, morpholine salicylate, parsalmide, salamidacetic acid and salsalate,
- thiazinecarboxamides like a.o. ampiroxicam, droxicam, lornoxicam, meloxicam, piroxicam, and tenoxicam,
- others like bucillamine, bucolome, bumadizon, diferenpiramide, ditazol, emorfazone, nabumetone, nimesulide, proquazone and piroxicam (e.g. in the form of a betacyclodextrin complex).

From a market point especially the following NSAIDs are interesting: lornoxicam, diclofenac, nimesulide, ibuprofen, piroxicam, piroxicam (betacyclodextrin), naproxen, ketoprofen, tenoxicam, aceclofenac, indometacin, nabumetone, acemetacin, morniflumate, meloxicam, flurbiprofen, tiaprofenic acid, proglumetacin, mefenamic acid, fenbufen, etodolac, tolfenamic acid, sulindac, phenylbutazone, fenoprofen, tolmetin, acetylsalicylic acid, dexibuprofen and pharmaceutically acceptable salts, complexes and/or prodrugs and mixtures thereof.

Other relevant active drug substances are COX-2 (COX is an abbreviation for cyclooxygenase) inhibitors like e.g. celecosib and flosulide.

At present, the most preferred drug substance is lornoxicam and pharmaceutically acceptable salts, complexes and prodrugs thereof. Lornoxicam may be present in a composition according to the invention as the sole drug substance or in combination with other drug substances.

The modified release oral dosage form of the present invention preferably includes an NSAID substance as the therapeutically active ingredient in an amount corresponding to from 1 to about 1600 mg of by weight. Alternatively, the dosage form may contain molar equivalent amounts of pharmaceutically acceptable salts thereof. The dosage form contains an appropriate amount to provide a substantially equivalent therapeutic effect.

A composition according to the invention may contain a further active drug substance. Relevant substances in this context are e.g. antidepressants, opioids, prostaglandine analogs (e.g. misoprostol), glucocorticosteroids, cytostatics (e.g. methotrexate), H_2 receptor antagonists (e.g. cimetidine, ranitidine), proton pump inhibitors (e.g. pantoprazole, omeprazole, lansoprazole), antacids, acetaminophen (paracetamol), penicillamine, sulfasalazine and/or auranorfin.

The term "antidepressant" used in the present context includes tricyclic antidepressants as well as other antidepressants and mixtures thereof. Pharmaceutically acceptable salts and/or complexes of antidepressant are also within the definition of antidepressant. Thus, the term "antidepressant" is used here to designate a group of drugs that have, to varying degrees, antidepressive properties and/or suitable properties with respect to alleviation or treatment of neurogenic pain and/or phantom pain. In the present context the term "antidepressant" encompasses drug substances mainly from the therapeutic class NO6 or from the following drug classification: Psychoanaleptics excluding anti-obesity preparations; anti-depressants/thymoanaleptics including substances used in the treatment of endogenous and exogenous depression such as, e.g., imipramine, nortriptyline, amitriptyline, oxipramol and MAO-inhibiting substances; lithium; combinations of drugs with ataractics; psychostimulants including drugs which increase the psychic and physical performance and which have a fatigue depressing, stimulating effect such as, e.g., fentyllines, fencamfamine, methylphenidate, amphetamines;

pyscholeptic-psychoanaleptic combinations; nootropics [which are a class of psychoactive drugs which are claimed to have a selective action on integrative functions of the CNS. Their action is alleged to be particularly associated with intellectual function, learning and memory. Nootropics include preparations containing substances such as piracetam, pyritinol, pyrisuccideanol maleate, meclofenoxate, cyprodenate and their combinations with other substances, excluding those products with a vasodilatory action (see the therapeutic class C04A). Combinations with cardiac glycosides are classified in the therapeutic class C01A.]; and neurotonics and other miscellaneous products including products which are not classified above such as single or combination products containing bisibutiamin, deanol and derivatives, GABA, GABOB, N-acetyl asparaginic acid glutaminic acid and salts, kavain, phospholipid, succinodinitrate.

The presently most interesting drug substances belong to the tricyclic antidepressants. Relevant examples of antidepressants are: tricyclic antidepressants such as, e.g. dibenzazepine derivatives like carpipramine, clomipramine, desipramine, imipramine, imipraminoxide, imipramine pamoate, lofepramine, metapramine, opipramol, quinupramine, trimipramine; dibenzocycloheptene derivatives like amitriptyline, amitriptyline and chlordiazepoxide, amitriptyline and medazepram, amitriptyline and pridinol, amitriptyline and perphenazine, amitriptylinoxide, butriptyline, cyclobenzaprine, demexiptiline, nortriptyline, nortriptyline and diazepam, nortriptyline and perphenazine, nortriptyline and fluphenazine, nortriptyline and flupentixol, noxiptilin, protriptyline; dibenzoxepine derivatives like doxepin; and other tricyclic anti-depressants like adinazolam, amoxapine, dibenzepin, dimetacrine, dosulepin, dosulepin and diazepam, dothiepin, fluacizine (fluoracyzine, toracizin), iprindole, maprotiline, melitracen, melitracene and flupentixol, pizotyline, propizepine, and tianeptine; other antidepressants like 5-hydroxytryptophan, ademetionine, amfebutamone, amfebutamone hydrochloride, amineptine, amineptine hydrochloride, amisulpride, fluoxetine hydrochloride, fluoxetine, hypericin, lithium carbonate, sertraline hydrochloride, sertraline, St John's wort dry extract, trimipramine maleate, citalopram, citalopram hydrobromide, clomipramine chloride, clomipramine hydrochloride, d-phenylalanine, demexiptiline, demexiptiline hydrochloride, dimethacrine tartrate, dothiepin, dothiepin hydrochloride, doxepin, fluphenazine hydrochloride, fluvoxamine, fluvoxamine hydrogen maleate, fluvoxamine maleate, ginkgo biloba, indalpine, isocarboxazide, johanniskrauttrockenestrakt, 1-tryptophan, lithium citrate, lithium sulfate, lofepramine,

maprotiline, maprotiline hydrochloride, maprotiline mesilate, medifoxamine, metaprimine fumarate, mianserin, moclobemide, nitroxazepine hydrochloride, nomifensine, nomifensine maleate, nomifensin hydrogenmaleat, oxitriptan, paroxetine, paraoxetine hydrochloride, phenelzine, phenelzine sulfate, piracetam, pirlindole, pivagabine, prolintane hydrochloride, propizepine hydrochloride, protriptyline hydrochloride, quinupramine, remoxipride hydrochloride, rubidium chloride, setiptiline maleate, tianeptine sodium, trazodone hydrochloride, venlafaxine hydrochloride, maprotiline, toloxatone, tranylcypromine, trazodone, trazodone hydrochloride, viloxazine, viloxazine hydrochloride,zimelidine, zimelidine dihydrochloride.

At present, the most interesting drug substances for use in a composition according to the invention are amitriptyline and/or imipramine and pharmaceutically acceptable salts, complexes and prodrugs thereof. Amitriptyline and/or imipramine may be present in a composition according to the present invention either as the sole drug substance or in combination with other drug substances. Amitriptyline is a very interesting drug candidate with respect to preventing and/or treating neurogenic pains and phantom pains.

The term "opioid" is used here to designate a group of drugs that are, to varying degrees, opium- or morphine-like in their properties. The term includes natural and synthetic opioids as well as active metabolites such as morphine-6-glucuronide and morphine-3-glucuronide, and mixtures of opioids. Pharmaceutically acceptable salts and/or complexes of opioids are also within the definition of opioids.

Further relevant examples of opioids for use in compositions according to the invention include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocondone, hydromorphone, hydroxypethidine, isomethadone, dextropropoxyphene, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicormorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum,

pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, salts thereof, mixtures of any of the foregoing, mixed μ-agonists/ antagonists, μ- and/or κ-agonists, combinations of the above, and the like.

Within the scope of the invention is of course that more than one active drug substance may be present in a composition, e.g. more than one NSAID substance and/or drug substances within the same or different therapeutic classes. Specific relevant therapeutic classes are M01A (NSAIDs), RO5D, N02 (analgesics), N2A (opioids) and N2B (non-narcotic analgesics).

Dose

In one embodiment of the present invention, the first fraction of multiple units comprises an amount of an NSAID substance corresponding to from about 50% to about 5% (between 1/2 and 1/20) of the daily dosage. In patients which are satisfactorily treated on 2-3 daily dosages of a conventional non-sustained formulation, the first fraction may in one example contain an amount of the NSAID substance corresponding to 40% of the daily dosage. The second fraction may then contain the remaining 60% of the daily dosage.

However, a preferred amount of the first fraction may comprise 30% of the daily dosage and the second fraction 70% of the daily dosage.

In another embodiment of the present invention, the first fraction of multiple units comprises an amount of an NSAID substance corresponding to the amount of the NSAID substance necessary for obtaining a therapeutic effect upon a first single oral dose of a conventional non-sustained formulation of the NSAID substance.

Formulation details

First fraction

As described above, the formulation of the first fraction depends on the specific active drug substance to be incorporated. If the solubility at room temperature in 0.1 N HCl is

low and the pK_a value is below about 5.5. or 5.0, then the first fraction is in the form of uncoated multiple-units. A very suitable formulation of the first fraction has under such conditions been found to be in the form of a granulate wherein special means have been employed in order to ensure a quick release of the poor soluble active drug substance. The granulate is typically prepared by wet-granulation (a process well known for a person skilled in the art) employing as little organic solvent as possible in order to reduce any environmental and personal risk. Furthermore, the present inventors have found that incorporation of an antacid-like substance like, e.g., sodium bicarbonate (sodium hydrogencarbonate), magnesium carbonate, magnesium hydroxide, magnesium metasilicate aluminate and other alkaline substance, has a pronounced increasing effect on the release rate.

In one embodiment, the individual units of the relatively fast release fraction according to the invention will normally be a granulate having a size (average diameter) of at the most about 250 μm such as, e.g. at the most about 240 μm, at the most about 230 μm, at the most about 220 μm, at the most abut 210 μm, at the most about 200 μm, at the most about 190 μm, at the most about 180 μm, at the most about 175 μm, at the most about 150 μm, at the most about 125 μm, at the most about 100 μm, at the most about 90 μm or at the most about 80 μm.

As described above, the first fraction may also be in the form of coated multiple-units such as coated pellets provided that the pK_a of the active drug substance is at least about 5.0 or 5.5. From the experimental section *inter alia* it appears that such coated cores may have the same coating as the coating of the second fraction, but the thickness of the coating differs in such a manner that the coating of the first fraction is much thinner than that of the second fraction. For further details with respect to coating see below.

Second fraction

The individual units of the extended release fraction according to the invention will normally be pellets or beads having a size (average diameter) of from about 0.1 to 2 mm. The most preferred pellet size is from 0.5 to 0.8 mm. The pellets or beads comprise a combination of active substance, the NSAID substance and excipients.

When the pellets or beads are not coated, the combination of the active substance and the excipients is referred to as a core.

In the present context, the term "cores which are cross-sectionally substantially homogeneous" designates cores in which the active substance is not confined to an exterior layer on the core body, in other words normally cores which, through the cross-section of the core body, contain substantially the same type of composition comprising minor particles containing active substance, in contrast to the non-pareil type of cores which each consists of an excipient body with active substance applied to its surface. From this definition, it will be understood that the cores which are cross-sectionally substantially homogeneous will normally consist of a mixture of active substance with excipient(s), this mixture will not necessarily be qualitatively or quantitatively homogeneous through the total cross-sectional area of the core but may show, e.g., a concentration gradient of the NSAID substance or they may consist substantially solely of NSAID substance. In the following specification and claims, such cores which are cross-sectionally substantially homogeneous will, for the sake of brevity, often simply be designated "cores".

It is contemplated that the core comprising the NSAID substance in a substantially homogeneous form provides a more reproducible release of the active ingredient than compared to e.g. particles in which the active ingredient forms part of the coating.

It should, however, be understood that the invention is not limited to pellet formulation containing the above-mentioned cores; in principle, the type of cores can be any kind such as, e.g. matrices, non-pareil cores as well.

It is preferred that the release profile of the core of the individual unit is substantially non-limiting with respect to the desired release of the coated pellet, e.g. that the core itself provides at least about 90% w/w such as, e.g., at least about 95% w/w, at least about 97% w/w, at least about 98% such as about 100% release within 1 hour, measured in the *in vitro* dissolution test described in the Examples. However, pellet cores showing a slower release of the active substance are still within the scope of the invention.

Dosage forms

The oral pharmaceutical modified release multiple-units formulation according to the invention will typically be a capsule containing a multiplicity of the units, typically more than 100, a sachet containing a multiplicity of the units, typically more than 1000, or a tablet made from a multiplicity of the units, typically more than 100, in such a manner that the tablet will disintegrate substantially immediately upon ingestion in the stomach into a multiplicity of individual units which are distributed freely throughout the gastro-intestinal tract.

In the present context the term "once daily"/"once-a-day" is intended to mean that it is only necessary to administer the pharmaceutical formulation once a day in order to obtain a suitable therapeutic and/or prophylactic response; however, any administration may comprise co-administration of more than one dosage unit, such as, e.g., 2-4 dosage units if the amount of active substance required may not be formulated in only one composition unit or if a composition unit of a minor size is preferred.

In agreement with the above-mentioned definition of "once daily"/"once-a-day", "twice daily"/"twice-a-day" is supposed to mean that it is only necessary to administer the pharmaceutical formulation at the most twice a day in order to obtain a suitable therapeutic and/or prophylactic response in the patient.

Irrespective of the above-mentioned definitions of "once" and "twice" daily, a dosage unit constructed to deliver the active ingredient after only one daily administration is preferred. However, due to individual circumstances some patients may need a new dosage after e.g. 12 or 18 hours if the patient e.g. has an abnormal absorption or bowel transit time. If the individual has a relatively fast bowel transit time, some of the active ingredient may be excreted before the full dosage is released, or may be released in the colon from which the absorption may be decreased.

A multiple unit pharmaceutical composition according to the present invention is preferably formed as a unit dosage form which upon oral administration disintegrates into a multiplicity of individual units. The dosage unit form is preferably a solid dosage unit form such as, e.g., a tablet, a capsule, or a sachet, especially in the form of capsules.

The actual load of the NSAID substance in a pharmaceutical composition according to the invention, i.e. the concentration in % w/w of the NSAID substance calculated on the total weight of the multiple units, may depend on the particular NSAID substance employed in the formulation. The formulation principle employed in the present invention is very flexible. As an example it can be mentioned that compositions can be designed so that the load of the NSAID substance in the individual multiple units of the two fractions and the content of the two fractions for one dosage unit comprising e.g. 10 mg of NSAID substance is identical with another dosage unit comprising e.g. 100 mg, the release profile for each of the dosages will be identical. Consequently, an individual total dosage can be administered to the patient by combining the relevant dosage units e.g. selected from a series of 4, 8, 12, 16, 24 and 32 mg of the NSAID substance without altering the overall release profile of the total amount of the NSAID substance administered.

The compositions mentioned above may be prepared by conventional methods known in the art. The invention also relates to a method for preparing an oral pharmaceutical modified release multiple-units composition.

Coating

In a further embodiment, the invention relates to a method for preparing an oral pharmaceutical modified release multiple-units formulation in which

a) individual units containing an active substance are coated with an inner film-coating mixture ("the inner coat") comprising a film-forming substance,
b) the thus coated units are optionally provided with a first outer film layer comprising e.g. a stabilizing agent ("the middle coat"),
c) the thus coated units of the second fraction are optionally provided with a second outer film layer comprising a film-forming agent ("the outer coat"),
d) a mixture of individual units of the first and second fraction are formulated in a dosage form in the desired ratio of the two fractions.

In general, the inner coating is applied in an amount corrsponding to 2-20% w/w. The middle coating, if present, is applied in an amount corresponding to about 4% w/w of

the uncoated units and the outer coat is applied in an amount corresponding to about 1-2% w/w of the uncoated units.

The film-forming agent of step c) may be so selected that adhesion between the units is prevented at elevated temperatures, the coated units are then subsequently heated to a temperature above 40 °C, preferably not above 65-75 °C, and thereby a continuous phase is formed in the inner film layer in homogeneous admixture with the film-forming substance. In some cases, this curing process may also take place before the outer coating layer may be applied.

The modified release coating is applied on the multiple units from a solution and/or suspension preferably in an aqueous solvent, but an organic coating composition may also be applied.

Examples of film-forming agents which are suitable for use in accordance with the present invention are agents selected from the group consisting of cellulose derivatives such as, e.g., ethylcellulose, cellulose acetate, cellulose propionate, cellulose butyrate, cellulose valerate, cellulose acetate propionate; acrylic polymers such as, e.g., polymethyl methacrylate; vinyl polymers such as, e.g., polyvinyl acetate, polyvinyl formal, polyvinyl butyryl, vinyl chloride-vinyl acetate copolymer, ethylene-vinyl acetate copolymer, vinyl chloride-propylene-vinyl acetate copolymer; silicon polymers such as, e.g., ladder polymer of sesquiphenyl siloxane, and colloidal silica; polycarbonate; polystyrene; polyester; coumarone-indene polymer; polybutadiene; and other high molecular synthetic polymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In one preferred embodiment, the acrylic coating is an acrylic resin lacquer used in the form of an aqueous dispersion, such as that which is commercially available from Rohm Pharma under the tradename Eudragit®. In further preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the tradenames Eudragit® RL 30 D and Eudragit® RS 30 D, re-

spectively. Eudragit® RL 30 D and Eudragit® RS 30 D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit® RL 30 D and 1:40 in Eudragit® RS 30 D. Eudragit® RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids. The Eudragit® RL/RS dispersions may be mixed together in any desired ratio in order to ultimately obtain a modified release formulation having a desirable dissolution profile. The most desirable modified release formulations may be obtained from a retardant coating based on Eudragit® NE 30D, which is a neutral resin having a molecular weight of 800,000.

The amount of coating applied is adapted so as to obtain a predetermined dissolution characteristic of the fraction of the composition. The percentage by weight of the modified release coating on the individual pellet will, for the fraction providing the extended duration of effect of the NSAID substance, be at the most about 20% w/w on an average, such as, e.g. about 15% w/w, about 12% w/w, preferably at the most about 10% w/w on an average, more preferred in the range of about 3% to 6 % w/w on an average, based on the weight of the uncoated individual pellet. The amount of coating applied depends on the predetermined dissolution characteristics of the particular core composition and the desired release profile of the fraction.

However, the amount of coating applied should also be adapted so that there will be no rupturing problems.

The coating may be admixed with various excipients such as plasticizers, anti-adhesives such as, e.g., colloidal silicium dioxide, inert fillers, and pigments in a manner known *per se*.

Tackiness of the water-dispersible film-forming substances may be overcome by simply incorporating an anti-adhesive in the coating. The anti-adhesive is preferably a finely divided, substantially insoluble, pharmaceutically acceptable non-wetting powder having anti-adhesive properties in the coating. Examples of anti-adhesives are metallic stearates such as magnesium stearate or calcium stearate, microcrystalline cellulose, or mineral substances such as calcite, substantially water-insoluble calcium phosphates or substantially water-insoluble calcium sulphates, colloidal silica, titanium dioxide, barium

sulphates, hydrogenated aluminium silicates, hydrous aluminium potassium silicates and talc. The preferred anti-adhesive is talc. The anti-adhesive or mixture of anti-adhesives is preferably incorporated in the coating in an amount of about 0.1-70% by weight, in particular about 1-60% by weight, and preferably about 8-50% by weight of the inner film layer. By selecting a small particle size of the talc, a larger surface area is obtained; the consequent higher anti-adhesive effect makes it possible to incorporate smaller amounts of specific anti-adhesives.

The individual modified release coated multiple-units may further comprise a middle coating between the "inner coat" and the "outer coat". Such coating may be adapted to stabilize the controlled release coated multiple-units and to prevent undesired changes of the release profile of each coated unit. Accordingly, the middle lacquer or coating may contribute to stability of the release profile of the dosage unit. Accordingly, the multiple units may further comprise an outer film layer.

In one aspect, the outer second layer comprises a water-based film-forming agent which prevents adhesion between the units at elevated temperatures and imparts flowability to the units, the water-based film-forming agent being anti-adhesive at temperatures above about 40 °C, especially temperatures above about 50 °C, such as a temperature between about 60 °C and about 120 °C, and being selected from diffusion coating materials such as ethylcellulose or enteric coating materials such as anionic poly(meth)acrylic acid esters, hydroxypropylmethylcellulosephthalate, cellulose-acetatephthalate, polyvinylacetatephthalate, polyvinylacetatephthalate-crotonic acid copolymerisates, or mixtures thereof, or water-soluble coating materials such as water-soluble cellulose derivatives, e.g. hydroxypropylcellulose, carboxymethylcellulose, methylcellulose, propylcellulose, hydroxyethylcellulose, carboxyethylcellulose, carboxymethylhydroxyethylcellulose, hydroxymethylcellulose, carboxymethylethylcellulose, methylhydroxypropylcellulose or hydroxypropylmethylcellulose.

Examples of plasticizers for use in accordance with the present invention include triacetin, acetylated monoglyceride, rape oil, olive oil, sesame oil, acetyl tributyl citrate, acetyl triethyl citrate, glycerin, sorbitol, diethyloxalate, diethylmalate, diethylmaleate, diethylfumarate, diethylsuccinate, diethylmalonate, dioctylphthalate, dibutylsebacetate, triethylcitrate, tributylcitrate, glyceroltributyrate, polyethyleneglycol, propyleneglycol,

1,2-propyleneglycol, dibutylsebacate, diethylsebacate and mixtures thereof. The plasticizer is normally incorporated in an amount of less than 10% by weight, calculated on the dry matter content of the coating composition.

Pharmaceutically acceptable excipients

Apart from the active drug substance in the multiple units, the pharmaceutical composition according to the invention may further comprise pharmaceutically acceptable excipients.

In the present context, the term "pharmaceutically acceptable excipient" is intended to denote any material which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se.* A pharmaceutically acceptable excipient may be added to the active drug substance with the purpose of making it possible to obtain a pharmaceutical formulation which has acceptable technical properties. Although a pharmaceutically acceptable excipient may have some influence on the release of the active drug substance, materials useful for obtaining modified release are not included in this definition.

Fillers/diluents/binders may be incorporated such as sucrose, sorbitol, mannitol, lactose (e.g., spray-dried lactose, α-lactose, β-lactose, Tablettose®, various grades of Pharmatose®, Microtose or Fast-Floc®), microcrystalline cellulose (e.g., various grades of Avicel®, such as Avicel® PH101, Avicel® PH102 or Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tai® and Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low-substituted) (e.g. L-HPC-CH31, L-HPC-LH11, LH 22, LH 21, LH 20, LH 32, LH 31, LH30), dextrins, maltodextrins (e.g. Lodex® 5 and Lodex® 10), starches or modified starches (including potato starch, maize starch and rice starch), sodium chloride, sodium phosphate, calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate), calcium sulfate, calcium carbonate. In pharmaceutical formulations according to the present invention, especially microcrystalline cellulose, L-hydroxypropylcellulose, dextrins, maltodextrins, starches and modified starches have proved to be well suited.

Disintegrants may be used such as cellulose derivatives, including microcrystalline cellulose, low-substituted hydroxypropyl cellulose (e.g. LH 22, LH 21, LH 20, LH 32, LH 31,

LH30); starches, including potato starch; croscarmellose sodium (i.e. cross-linked carboxymethylcellulose sodium salt; e.g. Ac-Di-Sol®); alginic acid or alginates; insoluble polyvinylpyrrolidone (e.g. Polyvidon® CL, Polyvidon® CL-M, Kollidon® CL, Polyplasdone® XL, Polyplasdone® XL-10); sodium carboxymethyl starch (e.g. Primogel® and Explotab®).

Surfactants may be employed such as nonionic (e.g., polysorbate 20, polysorbate 21, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85, polysorbate 120, sorbitane monoisostearate, sorbitanmonolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan sesquioleate, sorbitan tri oleate, glyceryl monooleate and polyvinylalkohol), anionic (e.g., docusate sodium and sodium lauryl sulphate) and cationic (e.g, benzalkonium chloride, benzethonium chloride and cetrimide) or mixtures thereof.

Other appropriate pharmaceutically acceptable excipients may include colorants, flavouring agents, and buffering agents.

In the following examples, the invention is further disclosed.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows a target plasma profile for lornoxicam together with a profile for plain tablets and solutions used to estimate the target profile,

figure 2 shows target *in vivo* dissolution profile for lornoxicam once daily and plain tablets,

figure 3 shows dissolution profiles of lornoxicam compositions containing 8 mg of lornoxicam; further details are given in Examples 14 and 15 herein,

figure 4 shows dissolution profiles of compositions according to Example 15,

figure 5 shows dissolution profiles of compositions according to Example 17.

MATERIALS AND METHODS

Materials employed in the compositions which were investigated in the course of development of the present invention were as given in the following. In those cases where reference is given to an official pharmacopoeia, the reference is to the current edition of the stated pharmacopoeia.

The following abbreviations are used:

Ph. Eur.:	European Pharmacopoeia
USP/NF:	United States Pharmacopoeia National Formulary
DLS:	Dansk Lægemiddelstandard

Materials	Quality	Manufacturer
Cellulosum microcristallinum (Avicel PH 101)	Ph.Eur.	FMC
Polysorbate 20	Ph.Eur.	Henkel
Lactose monohydrate	Ph.Eur.	DMV
Carmellose sodium (Blanose 7 LFD)	Ph.Eur.	Aqualon
Maltodextrin (Glucidex 2)	USPNF	Roquette
Pregelatinised Starch (Starch 1500)	USPNF	Colorcon
Hypromellose (Methocel E 5 Premium)	Ph. Eur.	Dow
Magnesii stearas	Ph.Eur.	Akcros Chemicals
Talcum	Ph.Eur.	Whittaker, Clark and Daniels
Eudragit NE 30 D	Ph.Eur.	Röhm Pharma GmbH
Croscarmellose sodium (Ac-Di-Sol)	Ph.Eur.	FMC
Dibasic Calcium Phosphate, Anhydrous (Calcium hydrogen phosphate, mean particle size approx. 30 µm)	USPNF	Kyowa
Sodium bicarbonate (sodium hydrogencarbonate, mean particle size approx. 120 µm)	USPNF	Kirsch
Hydroxypropylcellulose (HPC L fine)	Ph. Eur.	Nippon Soda
Low-substituted Hydroxy Propyl Cellulose (LH21)	USPNF	Shin-Etsu
Ethanol, 96 %	DLS	Danisco

Aqua Purificata	Ph. Eur.	
Naproxen	Ph. Eur.	Syntex Pharm.
Polyvidone 30	Ph. Eur.	BASF
Isopropanol	Ph. Eur.	Sveda Kemi

Whenever relevant, the mean particle size was determined by employment of a Malvern laser particle size analyser.

In the following five different dissolution methods I-V are described. In the table below is given an overview of the important differences between the five methods:

Dissolution method	Dissolution medium	
	pH	volume
I	7.4	900 ml
II	0.07 N HCl	900 ml
III	0.1 N HCl/7.3[a]	750 ml of medium 1 and 250 ml of medium 2
IV	0.1 N HCl/7.4[b]	750 ml of medium 1; after 1 hour this medium is changed to 900 ml of medium 2
V	7.3	1000 ml

[a] 750 ml 0.1 N HCl is employed in the first 1 hour of the test and then 250 ml of a medium 2 is added leading to a resulting pH of the dissolution medium of 7.3

[b] 750 ml 0.1 N HCl is employed in the first 1 hour of the test and is then replaced by 900 ml of a medium 2 having a pH of 7.4

The various dissolution methods have been employed to show that the method chosen for determining the dissolution profile of various compositions has an influence on the result obtained, i.e. different dissolution profiles are obtained when employing different dissolution methods.

The dissolution methods given below give details partly with respect to the test method and partly with respect to the analysis method. The following methods are directed to

compositions containing lornoxicam as an example of an NSAID substance; however, in the case of compositions containing other drug substances than lornoxicam the test methods and details with respect to procedure and preparation of reagents are the same apart from an adjustment of the analysis method and the drug substance included in the standard solutions to conditions which are suitable for the drug substance in question. A person skilled in the art will have no difficulties in selecting a suitable method of analysis for a specific drug substance.

DISSOLUTION METHOD I

pH 7.4 (lornoxicam)

Test method

Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

Dissolution medium: 900.0 ml dissolution medium pH 7.4

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring times: Every 5 minutes after the start of the test (details appear from the following examples)

Analysis method

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS – spectrophotometer, 1 cm cuvette

Preparation of reagents

Dissolution medium: An aqueous solution containing 10.1 mg/ml of sodium hydrogenphosphate dihydrate (Na_2HPO_4 $2H_2O$) and 1.6 mg/ml and sodium dihydrogenphosphate monohydrate (NaH_2PO_4 H_2O); the pH of the dissolution medium is 7.4.

Standards

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lornoxicam are prepared. Lornoxicam is dissolved in solvent for standards given below.

Standards: 20.00 ml of each of the stock solutions are added to the reference vessel (cf. below).
Solvent for standards:1.5% w/w aqueous sodium acetate solution : methanol (1:1 v/v)

Test procedure

900 ml of the dissolution medium are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C $\pm$ 0.5 °C. The product to be tested (e.g. a granulate, pellets, a final composition) is placed in the vessels, and the spindel is started. In the last vessel, 20.0 ml of each of the stock solutions are added. The absorbance of the samples and standards is measured at 378 nm with a zero setting towards the dissolution medium.

The percentage dissolved is measured over a suitable time interval.

DISSOLUTION METHOD II

0.07 HCl (lornoxicam)

Lornoxicam has a very low solubility in 0.1 N HCl *inter alia* in order to show that the relatively fast release fraction indeed releases lornoxicam at acidic pH (simulating the pH conditions in the stomach), dissolution method II is employed.

Test method

Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

Dissolution medium: 900.0 ml dissolution medium

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring time: Every 5 minutes after the start of the test (details appear from the following examples)

Analysis method

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS – spectrophotometer, 1 cm cuvette

Preparation of reagents

Dissolution medium: Weigh out 50.0 g of sodium chloride and measure out 141.6 ml of concentrated hydrochloric acid. Dissolve the chemical with distilled water and dilute to 25 l with distilled water.

Standards

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lornoxicam were prepared. Lornoxicam is dissolved in solvent for standards (cf. below).

Standards: 20.00 ml of each of the stock solutions is added to the reference vessel (cf. below).

Solvent for standards: 1.5% w/w aqueous sodium acetate solution : methanol (1:1 v/v)

Test procedure

900 ml of dissolution medium are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C ± 0.5 °C. The product to be tested (e.g. a granulate, pellets or a final composition) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindel is started, and the absorbance of the samples and standards is measured at 378 nm with zero setting towards the dissolution medium.

The percentage dissolved is measured over a suitable time interval.

DISSOLUTION METHOD III

0.1 N HCl / pH 7.3 (lornoxicam)

This dissolution method includes a change in pH to simulate the *in vivo* situation.

Test method

Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

Dissolution medium: 750 ml of dissolution medium 1, after 1 hour 250 ml of dissolution medium 2 are added

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring times: Every 5 minutes after the start of the test (details appear from the following examples)

Analysis method

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS – spectrophotometer, 1 cm cuvette

Preparation of reagents

Dissolution media

Dissolution medium 1: 0.1 N HCl

Dissolution medium 2: Weigh out 73,6 g trisodium phosphate, dodecahydrate (Na_3PO_4, $12H_2O$) and measure out 31,8 ml 0,1 N sodium hydroxide. Dissolve the chemicals in distilled water and dilute to 1000,0 ml with distilled water.

Standards

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lornoxicam were prepared. Lornoxicam is dissolved in solvent for standards (cf. below).

Standards: 20.00 ml of each of the stock solutions are added to the reference vessel (cf. below).

Solvent for standards:1.5% w/w aqeous sodium acetate solution : methanol (1:1 v/v)

Test procedure

750 ml of dissolution medium 1 are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C ± 0.5 °C. The product to be tested (e.g. a granulate, pellets or a final composition) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindel is started. After 1 hour 250 ml of dissolution medium 2 (37 C° ± 0.5 °C) are added.

The absorbance of the samples and standards is measured at 378 nm with zero setting towards the dissolution medium.

The percentage dissolved is measured over a suitable time interval.

DISSOLUTION METHOD IV

0.1 N HCl / pH 7.4 (lornoxicam)

This dissolution method includes a change in pH to simulate the *in vivo* situation. Furthermore, this dissolution method has been employed in experiments performed in order to clarify whether a pre-treatment of the product in 0.1 N hydrochloric acid has

any influence on the results obtained afterwards in a dissolution medium having a pH of 7.4.

Test method

Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

Dissolution medium: 750 ml of dissolution medium 1, after 1 hour the medium is changed to 900 ml of dissolution medium 2.

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring times: Every 5 minutes after the start of the test (details appear from the following examples)

Analysis method

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS – spectrophotometer, 1 cm cuvette

Preparation of reagents

Dissolution media:

Dissolution medium 1: 0.1 N HCl

Dissolution medium 2: Distilled water containing 10.1 mg/ml of sodium hydrogenphosphate dihydrate (Na_2HPO_4 $2H_2O$) and 1.6 mg/ml of sodium dihydrogenphosphate monohydrate (NaH_2PO_4 H_2O)

Standards

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 μg/ml lornoxicam were prepared. Lornoxicam is dissolved in solvent for standards (cf. below).

Standards: 20.00 ml of each of the stock solutions is added to the reference vessel (cf. below)

Solvent for standards: 1.5% w/w aqueous sodium acetate solution : methanol (1:1 v/v)

Test procedure

750 ml of dissolution medium 1 are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C $\pm$ 0.5 °C. The product to be tested (e.g. a granulate, pellets or a final composition) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindel is started. After 1 hour the medium is decanted carefully and the medium is discarded. To the remaining product in the vessel 900 ml of dissolution medium 2 (37 °C $\pm$ 0.5 °C) are added. The absorbance of the samples and standards is measured at 378 nm with zero setting towards the dissolution medium employed.

The percentage dissolved is measured over a suitable time interval.

DISSOLUTION METHOD V

pH 7.3 (lornoxicam)

This dissolution method was used to *inter alia* clarify the influence of pH and/or the specific dissolution medium on the release rate and also to clarify, if the results obtained at pH 7.3 - without any pre-treatment in 0.1 N hydrochloric acid – were different from those obtained with pre-treatment in 0.1 N hydrochloric acid.

The buffer capacity of the dissolution medium employed was investigated to ensure a sufficient capacity. pH in the medium was measured before a product was added and after the end of the test. Both measurements revealed the same pH value (7.28), i.e. the buffer capacity is sufficient.

Test method

Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

Dissolution medium: 750 ml of the dissolution medium 1 and 250 ml of dissolution medium 2, the resulting pH is 7.3

Number of revolutions: 50 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37 °C ± 0.5 °C

Measuring times: Every 5 minutes after the start of the test (details appear from the following examples)

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS – spectrophotometer, 1 cm cuvette

Preparation of reagents

Dissolution media:

Dissolution medium 1: 0.1 N HCl

Dissolution medium 2: Weigh out 73,6 g trisodium phosphate dodecahydrate (Na_3PO_4 $12H_2O$) and measure out 31,8 ml 0,1 N sodium hydroxide. Dissolve the chemicals in distilled water and dilute to 1000,0 ml with distilled water.

Standards

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lornoxicam were prepared. Lornoxicam is dissolved in solvent for standards (cf. below).

Standards: 20.00 ml of each of the stock solutions is added to the reference vessel (cf. below).

Solvent for standards: 1,5 % sodium acetate solution : methanol (1:1)

Test procedure

750 ml of the dissolution medium 1 and 250 ml of dissolution medium 2 are filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C $\pm$ 0.5 °C. The product to be tested (e.g. a granulate, pellets or a final composition) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindel is started. The absorbance of the samples and standards is measured at 378 nm with zero setting towards the dissolution medium.

The percentage dissolved is measured over a suitable time interval.

Calculation for all methods

Percentage dissolved was calculated with reference to an external standard in the reference vessel.

The concentration of the standard in the reference vessel is calculated by the formula below:

$$\text{mg lornoxicam per 1000 ml} = \left(\frac{q_1 \bullet 20}{V} + \frac{q_2 \bullet 20}{V}\right) \bullet \frac{1000}{940}$$

Where:

q_1	=	amount of standard weighed out for S_1 (mg)
q_2	=	amount of standard weighed out for S_2 (mg)
20	=	added volume of S_1 and S_2 to the reference vessel (ml)
V	=	dilution volume of the standard (ml)
940	=	volume in the reference vessel after addition of the standards (S_1 and S_2) to the vessel (ml)
1000	=	conversion factor to 1000 ml

The content of lornoxicam as percentage dissolved was calculated from the formula below:

$$\frac{abs_{sample} \bullet StA \bullet V \bullet 100}{abs_{StA}\, 1000 \bullet u} \bullet \frac{n}{100}$$

Where

abs_{sample}	=	absorbance measured in each vessel containing samples
StA	=	mg lornoxicam pr 1000 ml in the vessel containing standard
V	=	volume of the medium (ml)
100	=	factor converting to percent
abs_{StA}	=	absorbance measured in vessel containing the standard
u	=	declared content (mg)
n	=	potency of the standard (%)

100	=	factor converting to percent
1000	=	factor converting the concentration of the standard to mg/ml

The following examples are intended to illustrate specific embodiments of the present inventions but are not intended in any way to limit the invention.

EXAMPLES

The following Examples 1 – 8 relate to the preparation of various cores containing lornoxicam as an example of an NSAID substance. Example 9 relates to the preparation of a quick release granulate, Examples 10-17 illustrate *inter alia* the influence of the composition of the pellets or the coat on the release rate and Example 18 relates to an immediate release composition disclosed in EP-A-0 438 249.

EXAMPLE 1

Preparation of cores containing lornoxicam and coating of the cores with a CR coating

Batch Nos. 04029831 (uncoated pellet cores) and 05029833 (coated pellet cores) were prepared.

Lornoxicam pellet cores were prepared by manufacturing of pellet cores and subsequent coating with an inner and an outer coat.

The pellet cores were prepared by the use of an extrusion/spheronization technique.

The ingredients are listed in Table 1. The ingredients I and II were mixed in a beaker by stirring, wetted with 150 g water and then mixed to a homogenous mass. The ingredients III to VII were filled into a Moulinex laboratory size mixer and mixed for 5 min, whereafter the homogenous mass was added and mixed. The beaker was rinsed with the remaining water and added to the mixer.

Table 1

	Ingredients	Amount (g):
I	Lornoxicam	54
II	Polysorbate 20	54
III	Cellulose, microcrystalline	102
IV	Lactose	315
V	Carmellose sodium	3
VI	Maltodextrin	12
VII	Pregelatinized starch	60
VIII	Purified water	150 + 18

The resulting mass was extruded in a Nica E 140 extruder with a screen size of 0.6 mm. The extrudate was spheronized in a laboratory size spheronizer at a rotation speed of 700 rpm for 4 min. The pellet cores thus produced were dried in a laboratory size fluid bed dryer with an inlet temperature of approximately 40° C, and the drying process was continued until the outlet temperature has reached approximately 30° C. The total drying time was approximately 25 min.

The dried pellet cores were fractionated in a Retsch sieving apparatus with a lower screen of 0.5 mm and an upper screen of 0.8 mm.

The release of lornoxicam from the pellet cores obtained was determined by dissolution method I (pH 7.4) and is as follows:

Time	Release (%)
10 min.	52.1
1 h	97.6

Thus, the relase of lornoxicam from the uncoated pellets is rapid and is almost accomplished within about 1 hour.

100 g of these pellet cores were coated with an inner coat and an outer coat in a laboratory size bottom spray fluid bed coater with a spray pressure of 1 bar for both the

inner coat and the outer coat. The temperature of the coating process was maintained at an inlet temperature of approximately 35° C to 40° C.

The composition of the coating is shown in Table 2:

Table 2

Ingredient	Amount (g)
Inner coat	
Hypromellose (Methocel E prem)	3.25
Magnesium stearate	0.68
Talc	6.07
Eudragit NE 30 D	216
Purified water	274
Outer coat	
Hypromellose (Methocel E5 prem)	4.0
Talc	4.0
Purified water	96.0

In the coating process the following amount of inner and outer coat was applied. The amount of dry matter applied calculated in percentage of the pellet core weight also appears from the below:

Inner coat: 35.9 g coating solution (corresponding to a dry matter content of approximately 5.5% w/w of the pellet core weight)
Outer coat: 12.5 g coating solution (corresponding to a dry matter content of approximately 1% w/w of the pellet core weight)

After the application of the coatings, the coated pellet cores were cured at a bed temperature of approximately 70° C for 30 min, whereafter the coated pellet cores were cooled to a bed temperature below 35° C.

After the coating, the coated pellet cores are screened through a 1.2 mm screen. Oversized material is discarded.

EXAMPLE 2

Preparation of pellet cores according to the invention leaving out a surface active substance from the cores

Batch No. 09029831 (uncoated pellet cores) was prepared.

Lornoxicam pellet cores were prepared by using the ingredients listed in Table 3.

Table 3

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Cellulose,microcrystalline	54
III	Lactosemonohydrate	216
IV	Carmellosesodium	3
V	Purified water	84

The pellet cores were prepared by the use of the extrusion/spheronization technique as described in Example 1, wherein the ingredients I to IV were mixed for 5 min in a Moulinex laboratory size mixer, whereafter the ingredients V was added.

The release of lornoxicam from pellet cores was determined by dissolution method I (pH 7,4) and is as follows:

Time	Release (% w/w)
10 min	19.1
1 h	69.8

From the dissolution data given above it is seen that the release is not accomplished after 1 hour and compared with the result obtained with the uncoated pellet cores in Example 1 it seems as if the inclusion of a surface active agent like e.g. polysorbate 20 has a significant influence on the dissolution rate.

EXAMPLE 3

Preparation of pellet cores corresponding to the pellets in Example 1 but in a smaller batch size

Batch No. 09029832 (uncoated pellet cores) was prepared.

This Example is intended to illustrate any relevant variation which may turn up as a dependency of the batch size.

Lornoxicam pellet cores were prepared as described in Example 1 with the exception that in Example 3, the amounts of the ingredients listed in Table 4 were used.

Table 4

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Polysorbate 20	27
III	Cellulose, microcrystalline	51
IV	Lactose	157.5
V	Carmellose sodium	1.5
VI	Maltodextrin	6
VII	Pregelatinized starch	30
VIII	Purified water	60 + 15

The release of lornoxicam from these pellets cores was determined by dissolution method I (pH 7.4) and is as follows:

Time	Release (% w/w)
10 min	61.2
1 h	98.0

Thus, the pellet cores prepared have the same dissolution behaviour as the pellet cores prepared in Example 1, i.e. the batch size seems to be without any significant influence on the release rate.

EXAMPLE 4

Preparation of coated pellet cores having a thinner inner coating than the coated pellet cores of Example 1

Batches Nos. 11029831 (uncoated pellet cores) and 20029832 (coated pellet cores) were prepared.

Lornoxicam pellet cores were prepared as described in Example 1 with the exception that in Example 4, the amounts of the ingredients listed in Table 5 were used.

Table 5

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Polysorbate 20	27
III	Cellulose, microcrystalline	51
IV	Lactose	157.5
V	Carmellose sodium	1.5
VI	Maltodextrin	6
VII	Pregelatinized starch	30
VIII	Purified water	51 + 15

The release of lornoxicam from these pellets cores was determined by dissolution method I (pH 7.4) and is as follows:

Time	Release (% w/w)
10 min	63.8
1h	100.7

Accordingly, the release of lornoxicam from the pellet cores is accomplished within 1 hour.

The pellet cores were coated as described in Example 1 with the exception that in Example 4, 100 g pellet cores were coated with an amount of inner and outer coat as follows:

Inner coat: 20.0 g coating solution (corresponding to a dry matter content of approximately 3% w/w of the pellet core weight).
Outer coat: 12.5 g coating solution (corresponding to a dry matter content of approximately 1% w/w of the pellet core weight).

As appears from the above, the amount of dry matter of the inner coat is smaller than in Example 1, whereas the amount of dry matter of the outer coat is the same as in Example 1. Accordingly, it is expected that the release of lornoxicam from the coated pellets of Example 4 is faster than that of lornoxicam from the coated pellets of Example 1.

EXAMPLE 5

Preparation of pellet cores corresponding to those of Example 3 with the exception that the surface active agent is replaced by lactose

Batch No. 11029834 (uncoated pellet cores) was prepared.

Lornoxicam pellet cores were prepared as described in Example 2 with the exception that in Example 5, the ingredients listed in Table 6 were used. Compared with the above Example 3 it is seen that the composition of pellet cores of Example 5 is very similar to those of Example 3, the only differences are that in the pellet cores of Example 3 a

surface active agent (polysorbate 20) is included and the amount of water employed differs a little.

Table 6

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Cellulose, microcrystalline	51
III	Lactose	184.5
IV	Carmellose sodium	1.5
V	Maltodextrin	6.0
VI	Pregelatinized starch	30.0
VII	Purified water	84.0

The release of lornoxicam from these pellets cores were determined by dissolution method I (pH 7.4) and is as follows:

Time	Release (% w/w)
10 min	20.5
1h	62.4

In conclusion the same pattern is observed as in Example 2, namely that the exclusion of a surface active agent has a decreasing effect on the release rate of lornoxicam from the pellet cores.

EXAMPLE 6

Preparation of pellet cores having a content of a disintegrant

Batch No. 19029834 (uncoated pellet cores) was prepared.

Lornoxicam pellet cores were prepared by using the extrusion/spheronization technique as described in Example 1. However, the ingredients used in Example 6 are listed in Table 7:

Table 7

	Ingredients	Amount (g)
I	Lornoxicam	27
II	Polysorbate 20	27
III	Cellulose, microcrystalline	51
IV	Lactose	142.5
V	Carmellose sodium	1.5
VI	Maltodextrin	6
VII	Pregelatinized starch	30
VIII	Croscarmellose sodium	15
IX	Purified water	51 + 15 + 15

The ingredients I and II were mixed in a beaker, wetted with 51 g water and then mixed to a homogeneous mass. The ingredients III to VIII were added to a Moulinex laboratory size mixer and mixed for 5 min, whereto the homogeneous mass was added and mixed. The beaker was rinsed with 2 x 15 g water and added to the mixer.

The extrudation and spheronizing procedure were performed as described in Example 1.

The release of lornoxicam from the pellet cores was determined by dissolution method II (0.07 N HCl) and is as follows:

Time	Release (% w/w)
1h	5.7

Thus, only a very small amount of the lornoxicam present in the pellets is released at a pH corresponding to that of 0.07 N HCl. The inclusion of an disintegrant such as, e.g., croscarmellose sodium does not seem to have any increasing effect on the release rate of lornoxicam from the pellet cores. Furthermore, uncoated cores containing lornoxicam do not seem to be a suitable choice in order to obtain a relatively fast release of lornoxicam at low pH like the conditions in the stomach.

EXAMPLE 7

Preparation of pellet cores – modification of the composition of the pellets in order to influence the release rate of lornoxicam

Batch No. 19029836 (uncoated pellet cores) was prepared.

Lornoxicam pellet cores were prepared. The ingredients used are listed in Table 8.

Table 8

	Ingredients	Amount (g)
I	Lornoxicam	7.5
II	Sodium bicarbonate	37.7
III	Cellulose, microcrystalline	90.4
IV	Dibasic Calcium Phosphate, Anhydrous	104.1
V	Low-substituted Hydroxypropyl Cellulose	45.3
VI	Hydroxypropylcellulose	15
VII	Purified water	115.8
VIII	Ethanol 99.9 %	38.7

The ingredients II to IV were mixed in a Moulinex laboratory size mixer and mixed for 5 min. To 100 g of this mixture ingredient I was added and mixed in a cubus mixer for 5 min. The resulting mass was screened through a 0.5 mm screen and returned to the Moulinex mixer and mixed for further 6 min. A premixed mixture of ingredient VII and VIII was added to the powder mixture and massed for 6 min.

The resulting mass was then extruded and spheronized according to the method described in Example 1.

The release of lornoxicam from the pellet cores was determined by dissolution method II (0.07 N HCl) and is as follows:

Time	Release (% w/w)
After 1h	37.8

The release of lornoxicam from the pellets is significantly increased compared with the pellets of Example 6, but still not quite satisfactory.

EXAMPLE 8

Preparation of pellets coated with a coating having varying amounts of a hydroxypropylmethylcellulose (HPMC)

Batch No. 23029833 (uncoated pellets) was prepared

Lornoxicam pellet cores were prepared as described in Example 4 and with the same composition.

The release of lornoxicam from the pellet cores was determined by dissolution method III (0.1 N HCl followed by pH 7.3) for 3 hours (i.e. 1 hour at a pH corresponding to the pH of 0.1 N HCl and 2 hours at pH 7.3) and is as follows:

Time	Release (% w/w)
10 min	36.9
1h	37.2
1 + 1 h:	86.4
1 + 2h:	95.7

Thus. the release in 0.1 N HCl is not very high (most of the lornoxicam which releases in 0.1 N HCl is released within the first 10 min) and the release rate is certainly not fast enough to anticipate that lornoxicam is released *in vivo* sufficiently fast to lead to a therapeutic effect.

In the following, two different batches of coated pellets of 100 g each were prepared.

Batch 1 (Batch No. 24029832 – coated pellet cores) :

100 g pellet cores were coated according to the procedure described in Example 1. The composition of the coating is as follows:

Ingredients	Amount (g)
Inner coat	
Hypromellose (Methocel E5 prem)	11.3
Magnesium stearate	0.6
Talc	5.4
Eudragit NE 30 D	191.7
Purified water	291
Outer coat	
Hypromellose (method E% prem)	4.0
Talc	4.0
Purified water	96.0

The following amount of inner and outer coat was used:

Inner coat: 20.1 g coating solution (corresponding to a dry matter content of approximately 3% w/w of the pellet core weight; the HPMC content corresponds to 15.1% w/w).
Outer coat: 12.5 g coating solution (corresponding to a dry matter content of approximately 1% w/w of the pellet core weight).

Batch 2 (Batch No.. 26029832 – coated pellet cores):

100 g pellet cores were coated as described in Example 1. The composition of the coating is as follows:

Ingredients	Amount (g)
Inner coat	
Hypromelose (Methocel E5 prem.)	3.74
Magnesium stearate	0.17
Talc	1.48

Eudragit NE 30 D	31.9
Purified water	62.7

Outer coat

Hypromellose (method E% prem)	4.0
Talc	4.0
Purified water	96.0

The following amount of inner and outer coat was used:

Inner coat: 20.1 g coating solution (corresponding to a dry matter content of approximately 3% w/w of the pellet core weight; the HPMC content corresponds to 25% w/w).

Outer coat: 12.5 g coating solution (corresponding to a dry matter content of approximately 1% w/w of the pellet core weight).

EXAMPLE 9

Preparation of a quick release granulate containing lornoxicam

Batch No. 972510 (granulate) was prepared.

A granulate containing lornoxicam were prepared by using the ingredients listed in Table 9. The composition of the granulate is essentially the same as that of the pellet cores of Example 7. The granulate was prepared in order to investigate whether it is possible to achieve a faster release of lornoxicam from a granulate than from pellet cores. From the results given below it is seen that the step of preparing pellets from a particulate composition containing lornoxicam has a dramatically decrease on the release rate of lornoxicam from the composition.

Table 9

	Ingredients	Amount (kg)
I	Lornoxicam	2.00
II	Sodium hydrogencarbonate	10.00
III	Cellulose microcristalline	24.00
IV	Calcium hydrogen phosphate anhydrous	27.60
V	Hydroxy Propyl Cellulose	4.00
VI	Low-Substituted Hydroxy Propyl Cellulose	12.00
VII	Purified water	27.00
VIII	Ethanol 96 %	9.00
IX	Calcium stearate	0.40

Ingredients II, III IV, V and VI were added to a Diosna intensive mixer and mixed for 1 min with the impeller speed I and chopper speed I. Out of this mixture, 10 kg was added the ingredient I by sieving through a Quadro Comil U20 with the sieve 062R in the following way: A part of the 10 kg mixture was sieved followed by ingredient I, whereafter the remaining of the 10 kg mixture was sieved. Ingredient I was not added to the mixture and mixed in the Diosna mixer for approximately 1 min.

A mixture of ingredient VII and VIII was added to the Diosna mixer, whereafter the granulation was started for 6 min with impeller speed I and with no use of the chopper.

After the granulation, the granulate was dried in a fluid bed until the outlet temperature had reached approximately 50°C and water content was below 1.0%, determined as LOD (Loss on Drying) when a sample of approximately 10 g was heated to a temperature of 70°C in 30 min. The granulate was sieved through a 0.71 sieve using a Frewitt siever. Oversized material was discarded.

Ingredient IX was sieved in the Quadro Comil with a sieve 062R and an equal amount of the granulate described above was added and mixed. This mixture was mixed with the remaining of the granulate in the Diosna mixer for 25 sec with an impeller speed of I and without using the chopper.

This mixture was compressed into a 9,5 mm concave tablets with a hardness of 80 to 100 N (the compression of the granulate was performed in order to avoid any of the problems which could arise during dissolution testing of a granulate and which are related to such bad wetting properties of a granulate that the granulate would float on the top of the dissolution medium giving rise to a *in vitro* unsatisfactory release of lornoxicam. However, later results have shown that granulates prepared in accordance with the above have suitable wetting properties, i.e. the final step of compression before dissolution testing is not necessary.

The dissolution of tablet cores was determined by the dissolution method II (0.07 N HCl) and is as follows:

Time	Release (% w/w)
20 min	100.6

The disintegration time of the tablets tested was at the most about 5 min. Thus, the dissolution rate of the granulate is expected to be of the same or quicker order of magnitude.

The release data given above are most surprising and give evidence that a fast release fraction containing a drug substance which is almost insoluble under acidic conditions can only be obtained if the composition is designed to a very fast release. In other words, application of traditionally prepared granulates and/or compositions made from such traditional granulates or particulate formulations do not seem to release the drug substance sufficiently fast under acidic conditions as those prevailing in the stomach. Accordingly, such traditional compositions are expected to release only a minor amount of the drug substance in the stomach and to release the remaining amount of lornoxicam in the intestines, i.e. after the composition reaches the intestines 1-3 hours after intake.

Compared with the dissolution data given in Example 7 a dramatically increase in dissolution rate is observed for the granulate compared with the pellet cores. Thus, in order to achieve a very fast release of lornoxicam from a composition it seems as if the fast fraction advantageously may be constituted by a granulate rather than uncoated pellet cores or film-coated pellet cores.

Conclusion with respect to Examples 1-9

In the preceding examples it has been shown that pellets cores cannot release lornoxicam very quickly at pH 7,4 unless a surfactant is added (Examples 2 and 5), even though lornoxicam is soluble at pH 7,4. When a surfactant, e.g. polysorbate 20, was added the release at pH 7,4 was acceptable from the point of view that the core can enter an once daily formulations without significantly controlling the dissolution rate (Examples 1, 3 and 4). This control should ideally be taken care of by the applied lacquer.

When these pellet cores were analyzed with respect to dissolution behaviour under acidic conditions in which lornoxicam is only slightly soluble a satisfactory release was not obtained even if a surfactant was used (Examples 6 and 8). Therefore, another kind of subunits have to be used for the relatively fast releasing fraction. Subunits in the form of a granulate and with the composition as described in Example 9 seem to give a satisfactory fast release. However, subunits with the same formulation as in Example 9, but in the form of pellet cores, will not give a satisfactory release rate in acidic conditions as shown in Example 7.

EXAMPLE 10

Preparation of a composition containing a mixture of uncoated and coated pellet cores

The following example illustrate the dissolution behaviour of a composition containing a mixture of uncoated and coated pellet cores. The uncoated pellets are intended to simulate a fast release fraction and the coated pellets are intended to simulate a delayed release fraction.

Coated pellets obtained according to Example 1 were mixed with pellet cores obtained according to Example 4 and the final composition contained 40% of uncoated pellet cores and 60% coated pellets (the percentage is given as % w/w of the total dose of lornoxicam in the composition, i.e. the uncoated fraction accounts for 40% w/w of the total content of lornoxicam whereas the coated fraction accounts for 60% w/w of the

total content of lornoxicam. A unit dosage form of the composition contains 8 mg of lornoxicam.

The dissolution test was carried out according to dissolution method III. The following dissolution data were obtained:

Time (h)	11029831 (uncoated fraction) + 05029833 (coated fraction) (5.5/4.3)[a] Release (% w/w)
0	0
0.5	1.4
1	2.9
2	38.4
3	46.1
4	49.6
5	53.5
6	55.9
7	59
8	61.4
9	64.6
10	67.2
11	69.2
13	74
14	75.6
15	77.9
16	79.3
17	80.7
18	82.5
19	83.6
20	85.3
21	86.4
22	87
23	88.1
24	89

[a] (5.5/4.3) relates to the fact that the content of dry matter in the coat is 5.5% w/w and the HPML content is 4.3% w/w.

From the data given above it is seen that only 2.9% w/w lornoxicam is released after 1 hour. Thus, the "fast release fraction", i.e. the uncoated pellets, is not able to release all its content of lornoxicam under acidic conditions and during the first hour of the test. If this was the case, a release of about 40% is to be expected after 1 hour.

A dramatically increase in dissolution is observed after 2 hours reflecting the pH change of the dissolution medium 1 hour after the start of the test. Furthermore, a retardation of the release of lornoxicam is observed at pH 7.4 compared with the uncoated pellets cores, i.e. the coating is in control of the release rate. However, a composition containing a mixture of uncoated and coated pellets does not seem to enable a fast release of lornoxicam. Therefore, the fast release fraction has to been manipulated in some way in order to release the active substance (lornoxicam) faster).

EXAMPLE 11

Preparation of a composition containing a mixture of a quick release granulate and a delayed release fraction of coated pellet cores

The composition described below was prepared in order to investigate the influence on the overall release rate of the granulate prepared in Example 9 which seems to have favourable properties with respect to a quick and very fast release of lornoxicam even under acidic conditions.

Coated pellets obtained according to Example 4 were mixed with a granulate obtained according to Example 9, where the mixture contained 40% w/w of the total dose of lornoxicam in the form of the granulate and the remaining 60% w/w of the total dose of lornoxicam was in the form of coated pellets (the concentration of lornoxicam in the granulate is about 2-3 % w/w and about 9% w/w in the uncoated pellets). The dissolution test was carried out according to dissolution method III. The following dissolution data was obtained:

Time (h)	972510 (granulate) +20029832 (coated pellets) (3/4.3) Release (% w/w)
0	0
1	37.2
2	41.3
3	44.6
4	48.2
5	51.3
6	53.9
7	57
8	59.6
9	61.8
10	64.7
11	66.9
12	69.4
13	71.6
14	73.6
15	75.7
16	77.6
17	79.5
18	81.2
19	82.9
20	84.4
21	86
22	87.4
23	88.5
24	89.8

From the dissolution data given above, a fast release of lornoxicam is observed which is ascribed to the influence of the lornoxicam granulate.

In contrast to the results obtained in Example 10 a release of about 40% w/w of lornoxicam is observed after 1 hours. Thus, the above example gives evidence that a manipulation of the composition of the fast release fraction is necessary in order to achieve a suitable release even at a low pH. Furthermore, a delayed release is observed with respect to the coated pellets fraction.

EXAMPLE 12

Investigation of the controlled release lacquer composition on the overall dissolution rate

Coated pellets obtained according to Example 8 (batch 1, 15% w/w HPMC in the coat was mixed with granulate obtained according to Example 9. The mixture contained 40% w/w of the total dose of lornoxicam in the form of the granulate, whereas the remaining 60% w/w of lornoxicam was in the form of coated pellets. The dissolution test was carried out according to dissolution method III. The following dissolution data was obtained:

Time (h)	972510 (granulate) + 24029832 (coated pellets) (3/15.1) Release (% w/w)
0	0
0.5	35.7
1	35.7
2	43.2
3	50.0
4	55.8
5	60.9
6	66.2
7	70.7
8	74.4
9	78.3
10	81.5
11	84.8
12	87.3
13	89.3
14	91.1
15	92.6
16	93.8
17	95.0
18	95.9
19	96.6
20	97.2
21	97.5
22	97.8
23	98.0
24	97.5

From the dissolution data given above a much faster release of the delayed release fraction is observed compared with the results obtained in Example 11. Thus, the

composition of the coat can be adjusted to a suitable release rate. In this example the content of HPMC in the coat is 15.1% w/w.

EXAMPLE 13

Investigation of the influence of the composition of the controlled release coat on the release rate

Coated pellets obtained according to Example 8 (batch 2) were mixed with a granulate obtained according to Example 9. The mixture contained 40% w/w of the lornoxicam content in the form of the granulate and the remaining 60% w/w in the form of coated pellets. The dissolution test was carried out according to dissolution method III.

The following dissolution data was obtained:

Time (h)	972510 (granulate) + 26029832 (coated pellets) (3/25.0) Release (% w/w)
0	0
0.5	37.3
1	37.3
2	58
3	69.1
4	79.9
5	87.6
6	92.6
7	95.9
8	97.8
9	98.9
10	99.3
11	99.4
12	99.4
13	99.4
14	99.4
15	99.5

After 6 hours 92.6% w/w is released whereas only 69.4% w/w was released in Example 12. Thus, the increase of the concentration of HPMC in the coat (25% in the present example in contrast to 15% in Example 12) has an increasing effect on the release rate of lornoxicam from the composition.

EXAMPLE 14

Determination of release rate of lornoxicam from controlled release pellets

Dissolution data from coated pellets from Examples 1, 4 and 8 (batches 1 and 2) were determined by dissolution method I (pH 7.4). The following data have been obtained.

Time (h)	05029833 (coated pellets) (5.5/4.3) Example 1	20029832 (coated pellets) (3.0/4.3) Example 4	24029832 (coated pellets) (3.0/15.1) Example 8, batch 1	26029832 (coated pellets) (3.0/25.0) Example 8, batch 2
0	0	0	0	0
0.5	6.9	10.1	17.3	32.7
1	12.1	16.9	29	52.6
2	20.3	28.5	49.5	82.1
3	28.1	39.7	67.2	96.9
4	35.4	50	81.6	101.9
5	42	58.9	91.5	102.9
6	49.1	69.1	98.5	103
7	55.2	76.2	102.1	103.2
8	60.7	82.2	103.9	102.9
9	65.6	86.9	104.8	102.9
10	69.9	90.5	105.2	103.1
11	73.7	93.4	105.5	102.9
12	77.2	93.4	105.5	
13	80.3	95.2	105.8	
14	82.6	97.7	105.5	
15	85	97.9	105.8	
16	87.1	98	105.8	
17	88.6	98.7	105.9	
18	89.9	98.8	105.9	
19	91.2	99	105.8	

The data are also presented in Figure 3. Comparison of the results obtained from the composition of Example 1 with that of Example 4 illustrates that the thickness of the CR (controlled release) coat influences the release rate in such a manner that a thinner coat leads to a more rapid release. The influence of HPMC as an example of a substance which is capable of forming pores in the coat on the release rate is illustrated by the release rate of the two different batches of Example 8 and the results reveal an increasing release rate when the concentration of HPMC increases.

Conclusion with respect to Examples 10-14

In Examples 10-14, the preparation of a composition containing two fractions of subunits has been presented. One fraction representing a quick release part and the other fraction representing a controlled and delayed release part. Furthermore, the Examples illustrate the influence on the release rate of i) the composition of the quick release fraction and ii) composition and amount of lacquer applied on the controlled release fraction.

EXAMPLE 15

Investigation of the influence of the dissolution medium on the release rate

Dissolution data from coated pellets from Examples 4 and 8 (batch 2) were obtained using dissolution method V (pH 7.3), and are as follows:

Time (h)	20029832 (coated pellets) (3.0/4.3)[7.3] Example 4	26029832 (coated pellets) (3.0/25.0)[7.3] Example 8, batch 2
0	0	0
0.5	6.2	22
1	10.1	36.1
2	17.3	60.7
3	24.3	79.2
4	30.9	90.7
5	36.9	96.9
6	42.9	100.1
7	48.2	101.4
8	53.1	101.9
9	57.6	102
10	61.8	102
11	65.7	102
12	69.3	102
13	72.4	102
14	75.4	102
15	78	102
16	80.3	102
18	84.3	
20	87.3	

The data are compared with the data from Example 14 in Figure 3. An influence of the dissolution medium on the dissolution rate is observed, i.e. the choice of dissolution method is important (not only with respect to pH but also with respect to factors like, e.g., ionic strength, osmotic pressure etc.).

EXAMPLE 16

Investigation of the influence of a pre-treatment in 0.1 N hydrochloric acid on the dissolution rate at pH 7.4

Dissolution data from coated pellets from Example 4 and Example 8 (batch 2) was determined by dissolution method I (pH 7.4) and method IV (1hour at a pH corresponding to 0.1 N HCl and then at pH 7.4) and are as follows:

Time (h) in pH 7.4	26029832 (3,0/25)(HCl/7,4) Example 8, batch 2 Dissolution method IV	20029832 (3,0/4,3)(HCl/7,4) Example 4, Dissolution method IV	20029832 (3,0/4,3) Example 8 batch 2 Dissolution method I	26029832 (3,0/25,0) Example 4, Dissolution method I
0	0	0	0	0
0.5			10.1	32.7
1	47.6	16.9	16.9	52.6
2	77.5	29.1	28.5	82.1
3	92.4	39.6	39.7	96.9
4	98.1	48.3	50	101.9
5	100.2	56.9	58.9	102.9
6	100.6	64.8	69.1	103
7	100.6	71.6	76.2	103.2
8	100.7	77	82.2	102.9
9			86.9	102.9
10		85.7	90.5	103.1
11		88.8	93.4	102.9
12		91.3	93.4	
13		93.4	95.2	
14		94.8	97.7	
15		96	97.9	
16		97	98	
17		97.6	98.7	
18		98.3	98.8	
19		98.6	99	

The dissolution results from Example 16 reveal that a pre-treatment with acid does not have any significantly influence on the rate of release from the delayed release fraction, i.e. the coated pellets fraction.

In Figure 4 the data are presented and in order to make a proper comparison possible, the release data obtained by dissolution method IV have been displaced by 1 hour corresponding to the time period for treatment in 0.1 N HCl. Thus, in Figure 4, the zero setting for all compositions is when the dissolution medium has a pH of 7.4. The observed differences with respect to the dissolution of lornoxicam from Example 1 and 4, respectively, are not significant and are within the standard deviation observed.

Conclusion with respect to Examples 15 and 16

The results from Examples 15 and 16 have shown that coated pellets have the same release rate independent on whether a pre-treatment in acid has been included or not whereas a change in the dissolution method (from method I to method V) has a significant influence on the release rate.

EXAMPLE 17

Investigation on the influence of dose on the dissolution rate

In this Example the dissolution profiles of a dose of 16 mg of lornoxicam are compared to a dose of 8 mg of lornoxicam. Dissolution profiles are obtained according to dissolution method III.

Time (h)	972510+24029832 8 mg Example 12 8 mg lornoxicam pr. capsule	972510+24029832 Reanalysis of Example 12 (new sample) 8 mg lornoxicam pr. capsule	972510+24029832 Reanalysis of Example 12 (new sample) 16 mg lornoxicam pr. capsule
0	0	0	0
1	35.7	36.2	35.3
2	43.2	47	46.3
3	50.0	55.9	55
4	55.8	63.9	61.7
5	60.9	70.6	67.1
6	66.2	77.4	73.1
7	70.7	83	77.1
8	74.4	87.1	81.4
9	78.3	91.3	85.5
10	81.5	94.2	90.5
11	84.8	95.9	91.9
12	87.3	97.8	93.9
13	89.3	98.7	95.7
14	91.1	99	96.7
15	92.6	99.9	97.7
16	93.8	99.9	98.1
17	95.0	99.7	99
18	95.9	100.1	99.1
19	96.6		
20	97.2		
21	97.5		
22	97.8		
23	98.0		
24	97.5		

Data are presented in Figure 5 and the curves show that the dose is without any significant influence on the release rate. In Figure 5 a target profile calculated for

lornoxicam has been included and it is seen that the compositions tested have profiles very close to the target profile.

EXAMPLE 18

Investigation on whether a plain granulate quickly releases an NSAID substance

A granulate containing naproxen was prepared using the ingredients listed in Table 10. The granulate was prepared in order to investigate whether a plain granulate like the one disclosed in EP-A-0 438 249A1 (ELAN Corporation P.L.C.) releases naproxen quickly (as defined herein) when the dissolution testing is done according to dissolution method II (n = 2) described herein. No standards were used and, accordingly, a literature value for E (1%, 1 cm) = 63 was used to calculate the content in the samples. The composition of the granulate corresponds to the one disclosed in Example 1 of EP-A-0 438 249A1 (ELAN Corporation P.L.C.).

Table 10

Ingredients	Amount (g)
Naproxen	232.0
Polyvidone 30	7.2
Isopropanol	65.7

Naproxen and polyvidone 30 were mixed in a lab scale Kenwood mixer for 3 min. The mixture was granulated by slowly adding the isopropanol over a period of 2 min and the mixing was continued for 1 min. Then the granulate was dried on trays at 50 °C for 12 hours. Thereafter half of the granulate was sieved through a 500 µm sieve and the other half of the granulate was sieved through a 1000 µm sieve. Oversized material was discarded in both cases. The thus obtained two granulates were tested according to dissolution method II described herein.

Batch No. 26089831: 500 µm sieved granulate in an amount corresponding to a 150 mg tablet. In the following is given the results from the dissolution test.

Time (h)	Release (dissolved naproxen) % w/w
0	0
0.5	15
1	16.1
1.5	16.5
2	17.6

Batch No. 26089831: 1000 µm sieved granulate in an amount corresponding to a 150 mg tablet. In the following is given the results from the dissolution test.

Time (h)	Release (dissolved naproxen) % w/w
0	0
0.5	11.4
1	13.4
1.5	14.2
2	15.7

From the results given above, it is clear that such plain formulations do not release the NSAID substance very fast and, accordingly, such formulations or compositions do not fall under the definition of quick release defined herein (i.e. that at least about 50% of the NSAID substance is released within the first 20 min of the dissolution test).

CLAIMS

1. An oral pharmaceutical modified release multiple-units composition in unit dosage form for administration of a therapeutically and/or prophylactically effective amount of a non-steroid anti-inflammatory drug substance (an NSAID substance), a unit dosage form comprising at least two NSAID-containing fractions,

i) a first NSAID-containing fraction of multiple-units for quick release of the NSAID substance, and

ii) a second NSAID-containing fraction of multiple-units for extended release of the NSAID substance,

the first fraction which - when subjected to dissolution method II as defined herein employing 0.07 N HCl as dissolution medium - releases at least 50% w/w of the NSAID substance present in the fraction within the first 20 min of the test,

the second fraction being in the form of coated delayed release multiple units for extended release of the NSAID substance.

2. A composition according to claim 1, wherein the first fraction – when subjected to dissolution method II as defined herein employing 0.07 N HCl as dissolution medium – releases at least 55% w/w such as, e.g., at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w or at least about 80% w/w of the total NSAID substance present in the first fraction within the first 20 min of the test.

3. A composition according to claim 1 or 2, wherein the quick *in vitro* release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least 50% w/w release of the NSAID substance contained in the first fraction at the time when at the most 15% w/w such as at the most 10% w/w or at the most 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III defined herein.

4. A composition according to any one of the preceding claims, wherein the NSAID substance contained in the first fraction has a pK_a value between from about 3.0 to about 5.5 and the first fraction is in the form of uncoated units.

5. A composition according to any one of the preceding claims, wherein the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at the most about 0.5% w/v such as, e.g. at the most about 0.1% w/v, at the most about 0.05% w/v, at the most about 0.03% w/v, at the most about 0.01% w/w, at the most about 0.007% w/v, at the most about 0.005% w/v, at the most about 0.003% w/v, at the most about 0.002% w/v or at the most about 0.001% w/v.

6. A composition according to any one of claims 1-3, wherein the NSAID substance contained in the first fraction has a pK_a value of at least 5.0 such as at least about 5.5.

7. A composition according to claim 6, wherein the first fraction is present in the form of coated units.

8. A composition according to any one of claims 1-3 or 6-7, wherein the NSAID substance has a solubility in 0.1 N hydrochloric acid at room temperature of at least about 0.1% w/v such as e.g. at least about 0.5% w/v or at least about 1% w/v.

9. A composition according to any one of the preceding claims intended for administration once or twice daily.

10. A composition according to any one of the preceding claims for the administration of a therapeutically and/or prophylactically effective amount of an NSAID substance to obtain both a relatively fast onset of the therapeutic effect and the maintenance of therapeutically active plasma concentration for a relatively long period of time, a unit dosage of the composition comprising at least two fractions as follows:

a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically and/or prophylactically active plasma concentration within a relatively short period of time, and

a second fraction of coated modified release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically and/or prophylactically active plasma concentration in order to enable dosing once or twice daily,

the formulation of the first and the second fractions, with respect to release therefrom and with respect to the ratio between the first and the second fraction in the unit dosage, being adapted so as to obtain:

a relative quick *in vitro* release of the NSAID substance from the first fraction of quick release multiple-units, as measured by the dissolution method II as defined herein,

an extended *in vitro* release of the NSAID substance from the second fraction of extended release multiple-units relative to the *in vitro* release of the first fraction of the NSAID substance, as measured by e.g. the dissolution method III as defined herein,

the quick release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least 50% w/w release of the NSAID substance contained in the first fraction at the time when at least about 15% w/w such as, e.g., at least about 10% w/w or at least about 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III defined herein.

11. A composition according to any one of the preceding claims, wherein the NSAID substance is selected from the group consisting of lornoxicam, diclofenac, nimesulide, ibuprofen, piroxicam, piroxicam (betacyclodextrin), naproxen, ketoprofen, tenoxicam, aceclofenac, indometacin, nabumetone, acemetacin, morniflumate, meloxicam, flurbiprofen, tiaprofenic acid, proglumetacin, mefenamic acid, fenbufen, etodolac, tolfenamic acid, sulindac, phenylbutazone, fenoprofen, tolmetin, acetylsalicylic acid, dexibuprofen, and pharmaceutically acceptable salts, complexes and/or prodrugs thereof and mixtures thereof.

12. A composition according to any one of the preceding claims, wherein the NSAID substance in the first fraction is the same as the NSAID substance contained in the second fraction.

13. A composition according to any one claims 1-11, wherein the NSAID substance in the first fraction is different from the NSAID substance contained in the second fraction.

14. A composition according to any one of the preceding claims, wherein the NSAID substance in the first fraction is lornoxicam.

15. A composition according to any one of the preceding claims, wherein the NSAID substance in the second fraction is lornoxicam.

16. A composition according to any one of the preceding claims comprising a further active drug substance.

17. A composition according to any one of the preceding claims, wherein a further active drug substance is included in at least one of the first and second fraction.

18. A composition according to claim 16 or 17, wherein the further active drug substance is an antidepressant, an opioid, a prostaglandine analog (e.g. misoprostol), a glucocorticosteroid, a cytostaticum (e.g. methotrexate), a H_2 receptor antagonist (e.g. cimetidine, ranitidine), a proton pump inhibitor (e.g. pantoprazole, omeprazole, lansoprazole) and/or an antacidum.

19. A composition according to claim 16 or 17, wherein the further active drug substance is paracetamol, penicillamine, sulfasalazine and/or auranorfin.

20. A composition according to any one of the preceding claims, wherein the NSAID substance is lornoxicam.

21. A composition according to any one of the preceding claims, wherein the quick release multiple-units of the first fraction have a mean particle size of at the most about 250 μm such as, e.g. at the most about 240 μm, at the most about 230 μm, at the most about 220 μm, at the most abut 210 μm, at the most about 200 μm, at the most about 190 μm, at the most about 180 μm, at the most about 175 μm, at the most about 150 μm, at the most about 125 μm, at the most about 100 μm, at the most about 90 μm or at the most about 80 μm.

22. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the first fraction of quick release multiple-units provides within 1 hour a release as defined by the dissolution method II defined herein of at least 50% w/w, such as, e.g., at least about 60% w/w, at least about 70% w/w, at at least about 80% w/w, at least about 85% w/w at least about 90% w/w or at least about 95% w/w of the NSAID substance.

23. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of extended release multiple-units provides within 1 hour a release as defined by the dissolution method III defined herein in the range of 0%-30% w/w, such as in the range of 0%-20% w/w, in the range of 0%-10% w/w, such as at the most about 5% w/w of the NSAID substance.

24. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of extended release multiple-units provides within 3 hours a release as defined by the dissolution method III defined herein in the range of about 10%-70% w/w, such as, e.g., in the range of about 10%-60% w/w, in the range of about 12%-50% w/w, in the range of 14%-45% w/w, in the range of about 15%-30% w/w, in the range of about 15%-20% w/w such as, e.g., about 17% w/w of the NSAID substance.

25. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of extended release multiple-units provides within 6 hours a release as defined by the dissolution method III defined herein in the range of about 35%-95% w/w, such as, e.g., in the range of about 50%-90% w/w, in the range of about 50%-80% w/w, in the range of 50%-75% w/w, in the range of about 50%-60% w/w, in the range of about 53%-59% w/w such as, e.g. about 56% w/w of the NSAID substance.

26. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the second fraction of modified release multiple-units provides within 9 hours a release as defined by the dissolution method III defined herein in the range of about 50%-100% w/w, such as, e.g., in the range of about 60%-98% w/w, in the range of about 65%-95% w/w, in the range of about 70%-90% w/w, in the range of about 70%-80% w/w such as, e.g., about 76% w/w of the NSAID substance.

27. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the first and second fractions are adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least 50% w/w of the first fraction at the time at the most about 15% w/w such as, e.g., at the most about 10% w/w or at the most about 5% w/w of the second fraction is released as measured by the dissolution method III defined herein.

28. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the first and second fractions are adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least 70% w/w release of the first fraction at the time at the most about 20% w/w such as, e.g. at the most about 15% or at the most about 10% w/w of the second fraction is released as measured by the dissolution method III as defined herein.

29. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 1 hour a release of the NSAID substance from the composition in the range of about 5-50% w/w, such as, e.g., in the range of about 5-45% w/w, in the range of about 15-40% w/w, in the range of about 20-35% w/w such as about 29% w/w, as defined by the dissolution method III as defined herein.

30. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 3 hours a release as defined by the dissolution method III as defined herein in the range of about 20-80% w/w, such as, e.g., in the range of about 25-70% w/w, in the range of about 30-60% w/w, in the range of about 35-55% w/w such as about 42% w/w.

31. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 6 hours a release as defined by the dissolution method III defined herein in the range of about 40-98% w/w, such as, e.g., in the range of about 50-95% w/w, in the range of about 60-90% w/w, in the range of about 60-85% w/w, most preferred in the range of about 60-83% w/w such as about 69% w/w.

32. A composition according to any one of the preceding claims, wherein the *in vitro* dissolution characteristics of the composition provides within 9 hours a release as defined by the dissolution method III as defined herein in the range of about 50-100% w/w, such as, e.g., in the range of about 60-99% w/w, in the range of about 70-98% w/w, in the range of about 70-97% w/w, in the range of about 75-96% w/w, in the range of about 80-96% w/w, about 80-85% w/w such as about 83% w/w.

33. A composition according to any one of the preceding claims, wherein the percentage of NSAID substance in the first fraction is in the range of about 5%-50% w/w such as, e.g., in the range of about 10%-45% w/w, in the range of about 15%-45% w/w, in the range of about 20%-40% w/w, in the range of about 25%-40% w/w, in the range of about 25%-35% w/w such as, e.g., about 30% w/w, calculated on the total amount of NSAID substance in the composition.

34. A composition according to any one of the preceding claims, wherein the percentage of NSAID substance in the second fraction is in the range of about 30%-99% w/w such as, e.g. in the range of about 40%-98% w/w, in the range of about 45%-95% w/w, in the range of about 50%-95% w/w, in the range of about 55%-85% w/w, in the range of about 60%-80% w/w, in the range of about 60%-75% w/w, in the range of abut 65%-75% w/w such as, e.g., about 70% w/w, calculated on the total amount of NSAID substance in the composition.

35. A composition according to any one of the preceding claims, wherein the multiple-units of the second fraction are coated cross-sectionally substantially homogeneous pellets.

36. A composition according to any one of the preceding claims, wherein the multiple-units of the first fraction are cross-sectionally substantially homogeneous pellets.

37. A composition according to any one of the preceding claims, wherein the first fraction results in a peak plasma concentration of NSAID substance which is substantially the same as the peak plasma concentration resulting from the second fraction.

38. A composition according to any one of claims 1-36, wherein the first fraction results in a peak plasma concentration of the NSAID substance which is higher than the peak plasma concentration resulting from the second fraction.

39. A composition according to any one of claims 1-36, wherein the first fraction results in a peak plasma concentration of the NSAID substance which is lower than the peak plasma concentration resulting from the second fraction.

40. A composition according to any one of the preceding claims, wherein the first fraction results in a therapeutically active plasma concentration of the NSAID substance until the extended release of an NSAID substance from the second fraction of modified release multiple-units contributes to the maintenance of a therapeutically active plasma concentration of the NSAID substance.

41. A composition according to any one of the preceding claims, wherein the extended release coating of the second fraction is substantially water-insoluble, but water-diffusible and substantially pH-independent.

42. A composition according to any one of the preceding claims, wherein the first fraction is coated units and the coating is a substantially water-insoluble, but water-diffusible and substantially pH-independent coating.

43. A composition according to any one of the preceding claims, wherein a unit dosage of the composition comprises from about 1 to about 32 mg of the NSAID substance.

44. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 1 mg to about 1.6 g such as from about 1 mg to about 1.2 g of the NSAID substance.

45. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 50 mg to about 1.1 g of the NSAID substance.

46. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 100 mg to about 1.0 g of the NSAID substance.

47. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 200 mg to about 900 mg of the NSAID substance.

48. A composition according to any one of claims 1-42, wherein a unit dosage comprises from about 300 mg to about 800 mg of the NSAID substance.

49. A composition according to any one of the preceding claims comprising a unit dosage for the administration of the therapeutically effective amount of the NSAID substance twice daily.

50. A composition according to any one of claims 1-48 comprising a unit dosage for the administration of the therapeutically effective amount of the NSAID substance once daily.

51. A composition according to any one of the preceding claims wherein the unit dosage of the composition is in the form of a capsule, tablet or sachet.

52. A composition according to any one of the preceding claims, wherein the NSAID substance is lornoxicam and the unit dosage of the composition contains 4, 8, 12, 16, 20, 24, 28, 32 or 36 mg of lornoxicam.

53. A process for the preparation of a unit dosage form of an oral pharmaceutical modified release composition according to any one of the preceding claims, the process comprising incorporating into the unit dosage form at least two fractions as follows: a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically or prophylactically active plasma concentration within a relatively short period of time, and a second fraction of coated extended release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically active plasma concentration in order to enable dosing once or twice daily,

the formulation of the first and the second fractions, with respect to release therefrom and with respect to the ratio between the first and the second fraction in the unit dosage, being adapted so as to obtain:

a relative quick *in vitro* release of the NSAID substance from the first fraction of quick release multiple-units, as measured by the dissolution method II defined herein,

an extended *in vitro* release of the NSAID substance from the second fraction of extended release multiple-units relative to the *in vitro* release of the first fraction of the NSAID substance, as measured by the dissolution method III as defined herein, the quick release and the extended *in vitro* release being adapted so that the first fraction is substantially released when the release from the second fraction is initiated corresponding to at least about 50% w/w release of the NSAID substance contained in the first fraction at the time when at the most about 15% w/w such as, e.g., at the most about 10% w/w or at the most about 5% w/w of the NSAID substance contained in the second fraction is released as measured by the dissolution method III as defined herein.

54. A method for treating a patient suffering from pain and/or inflammatory conditions and/or the like comprising administering to the patient an effective amount of an NSAID substance in the form of a composition according to any one of claims 1-52 once or twice daily.

55. A method for administering a therapeutically and/or prophylactically effective amount of an NSAID substance to a patient in need thereof to obtain both a relatively fast onset of the therapeutic effect and the maintenance of therapeutically active plasma concentration for a relatively long period of time, the method comprising administering once or twice daily a unit dosage of a composition comprising at least two fractions as follows:

a first fraction of quick release multiple-units for relatively quick release *in vivo* of an NSAID substance to obtain a therapeutically and/or prophylactically active plasma concentration within a relatively short period of time, and

a second fraction of coated modified release multiple-units for extended release *in vivo* of an NSAID substance to maintain a therapeutically and/or prophylactically active plasma concentration.

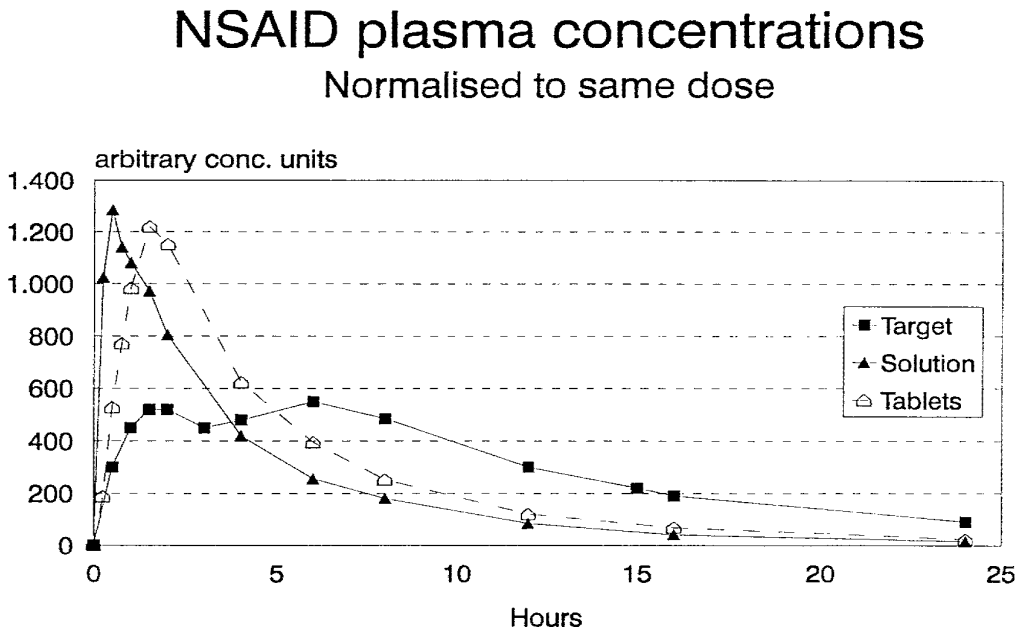
NSAID plasma concentrations
Normalised to same dose
arbitrary conc. units
1.400
1.200
1.000
800
600
400
200
0
0
5
10
15
20
25
Hours
Target
Solution
Tablets

Fig. 1

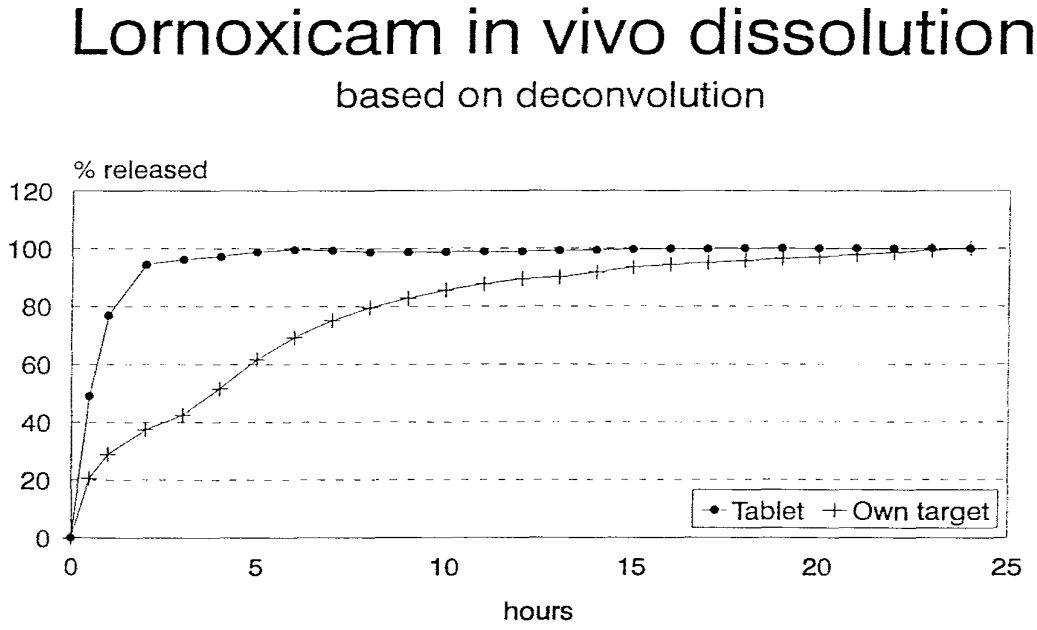
Lornoxicam in vivo dissolution
based on deconvolution
% released
120
100
80
60
40
20
0
0
5
10
15
20
25
hours
Tablet
Own target

Fig. 2

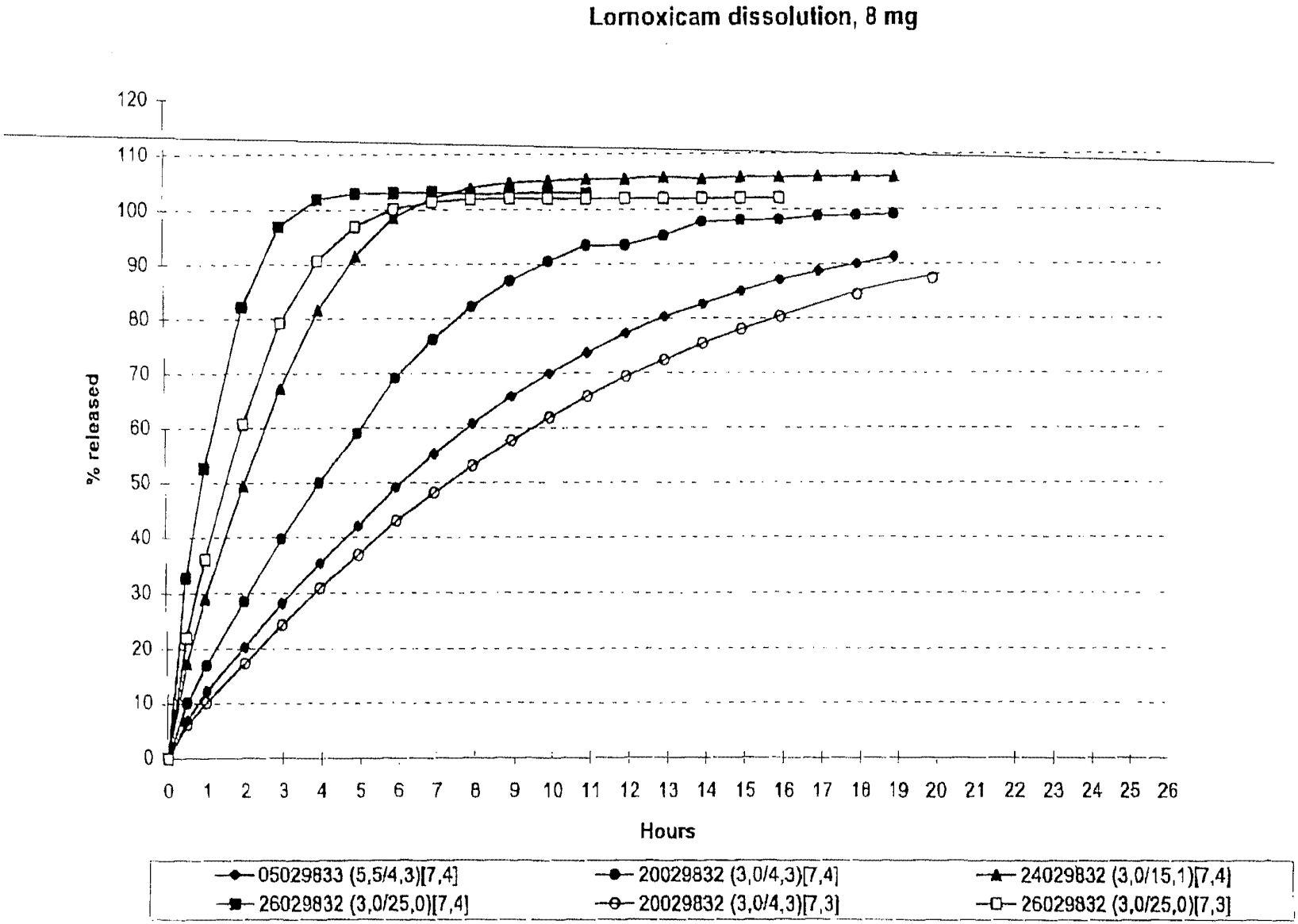
Lornoxicam dissolution, 8 mg
% released
Hours
0
10
20
30
40
50
60
70
80
90
100
110
120
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
05029833 (5,5/4,3)[7,4]
20029832 (3,0/4,3)[7,4]
24029832 (3,0/15,1)[7,4]
26029832 (3,0/25,0)[7,4]
20029832 (3,0/4,3)[7,3]
26029832 (3,0/25,0)[7,3]

Fig. 3

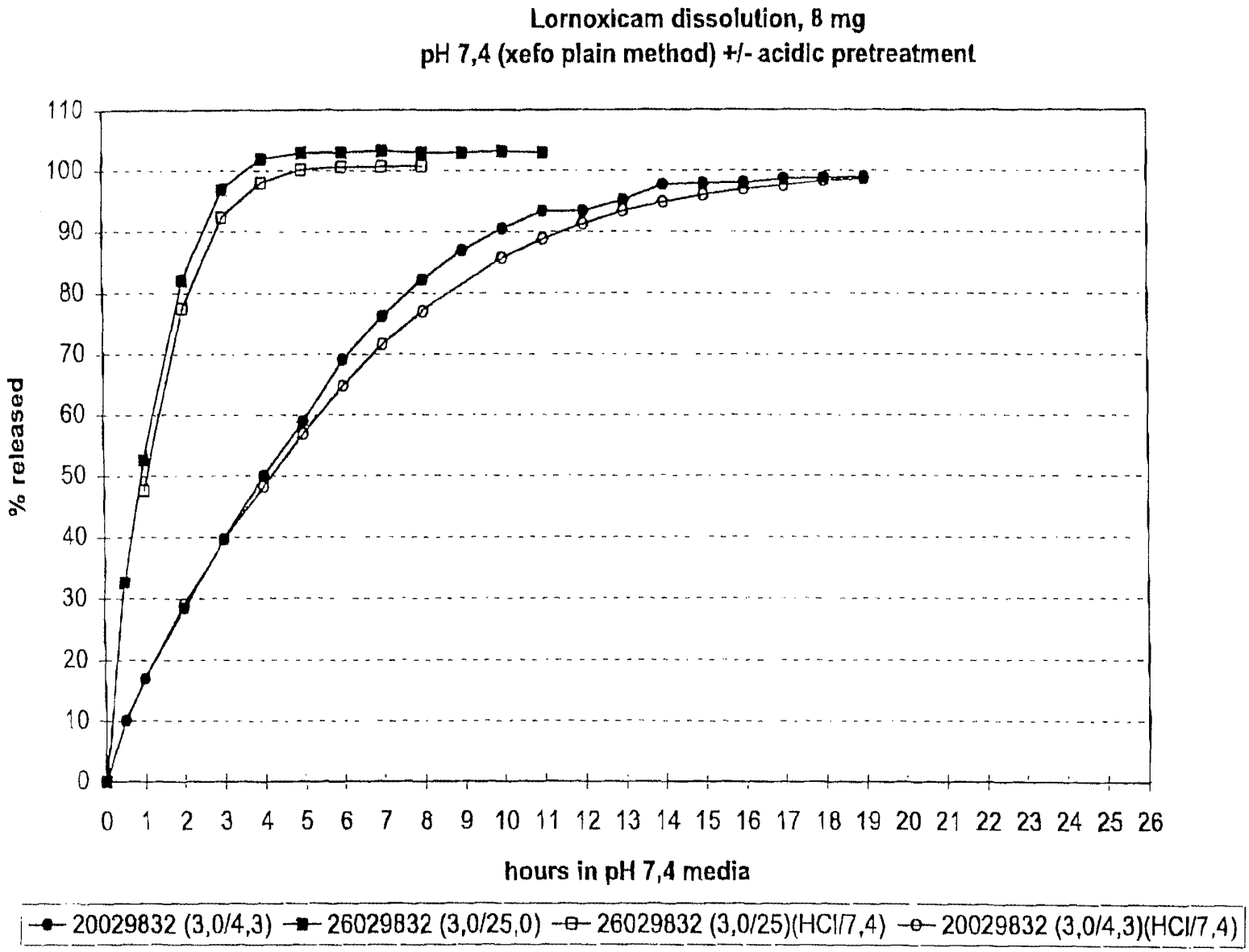
Lornoxicam dissolution, 8 mg
pH 7,4 (xefo plain method) +/- acidic pretreatment
% released
hours in pH 7,4 media
20029832 (3,0/4,3)
26029832 (3,0/25,0)
26029832 (3,0/25)(HCl/7,4)
20029832 (3,0/4,3)(HCl/7,4)

Fig. 4

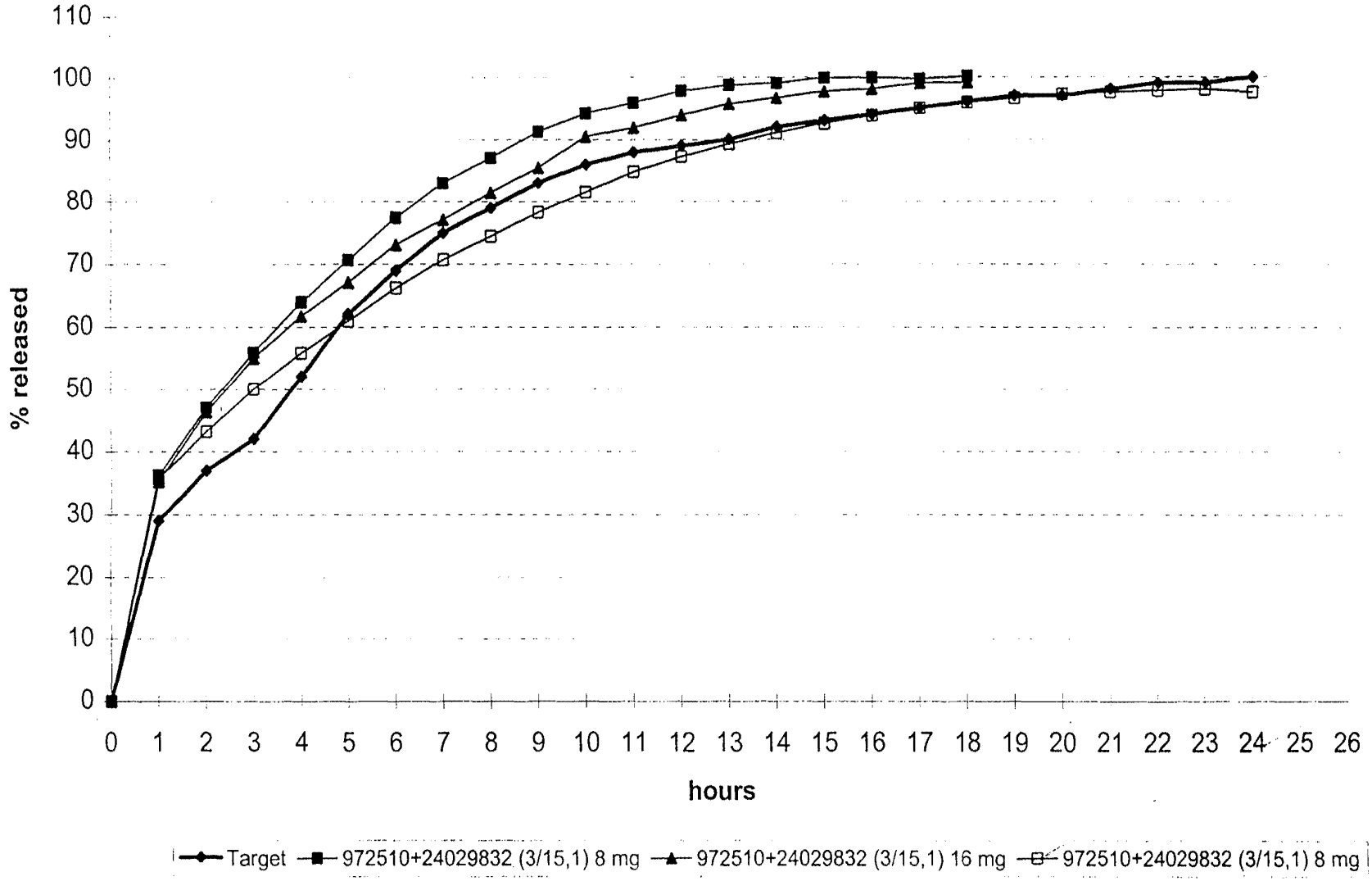
Lornoxicam dissolution, 8/16 mg dose
0,1 N HCl 1h, then pH 7,3
% released
110
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26
hours
Target
972510+24029832 (3/15,1) 8 mg
972510+24029832 (3/15,1) 16 mg
972510+24029832 (3/15,1) 8 mg

Fig. 5

INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/DK 98/00388

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20 A61K9/50 A61K31/00

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)
IPC 6 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	US 5 043 167 A (ROTINI LEONE G ET AL) 27 August 1991	1-13, 16-19, 21-51, 53,54
Y	see the whole document	14,15, 20,52

X,Y	EP 0 438 249 A (ELAN CORP PLC) 24 July 1991	1-13, 16-19, 21-51, 53,54
	see the whole document	

Y	US 5 478 577 A (SACKLER RICHARD ET AL) 26 December 1995 see the whole document	1-13

	-/--	

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 December 1998	21/12/1998

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interi nal Application No
PCT/DK 98/00388

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 06787 A (DYER ALISON MARGARET ;CSIR (ZA); ROLFES HEIDI (ZA); MERWE THILO LO) 27 February 1997 see abstract see page 5, line 25-29 see page 14, line 1 - line 4	14,15, 20,52
P,X, Y	WO 97 32573 A (NYCOMED DANMARK A S ;SKINHOEJ ANETTE (DK)) 12 September 1997	1-13, 16-19, 21-51, 53,54
L	"L": DOCUMEMENT SO QUOTED SINCE IT CASTS DOUBT ON THE VALIDITY OF THE CONVENTION-PRIORITY CLAIMED see the whole document	

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00388

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 54
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 54 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 54 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Claims Nos.: 54

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/DK 98/00388

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(30) Priority Data:

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198 22 549.0	20 May 1998 (20.05.98)	DE

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(72) Inventors; and

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(74) Common Representative: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; Byk–Gulden–Strasse 2, D–78467 Konstanz (DE).

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Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL ADMINISTRATION FORM COMPRISING AN ACID–LABILE ACTIVE COMPOUND

(57) Abstract

Novel administration form for acid–labile active compounds are described. The novel administration forms have no enteric layers and are suitable for oral administration.

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Novel administration form comprising an acid-labile active compound

Technical field

The present invention relates to the field of pharmaceutical technology and describes a novel administration form comprising an acid-labile active compound, in particular an acid-labile proton pump inhibitor. The novel administration form is suitable for oral administration. Furthermore, the invention also relates to a process for the production of the administration form and preparations which can be used for the production of the administration form.

Prior art

It is generally known to coat oral administration forms, e.g. tablets or pellets, which contain an acid-labile active compound, with an enteric coating which is rapidly dissolved in the alkaline medium of the intestine after gastric passage. An example of such acid-labile active compounds is acid-labile proton pump inhibitors (H^+/K^+ ATPase inhibitors), in particular pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, such as are disclosed, for example, in EP-A-0 005 129, EP-A-0 166 287, EP-A-0 174 726 and EP-A-0 268 956. On account of their H^+/K^+ ATPase-inhibiting action, these are of great importance in the therapy of diseases which result from increased gastric acid secretion. Examples of already commercially available active compounds from this group are 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylsulfinyl]-1H-benzimidazole (INN: omeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)-methylsulfiny]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)-methylsulfinyl]-1H-benzimidazole (INN: lansoprazole) and 2-{[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulfinyl}-1H-benzimidazole (INN: rabeprazole).

Because of their strong tendency to decompose in a neutral and, in particular, acidic environment, strongly colored decomposition products also being formed, it is also necessary in this case for oral preparations to protect the active compounds from the action of acids and moisture and destruction by undesired interaction with pharmaceutical auxiliaries. In the case of the highly acid-labile pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, it is moreover necessary to process these in the tablet core or in pellets in the form of their alkaline salts, for example as sodium salts, or together with alkaline substances. Since the substances possible for enteric coatings are those having free carboxyl groups, the problem results that the enteric coating, because of the alkaline medium in the interior, begins to dis-

solve or is even dissolved from the inside out and the free carboxyl groups promote the decomposition of the active compounds. It is therefore necessary to provide an insulating intermediate layer (subcoating) between the enteric coating and the alkaline tablet core or pellet. In EP-A-0 244 380, it is proposed to coat cores which contain the active compound together with alkaline compounds or as an alkaline salt with at least one layer of nonacidic, inert pharmaceutically acceptable substances, which is soluble in water or rapidly disintegrates in water, before the enteric layer is applied. The intermediate layer or intermediate layers act as pH-buffering zones in which the hydrogen ions diffusing in from outside can react with the hydroxyl ions diffusing out of the alkaline core. In order to increase the buffer capacity of the intermediate layer, it is proposed to incorporate buffer substances into the intermediate layer(s). In practice, it is possible by this process to obtain preparations which are stable to a certain extent. However, relatively thick intermediate layers are needed to avoid the unattractive discolorations which occur even in the case of only slight decomposition. Additionally, a considerable effort has to be made during preparation to avoid traces of moisture.

In EP-A-0 519 365, a formulation for the active compound pantoprazole on the principle of the alkaline core coated with a water-soluble intermediate layer and an enteric layer is proposed, in which an improved stability is achieved by use of polyvinylpyrrolidone and/or hydroxypropylmethylcellulose as a binder for the alkaline core.

In EP-A-0 342 522, a formulation for acid-sensitive benzimidazoles is disclosed in which between the alkaline core and the enteric coating is situated an intermediate layer which is composed of an only slightly water-soluble film-forming material, such as ethylcellulose or polyvinyl acetate, and a slightly water-soluble fine-grain inorganic or organic material suspended therein, such as, for example, magnesium oxide, silicon oxide or sucrose fatty acid esters.

EP-A-0 277 741 describes spherical grains or granules having a core which is coated with spray powder which contains low-substituted hydroxypropyl-cellulose and a benzimidazole compound having antiulcer activity. These grains can be coated with an enteric coating agent.

WO96/01623, WO96/01624 and WO96/01625 describe an administration form for acid-labile H^+/K^+ ATPase inhibitors in which active compound pellets together with tablet auxiliaries are compressed to give a tablet. The pellets consist of cores which contain the acid-labile H^+/K^+ ATPase inhibitor together with alkaline compounds or as an alkaline salt. The cores of the pellets are coated with one or more layers, at least one layer having enteric properties. The enteric layer must in this case be mechanically constituted such that on compression to give tablets the acid resistance of the pellets is not adversely affected. It is mentioned that the preparation of the cores of the pellets can be effected by spray drying.

WO97/25030 describes the processing of the abovementioned pellets to give an effervescent tablet.

As the abovementioned prior art shows, the preparation of oral administration forms for acid-labile active compounds requires technically complicated processes.

Description of the invention

It is an object of the present invention to provide a novel oral administration form for acid-labile active compounds in which the acid-labile active compound does not have to be protected by an enteric coating and which can be prepared without great technical effort.

It has now surprisingly been found that this object can be achieved by an administration form which comprises a plurality of individual active compound units.

The invention relates to an oral administration form comprising an acid-labile active compound and pharmaceutical auxiliaries, wherein the auxiliaries are not suitable for the formation of enteric layers (enteric coating). Preferably the active compound in the oral administration form is present in the form of a plurality of individual active compound units.

Further subjects follow from the patent claims.

The plurality of individual active compound units in the sense of the invention is a plurality of individual units (multiple individual units) in which at least one active compound particle is present. Preferably in the individual units, the active compound is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

Further subject of the invention is an oral administration form for acid-labile active compounds, comprising at least one pharmaceutical auxiliary and a plurality of individual active compound units, wherein the acid-labile active compound in the individual active compound units is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

A preferred subject of the invention is an oral administration form for acid-labile active compounds, comprising at least one pharmaceutical auxiliary and a plurality of individual active compound units, wherein the acid-labile active compound in the individual active compound units is surrounded by a mixture of at least one sterol and at least one polymer.

Further subject of the invention is an active compound unit comprising an acid-labile active compound, wherein the acid-labile active compound is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

The particle size of the individual units is advantageously less than 200 µm, preferably less than 100 µm. Preferably, the particle size is in the range from 2 µm to 50 µm, particularly preferably in the range from 4 µm to 20 µm.

Acid-labile active compounds in the sense of the present invention are, in particular, acid-labile proton pump inhibitors.

Acid-labile proton pump inhibitors (H^+/K^+ ATPase inhibitors) which may be mentioned in the sense of the present invention are, in particular, substituted pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, such as are disclosed, for example, in EP-A-0 005 129, EP-A-0 166 287, EP-A-0 174 726, EP-A-0 184 322, EP-A-0 261 478 and EP-A-0 268 956. Preferably, mention may be made here of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: omeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methyl-sulfinyl]-1H-benzimidazole (INN: lansoprazole) and 2-{[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methyl-sulfinyl}-1H-benzimidazole (INN: rabeprazole).

Further acid-labile proton pump inhibitors, for example substituted phenylmethylsulfinyl-1H-benzimidazoles, cycloheptapyridin-9-ylsulfinyl-1H-benzimidazoles or pyridin-2-ylmethylsulfinylthienoimidazoles are disclosed in DE-A-35 31 487, EP-A-0 434 999 or EP-A-0 234 485. Mention may be made by way of example of 2-[2-(N-isobutyl-N-methylamino)benzylsulfinyl]benzimidazole (INN: leminoprazole) and 2-(4-methoxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ylsulfinyl)-1H-benzimidazole (INN: nepaprazole).

The acid-labile proton pump inhibitors are chiral compounds. The term acid-labile proton pump inhibitor also includes the pure enantiomers of the acid-labile proton pump inhibitors and their mixtures in any mixing ratio including the racemates. Enantiomerically pure acid-labile proton pump inhibitors are disclosed, for example, in WO92/08716. Esomeprazole may be mentioned by way of example.

The acid-labile proton pump inhibitors are present here as such or preferably in the form of their salts with bases. Examples of salts with bases which may be mentioned are sodium, potassium, magnesium or calcium salts. If desired, the salts of the acid-labile proton pump inhibitors with bases can also

be present in hydrate form. Such a hydrate of the salt of an acid-labile proton pump inhibitor with a base is disclosed, for example, in WO 91/19710.

Particularly preferred acid-labile proton pump inhibitors which may be mentioned are pantoprazole sodium and pantoprazole sodium sesquihydrate (= pantoprazole sodium × 1.5 H_2O).

The sterol is preferably a phytosterol or a zoosterol. Phytosterols which may be mentioned by way of example are ergosterol, stigmasterol, sitosterol, brassicasterol and campesterol. Zoosterols which may be mentioned by way of example are cholesterol and lanosterol. If desired, mixtures of sterols can also be present.

The polymer is preferably a polymer having nonacidic groups. Polymers which may be mentioned by way of example are polyvidone (e.g. Kollidon 17, 30 and 90 from BASF), vinylpyrrolidone/vinyl acetate copolymer and polyvinyl acetate. Cellulose ethers such as, for example, methylcellulose, ethylcellulose (Ethocel) and hydroxypropylmethylcellulose and cellulose esters (e.g. cellulose acetate phthalate) may furthermore be mentioned. If desired, mixtures of polymers can also be present.

The fatty alcohol is preferably a linear, saturated or unsaturated primary alcohol having 10-30 carbon atoms. Fatty alcohols which may be mentioned by way of example are cetyl alcohol, myristyl alcohol or stearyl alcohol. If desired, mixtures of fatty alcohols can also be present.

The amount (in % by weight) of active compound in the individual active compound unit is advantageously 1-90%. In case of units in which at least one active compound particle is present, surrounded by a mixture of at least one sterol and at least one polymer the amounts of sterol and of polymer are in each case advantageously 5-80%. Preferably, the amount of active compound is 10-50%, the amount of sterol is 10-40% and the amount of polymer is 10-50%.

In case of units in which at least one active compound particle is present, surrounded by at least one fatty alcohol, preferably the amount of active compound is 2-70 % and the amount of fatty alcohol is 30-98 %.

In case of units in which at least one active compound particle is present, surrounded by at least one fatty alcohol and at least one sterol, preferably the amount of active compound is 2-70 %, the amount of fatty alcohol is 20-90 % and the amount of sterol is 8-50 %.

In case of units in which at least one active compound particle is present, surrounded by at least one fatty alcohol and at least one polymer, preferably the amount of active compound is 10-60 %, the amount of fatty alcohol is 10-50 % and the amount of polymer is 10-40 %.

In case of units in which at least one active compound particle is present, surrounded by at least one fatty alcohol, at least one polymer and at least one sterol, preferably the amount of active ingredient is 2-70 %, the amount of fatty alcohol is 20-85 %, the amount of polymer is 2-25 % and the amount of sterol is 10-50 %.

It is possible for the person skilled in the art, on account of his/her expert knowledge, to select the best suited sterols and polymers depending on the active compound.

The individual active compound units can be prepared, for example, by spray-congealing (spray solidification) or preferably by spray-drying. Preferably spray-drying is used for the preparation of individual active compound units in which the active compound is surrounded by a mixture of at least one sterol and at least one polymer. Spray-drying takes place from a suitable solvent. Suitable solvents for the spray drying are preferably those in which the sterol and the polymer are soluble, while the active compound is insoluble. Suitable solvents can also be solvent mixtures.

If an acid-labile proton pump inhibitor, in particular a substituted pyridin-2-ylmethylsulfinyl-1H-benzimidazole, is employed as an active compound, the suitable solvents are, for example, hydrocarbons, chlorinated hydrocarbons and ethyl acetate. Hydrocarbons which may be mentioned are, in particular, linear or branched alkanes or alternatively cycloalkanes. Examples of linear alkanes are pentane, hexane and heptane. Examples of branched alkanes which may be mentioned are 2-methylpentane and 3-methylpentane. Examples of cycloalkanes which may be mentioned are cyclohexane and cyclopentane. If desired, mixtures of the hydrocarbons such as, for example, petroleum ether can also be employed. As a chlorinated hydrocarbon, chloroform and preferably dichloromethane may be mentioned.

On account of his/her expert knowledge in the field of spray drying and, if necessary, by means of customary tests, it is possible for the person skilled in the art, depending on the active compound employed, to select the best suited sterols, polymers and solvents.

For spray-drying, the sterol and the polymer are dissolved in the suitable solvent and the active compound is suspended therein. If desired, the active compound can also be suspended first and the sterol and polymer then dissolved. The suspension obtained is then sprayed in a spray drier.

Spray drying is carried out in a manner known per se. A detailed presentation of this technique is found in K. Masters, Spray Drying Handbook, 5th edition 1991, and J. Broadhead, S. K. Edmond Ronan, C. T. Rhodes, The Spray Drying of Pharmaceuticals, Drug Dev. Ind. Pharm. 18, 1169 (1992). The principle of spray drying consists in breaking down a solution or suspension of the product to be

dried into fine droplets and drying it using a hot stream of gas. The solid components remaining after evaporation of the solvent are separated off from the stream of gas by means of a cyclone and/or by a filter unit and collected.

Possible drying gases are, in particular, air and preferably nitrogen. The gas inlet temperature depends on the solvent.

Further subject of the invention is a preparation comprising an acid-labile active compound, at least one sterol and at least one polymer obtainable by spray-drying of a suspension of the acid-labile active compound in a solution of the sterol and the polymer in a suitable solvent.

Preferably spray-congealing is used for the preparation of individual active compound units in which the active compound is surrounded by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

For spray-congealing the fatty alcohol is fused and, if desired, the polymer and/or the sterol are dissolved therein to give a homogeneous solution. The active compound is then suspended in the solution. The suspension obtained is then sprayed in a spray-dryer.

Spray-congealing is carried out in a manner known per se. A detailed presentation of this technique is found for example in P.B. Deasy, Microencapsulation and Related Drug Process (1984).

Further subject of the invention is a preparation comprising an acid-labile active compound, at least one fatty alcohol or a mixture of at least one fatty alcohol and at least one polymer and/or sterol obtainable by spray-congealing of a suspension of the acid-labile compound in a solution, if desired, of the polymer and/or sterol in the fatty alcohol.

The particle size of the active compound used in the spray-drying or spray-congealing process is advantageously less than 100 µm, preferably less than 40 µm. Preferably, the particle size is in the range from 1-20 µm, particularly preferably in the range from 3-15 µm. Such particle size of the active compound for example can be achieved by milling the active compound in a suitable mill.

The individual active compound units, subsequently also designated as preparations, can then serve as a base for the production of the oral administration forms according to the invention. Examples of oral administration forms according to the invention to which the preparations can be processed are solutions, suspensions, emulsions, gels, tablets, effervescent tablets, powder in sachets, coated tablets or capsules. The person skilled in the art is familiar on the basis of his/her expert knowledge with auxiliaries which are suitable for the desired administration form. For the administration forms, it is

surprisingly possible to dispense with the enteric coating and in spite of this to achieve a therapeutic action on oral administration.

The oral administration forms according to the invention contain the acid-labile active compound in a dose customary for the treatment of the appropriate disorder. The oral administration forms according to the invention comprising acid-labile proton pump inhibitors are suitable for the treatment and prevention of all diseases for the treatment or prevention of which pyridin-2ylmethylsulfinyl-1H-benzimidazoles are employed. In particular the oral administration forms according to the invention can be employed in the treatment of diseases of the stomach. Thus, the oral administration forms according to the invention contain between 1 and 500 mg, preferably between 5 and 60 mg, of an acid-labile proton pump inhibitor. Examples which may be mentioned are tablets or capsules which contain 10, 20, 40 or 50 mg of pantoprazole sodium sesquihydrate. The daily dose (e.g. 40 mg of active compound) can in this case be administered in the form of a single administration or in several administrations using the oral administration forms according to the invention.

The oral administration forms comprising acid labile compounds according to the invention can also be combined with other active compounds, either in fixed or in free combination. Fixed combination in this connection relates to an administration form wherein all active compounds are present in a single dosage unit. Free combination in this connection relates to an administration form, wherein the active compounds are present in separated dosage units. In connection with oral administration forms comprising acid-labile proton pump inhibitors a combination with antimicrobially active compounds or NSAIDs (non steroidal anti inflammatory drugs) may be mentioned. Particularly mention may be made of a combination with antimicrobially active compounds which can be used in the control of Helicobacter pylori (H. pylori).

Examples of suitable antimicrobially-active ingredients (active against Helicobacter pylori) are enumerated in European Patent Application EP-A-282131. These active ingredients include, for example, bismuth salts (such as bismuth subcitrate or bismuth subsalicylate), sulfonamides, nitrofurans (such as nitrofurazone, nitrofurantoin or furazolidone), metronidazole, tinidazole, nimorazole or antibiotics. Examples of antibiotics which may be mentioned in this connection are, arranged according to particular classes of active ingredient: aminoglycosides, such as gentamicin, neomycin, kanamycin, amikacin or streptomycin; macrolides, such as erythromycin, azithromycin, clarithromycin, clindamycin or rifampicin; penicillins, such as penicillin G, penicillin V, ampicillin, mezlocillin or amoxicillin; polypeptides, such as bacitracin or polymyxin; tetracyclines, such as tetracycline, chlorotetracycline, oxytetracycline, minocycline or doxycycline; carbapenems, such as imipenem, loracarbef, meropenem or panipenem; cephalosporins, such as cefalexin, cefoxitin, cefuroxime axetil, cefotaxime, cefpodoxime proxetil, cefaclor, cefadroxil or cephalothin; gyrase inhibitors, such as ciprofloxacin, norfloxacin, ofloxacin or pefloxacin; or other different antibiotics, such as chloramphenicol. Particularly worthy of men-

tion in this connection is also the combination of a plurality of antimicrobially-active ingredients, for example the combination of a bismuth salt and/or tetracycline with metronidazole, or the combination of amoxicillin or clarithromycin with metronidazole and amoxicillin with clarithromycin.

Particularly worthy of mention in this connection is also administration of a proton pump inhibitor together with a plurality of antimicrobially-active ingredients, for example with the combination of a bismuth salt and/or tetracycline with metronidazole or with the combination of amoxicillin or clarithromycin or with metronidazole.

The preparation of administration forms according to the invention is described by way of example below. The examples below illustrate the invention in greater detail without restricting it.

Production of the preparations by spray-drying

Example 1

7.0 g of cholesterol and 5.0 g of Ethocel are dissolved in 100 ml of dichloromethane. 5.0 g of pantoprazole sodium sesquihydrate are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions: drying gas nitrogen, inlet temperature 51°C; pump output 10%. A white, free-flowing powder is obtained.

Example 2

5.0 g of cholesterol and 5.0 g of Kollidon 17 are dissolved in 80 ml of dichloromethane. 5.0 g of omeprazole magnesium are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions: drying gas nitrogen, inlet temperature 51°C; pump output 10%. A white, free-flowing powder is obtained.

Example 3

5.0 g of cholesterol and 8.0 g of polyvidone 17 PF are dissolved in 60 ml of dichloromethane. 5.0 g of pantoprazole sodium sesquihydrate are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions: drying gas nitrogen, inlet temperature 52°C; pump output 12%. A white, free-flowing powder is obtained.

Example 4

5.0 g of cholesterol and 8.0 g of polyvidone 17 PF and 2.0 g of ethylcellulose are dissolved in 60 ml of dichloromethane. 5.0 g of pantoprazole sodium sesquihydrate are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions: drying gas nitrogen, inlet temperature 52°C; pump output 12%. A white, free-flowing powder is obtained.

Example 5

5.0 g of β-sitosterol, 8.0 g of polyvidone 17 PF and 1.0 g of ethylcellulose are dissolved in 60 ml of dichloromethane. 5.0 g of pantoprazole sodium sesquihydrate are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions:

drying gas nitrogen, inlet temperature 52°C; pump output 12%. A white, free-flowing powder is obtained.

The preparations obtained according to Examples 1 to 5 have a particle size in the range 10-40 µm. By variation of the spraying conditions, it is possible, for example, to obtain larger or smaller particles.

Production of the preparations by spray-congealing

Example 6

100 g of cetyl alcohol are heated to 65°C. 50 g of pantoprazole sodium sesquihydrate are slowly added. The mixture is stirred until a homogeneous suspension is obtained and subsequently sprayed through a nozzle in a spray dryer.

Example 7

80 g of stearyl alcohol and 10 g of ethylcellulose are heated to 70°C and stirred until a clear solution is obtained. 40 g of pantoprazole sodium sesquihydrate are added and stirred. The homogeneous suspension is spray-congealed in a spray dryer.

Preparation of the administration forms

Example A (Granules)

134.7 g of mannitol, 30 g of Kollidon 30 and 20 g of xanthan are mixed dry. The mixture is granulated with water in a fluidized bed granulator. Granules having a particle size of 0.8-1.5 mm are obtained, which are mixed with the preparation (15.3 g) obtained according to Example 1. The mixture thus obtained is filled into sachets or compressed to give tablets - if desired together with further tablet auxiliaries - in a manner known to the person skilled in the art.

Example B

An amount corresponding to 22.6 mg pantoprazole sodium sesquihydrate of the powder formulation as described in Example 5 is mixed with appropriate amounts of lactose. This mixture is flavoured according to individual taste and filled into minibags (Sachets) each containing one individual dose.

The contents of one minibag are dispersed in a glass of tap water under stirring to obtain a suspension for oral intake.

Example C

An amount corresponding to 45.2 mg pantoprazole sodium sesquihydrate of the powder formulation as described in Example 1 is mixed with appropriate amounts of lactose. This mixture is combined with a mixture of citric acid and sodium carbonate. After addition of a suitable lubricant (e.g. sodium stearyl fumarate) and appropriate flavouring the mixture is directly (without further granulation) compressed to effervescent tablets. One tablet is to be thrown into a glass of a water to obtain a drinking suspension after tablet disintegration.

Example D

An amount corresponding to 45.2 mg pantoprazole sodium sesquihydrate of the powder formulation as described in Example 4 is mixed with appropriate amounts of (fast flowing) lactose for improvement of powder flow properties. This mixture is filled into appropriately sized hard gelatine capsules together with suitable concomitant medication like antibiotics (e.g. amoxicillin for Helicobacter pylori eradication) or NSAIDs (non steroidal anti inflammatory drugs) in available dosage forms.

Patent Claims

1. An oral administration form for acid-labile active compounds comprising an acid-labile active compound and pharmaceutical auxiliaries, wherein the auxiliaries are not suitable for the formation of enteric layers.

2. An oral administration form as claimed in claim 1, wherein the active compound is present in the form of a plurality of individual active compound units, the units having a particle size less than 200 µm.

3. An oral administration form as claimed in claim 1, wherein the active compound is present in the form of a plurality of individual active compound units, the units having a particle size less than 100 µm.

4. An oral administration form as claimed in claim 1, wherein the active compound is present in the form of a plurality of individual active compound units, the units having a particle size in the range from 4-20 µm.

5. An oral administration form for acid-labile active compounds comprising pharmaceutical auxiliaries and a plurality of individual active compound units, wherein the acid-labile active compound in the individual active compound units is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

6. An oral administration form as claimed in claim 5, wherein the acid-labile active compound in the individual active compound units is surrounded by a mixture of at least one sterol and at least one polymer.

7. An administration form as claimed in claim 1 and 5, wherein the acid-labile active compound is an acid-labile proton pump inhibitor.

8. An administration form as claimed in claim 1 and 5, wherein the acid-labile proton pump inhibitor is pantoprazole, omeprazole, esomeprazole, lansoprazole or rabeprazole.

9. An administration form as claimed in claim 1 and 5, wherein the acid-labile proton pump inhibitor is pantoprazole sodium sesquihydrate.

10. An administration form as claimed in claim 5, wherein the sterol is cholesterol, lanosterol, ergosterol, stigmasterol, sitosterol, brassicasterol, campesterol or mixtures thereof.

11. An administration form as claimed in claim 5, wherein the polymer is polyvidone, vinylpyrrolidone/vinyl acetate copolymer, polyvinyl acetate, methylcellulose, ethylcellulose, hydroxypropylcellulose, cellulose ester or mixtures thereof.

12. An administration form as claimed in claim 5, wherein the fatty alcohol is cetyl alcohol, myristyl alcohol, stearyl alcohol or mixtures thereof.

13. Use of an active compound unit comprising an acid-labile active compound, wherein the acid-labile active compound is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol for the manufacture of an oral administration form.

14. Process for the production of an oral administration form according to claim 1 and 5, characterized in that preparations comprising an acid-labile active compound, wherein the acid-labile active compound is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol are mixed with suitable pharmaceutical auxiliaries.

INTERNATIONAL SEARCH REPORT

Internati... Application No
PCT/EP 98/08036

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/44 A61K9/50

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)
IPC 6 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 709 087 A (FLAMEL TECHNOLOGIES) 1 May 1996 see claims 1,6,12	1-4
P,X	WO 98 52564 A (CIPLA LIMITED) 26 November 1998 see claims 1,4,9,10,16	5,7-9, 11-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
16 April 1999	23/04/1999

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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(54) Title: ANTI–INFLAMMATORY PHARMACEUTICAL FORMULATIONS

(57) Abstract

A pharmaceutical dosage form comprising a tablet containing a non–steroidal anti–inflammatory drug and misoprostol, wherein the non–steroidal anti–inflammatory drug is in the form of coated pellets.

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ANTI-INFLAMMATORY PHARMACEUTICAL FORMULATIONS

This invention relates to pharmaceutical formulations of anti-inflammatory drugs, particularly non-steroid and anti-inflammatory drugs (NSAIDs).

These NSAIDs are used for the treatment of inflammatory conditions such as osteoarthritis or rheumatoid arthritis. A side effect of the oral administration of NSAIDs particularly with long term usage, is a liability to ulcerogenic effects. NSAID induced ulcers in the stomach are potentially dangerous because few or no symptoms may be detected until significant damage has been caused. Certain prostoglandins, for example misoprostol have been shown to reduce and even prevent such ulcers.

It has been found experimentally that it is necessary for the prostaglandin to be released before the NSAID so as to protect the stomach from the effects of the NSAID. It is therefore preferable that the NSAID is coated to delay release. The coating may be a standard hydroxypropyl methyl cellulose coat of a thickness sufficient to delay release in the stomach for a short period, an enteric coat to delay NSAID release until it reaches the intestine, or a delay release coating to allow drug release over a period of time to permit less frequent dosing.

In addition the coating may act as a barrier between the NSAID and the prostaglandin to prevent decomposition of the prostaglandin caused by instability in the pressure of the NSAID.

EP-527887B discloses a pharmaceutical composition comprising a core of an NSAID surrounded by a coating containing the prostaglandin. The core is preferably coated

with a barrier of enteric coat before a mantle coat is added. No experimental details are given. It appears that this dosage form is made by press-coating, ie a tablet core containing the drug is made, and coated before being put in a second tableting operation to cover the coated core. Such a procedure requires use of specialised equipment which is not a normal pharmaceutical production tool and hence would need significant investment.

According to the present invention an oral pharmaceutical dosage form comprises a tablet containing a non-asteroidal anti inflammatory drug and misoprostol, wherein the non-asteroidal anti inflammatory drug is in the form of coated pellets.

The NSAID is preferably but not exclusively one of reasonably low weight per standard dose. That is an NSAID where the usual dose is 200 mg or below. Examples of such NSAIDs include indomethacin, piroxicam, meloxicam, flubiprofen, naproxan, ketoprofen, tenoxicam or similar molecules. Most preferably the drug is diclofenac sodium.

Enteric coated or delay release coated pellets have not been widely used because many workers have found damage or cracking to the enteric or delay release coating during the tablet compression stage. The present invention will work most effectively if the coating remains intact during compression.

It is possible to produce such pellets by conventional means although care is needed to ensure coat cracking does not occur. Techniques which can be used include coating the drug on a non-pariel core preferably composed of inert sugar or similar substance and then overcoating with the required coating before compression.

A preferred method is to form pellets by co-acervation or alternatively by precipitation of the pellets from solution as described by Zaruboru, Fell and Collett, (Int.J.Pharm, 1995, 125, 151-5).

In another preferred technique the pellets may be formed by spheronisation, rotogranulation or a similar technique. Preferably the pellets should be soft enough to deform slightly under compression to avoid cracking but not too soft so as to deform significantly which will also cause cracking or rupture of the coat. A suitable mixture of drug with a suitable amount of an excipient or several excipients can be found by simple, routine experiments. Suitable excipients include polyvinyl pyrolidone, sugars and cellulose derivatives particularly microcrystalline cellulose. A coating for the pellets may employ cellulose derivatives eg hydroxypropyl methyl cellulose, methacrylic acid and derivatives eg methyl methacrylates for example, Eudragrit® (Rhom Pharma), especially Eudragrit L or S. Other standard enteric coating materials for example phthalates, eg cellulose acetate phthalate or preferably hydroxypropylacetate phthalate or polyvinylacetate phthalate. Mixtures of these and other materials may be used to produce delay release coated beads. Normally coating will include plasticisers eg polyethylene glycol, triacilin or phthalate esters.

It has been found in practice that smaller pellets are better for use in accordance with this invention, preferably between 0.25 mm to 1.5 mm in diameter. Most preferably pellets between 0.8 mm to 1.2 mm diameter are employed. Pellets of this diameter show less tendency to crack under the compression forces.

The external compression material will include a prostaglandin, preferably misoprostol together with inert excipients. The prostaglandin may be used neat or it may be preferably diluted on an inert material. A preferred material is misoprostol diluted on hydroxypropyl methyl cellulose or polyvinyl pyrolidone. Other diluents may be used. The other materials which may be employed include inert fillers, binders, lubricants and colorants as used in normal pharmaceutical tablet making. An especially useful material for this invention is microcrystalline cellulose. The dosage of prostaglandin will be chosen to be suitable to prevent or reduce stomach ulceration caused by the NSAID. A suitable dose of misoprostol is between 100 - 200 micrograms per tablet but this may be increased or decreased depending on the NSAID used.

The coated pellets and prostaglandin mixture are then compressed on conventional tableting equipment. Tablets may have a break line or break lines to facilitate smaller doses. The tablet may be film or sugar coated if required.

Bilayer tablets may be employed. The non-steroidal anti inflammatory drug and excipients may be compressed into the lower half of the tablet and the misoprostol together with excipients superimposed and pressed onto it. A barrier layer may be provided between the two active ingredient-containing layers. The misoprostol containing layer may incorporate excipients to facilitate rapid dissolution of this active ingredient.

The invention is further described by means of example but not in any limitative sense.

EXPERIMENT 1

The following ingredients were employed.

	Diclofenac Pellets Enteric Coated 40%	123 mg
	Misoprostol Dispersion on HPMC (1:100)	20 mg
1)	Microcrystaline Cellulose (Avicel 102)	33 mg
2)	Sodium Stored Glycollate	3 mg
3)	Hydrogenated Cottonseed Oil	1 mg

The excipients 1 + 2 and misoprostol were sieved through a 250 μm screen. The diclofenac pellets were added and blended for 15 min in a cube blender. The lubricant 3) was added and the mixture was reblended for 5 min and compressed at 180 mg/tablet.

EXPERIMENT 2

The mixture from Experiment 1 was blended with the equivalent of another 100 mg of microcrystalline cellulose and was then compressed at 280 mg/tablet.

EXPERIMENT 3

The following ingredients were employed.

Mix 1	Diclofenac Pellets Enteric Coated 40%	123 mg
	Microcrystalline Cellulose	133 mg
	Sodium Starch Glycollate	3 mg
	Hydrogenated Cottonseed Oil	1 mg

Mix 2	Misoprostol dilution (1:100)	20 mg
	Microcrystalline Cellulose	196 mg
	Sodium Starch Glycollate	3 mg
	Hydrogenated Cottonseed Oil	1 mg

Mixture 1 was prepared with sieved excipients and then compressed to form a layer, having a weight of 260 mg. Mixture 2 was prepared and compressed on top of the diclofenac layer to atop weight of 120 mg, ie total 360 mg.

The resulting bilayer tablets were overcoated with an HPMC taste masking coat. The bead diameter was 1.05 to 1.16 mm.

Results.

Experiment 1 using USP baskets
Dissolution in acid 0.1 MHCL for 2 hrs
Less than 4% release.

Dissolution in pH 6.8 buffer
98-106% release after 1 hr

Scanning Electronic Microscopy showed no breakage of the enteric coating of the pellets after compression.

CLAIMS

1. A pharmaceutical dosage form comprising a tablet containing a non-steroidal anti inflammatory drug and misoprostol, wherein the non-steroidal anti inflammatory drug is in the form of coated pellets.

2. A dosage form as claimed in claim 1 containing a uniform mixture of coated non-steroidal anti inflammatory pellets and misoprostol.

3. A dosage form as claimed in claim 1 comprising a bilayer tablet containing coated non-steroidal anti inflammatory pellets in one layer and misoprostol in a second layer.

4. A dosage form as claimed in any preceding claim wherein the pellets include an overcoating of a barrier layer upon a pellet including a layer of non-steroidal anti inflammatory drugs sprayed or otherwise coated on a non-pariel core.

5. A dosage form as claimed in any preceding claim wherein the coating is an enteric coating.

6. A dosage form as claimed in claim 5 wherein the enteric coating is selected from: a methylmethacrylate copolymer, a polyvinylacetate phthalate, cellulose acetate phthalate, or hydroxypropylmethyl cellulose phthalate.

7. A dosage form as claimed in claim 6 wherein the enteric coat includes a plasticiser.

8. A dosage form as claimed in any of claims 5 to 7 including a barrier inert coat disposed between the drug core and the enteric coating.

9. A dosage form as claimed in claim 7 wherein the barrier coat is a cellulose derivative.

10. A dosage form as claimed in any of claims 1 to 4 wherein the pellets are coated with a barrier coat adapted to delay release of the non-asteroidal anti inflammatory drug.

11. A dosage form as claimed in any of claims 1 to 4 wherein the pellets are coated with a delay release coat adapted to release the drug throughout the gastrointestinal tract.

12. A dosage form as claimed in claim 11 wherein the delay release coat is formed from a methacrylate polymer or a mixture of a methacrylate polymer and a cellulose derivative.

13. A dosage form as claimed in any preceding claim wherein the pellets have a diameter of 0.25 to 1.5 mm.

14. A dosage form as claimed in claim 13 wherein the pellets have a diameter of 0.8 to 1.2 mm.

15. A dosage form as claimed in any preceding claim including one or more excipients selected from binders, lubricants, colorants, bulking agents and disintegrants.

16. A dosage form as claimed in any preceding claim wherein the non-steroidal anti inflammatory drug is diclofenac.

17. A dosage form as claimed in any of claims 1 to 15 wherein the non-steroidal anti inflammatory drug is ketoprofen.

18. A dosage form as claimed in any of claims 1 to 15 wherein the non-steroidal anti inflammatory drug is naproxen.

19. A dosage form as claimed in any of claims 1 to 15 wherein the non-steroidal anti inflammatory drug is selected from piroxicam and meloxicam.

20. A dosage form as claimed in any preceding claim comprising a tablet overcoated with a sugar or cellulose film barrier coating.

21. A dosage form as claimed in any preceding claim comprising a tablet overcoated with a barrier or taste masking coating.

22. A dosage form as claimed in any preceding claim comprising a tablet wherein the ratio of diclofenac to

excipients either in the whole tablet or in the diclofenac layer is between 70:30 and 30:70 parts by weight.

23. A method of manufacture of a pharmaceutical dosage form as claimed in claim 1 wherein the pellets are formed by extrusion and spheronisation of a mixture containing a non-steroidal anti inflammatory drug, followed by coating with a barrier coat.

24. A method of manufacture of a dosage form as claimed in claim 1 wherein the pellets are made by coasservation or precipitation from solution.

25. A method as claimed in claim 24 wherein an enteric coat is formed by contacting solutions of an alkali salt of a non-steroidal anti inflammatory drug, and enteric form forming polymer and an acid.

26. A method as claimed in claim 24 or 25 wherein the misoprostol is absorbed onto hydroxypropylmethylcellulose or other cellulose derivative prior to incorporation into a tablet.

27. A method of manufacture of a pharmaceutical tablet comprising the steps of mixing a coated pellet containing a non-steroidal anti inflammatory drug together with a powder containing misoprostol absorbed on a cellulose, polyvinylchloride or other excipient optionally together with one or more binding agents, bulking agents, disintegrants and lubricants and compressing the mixture to form tablets.

28. A method of manufacture of a pharmaceutical bilayer tablet consisting of mixing coated pellets containing a non-steroidal anti inflammatory drug with optional excipients selected from binders, bulking agents, disintegrants and lubricants; compressing the mixture to form the bottom half of a tablet and superimposing a mixture of misoprostol absorbed on a cellulose or polyvinylchloride or other material together with or more optional excipients selected from binders, bulking agents, disintegrants and lubricants; to form a tablet suitable for human administration.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/26 A61K9/24 A61K31/557 //(A61K31/557,31:195)

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)
IPC 7 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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(54) Title: QUICK RELEASE PHARMACEUTICAL COMPOSITIONS OF DRUG SUBSTANCES

(57) Abstract

The present invention relates to an oral modified release pharmaceutical composition for the administration of a therapeutically and/or prophylactically effective amount of an active substance (a drug substance) to obtain a relatively fast or quick onset of the therapeutic and/or prophylactic effect. The drug substances contained in a modified release pharmaceutical composition according to the invention are suitably a drug substance which has a very low solubitity under acidic conditions, i.e. under conditions similar to those present in the stomach and/or drug substances which have a pK_a value below about 5.5 such as in a range of from about 4 to about 5. The composition is based on a powder comprising a therapeutically and/or prophylactically active substance and has such a particle size that: when the powder is subjected to a sieve analysis, then at least about 90 % w/w of the particles passes through sieves 180 μm and the powder is contacted with an aqueous medium to form a particulate composition, which has such a particle size that when the particulate composition is subjected to a sieve analysis, then at least about 50 % w/w of the particles passes through sieve 180 μm. Furthermore, the composition, when tested in accordance with the dissolution method (I) defined herein employing 0.07 N hydrochloric acid as dissolution medium, releases at least about 50 % w/w of the active substance within the first 20 min of the test.

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QUICK RELEASE PHARMACEUTICAL COMPOSITIONS OF DRUG SUBSTANCES

The present invention relates to an oral modified release pharmaceutical composition for the administration of a therapeutically and/or prophylactically effective amount of an active substance (a drug substance) to obtain a relatively fast or quick onset of the therapeutic and/or prophylactic effect. The drug substances contained in a modified release pharmaceutical composition according to the invention are suitably a drug substance which has a very low solubility under acidic conditions, i.e. under conditions similar to those present in the stomach and/or drug substances which have a pK_a value below about 5.5 such as in a range of from about 4 to about 5. The compositions have been designed in such a manner that two important requirements are obtained, namely i) that the pharmaceutical composition releases the drug substance very fast under acidic conditions whereby the drug substance will become dissolved and, accordingly, available for absorption already almost immediately upon entrance into the stomach, and ii) that the mechanical strength of a composition according to the invention is sufficiently high to withstand normal handling of a pharmaceutical composition and to enable the composition to be coated using traditional coating equipment well known by a person skilled in the art. A composition according to the invention is suitable for use in those cases in which a fast onset of a therapeutic and/or prophylactic effect is desired, e.g. in connection with acute pain or mild to moderate pain. Accordingly, suitable therapeutically and/or propylactically active substances may *inter alia* be found in the class of drug substances denoted non-steroid anti-inflammatory drug substances (abbreviated in the following: NSAID substances or NSAIDs).

DESCRIPTION OF THE INVENTION

Pharmaceutical compositions designed to immediate release of a drug substance is known in the art.

Generally, however, the rationale which lies behind the kind of compositions which have been described to enable an immediate release of a drug substance is to employ a traditional formulation approach (such as, e.g., i) plain tablets which have a disintegration time in water of at the most about 30 min, ii) a traditionally formulated granulate or iii) loose powder of the drug substance itself. By doing so the immediate release part of the composition is intended to release the drug substance in a manner which corresponds to

a plain tablet formulation or the like and the term "immediate" is in such a context intended to denote that the release of the drug substance is faster than the release from a sustained release composition. The development of the so-called SplashDose®, FlashDose® and Flashtabs® are examples of pharmaceutical compositions wherein the focus has been to obtain a very fast disintegration time. Such formulations are suitable for use for drug substances which are readily soluble in the gastro-intestinal tract, but basically they do not solve the problems related to drug substances which have poor solubility characteristics.

Especially in those cases where the drug substance has a low solubility in an acidic medium having a pH of from about 1 to about 3, i.e. a pH corresponding to the pH in the stomach, the traditional formulation approach will lead to a pharmaceutical composition which has a suitable fast disintegration time but not necessarily a suitable fast dissolution rate of the drug substance under acidic conditions, i.e. a plain tablet will rapidly disintegrates into granules but the dissolution of the drug substance from the composition and/or the disintegrated composition under acidic conditions may be unsuitable low due to the solubility properties of the drug substance itself. The availability of a drug substance with respect to absorption, i.e. entrance into the circulatory system, is dependant on the presence of the drug substance on dissolved form as it is generally accepted that only dissolved substances are capable of passing the mucous membranes in the gastro-intestinal tract. Therefore, it is important that the dissolution of the drug substance is suitably fast even under acidic conditions in order to enable a fast and initial absorption so that a true fast or immediate therapeutic response is obtainable.

For drug substances which are weak acids it is very important to ensure a proper bioavailability of the drug substance already under acid conditions in order to achieve a true rapid therapeutic effect. However, the various approaches disclosed with respect to achievement of a combination of a rapid effect do not seem to take all the above-mentioned factors into account and, hence, there is a need for developing compositions which enable a true rapid onset of the therapeutic effect. To this end, we have especially focused on compositions comprising a drug substance belonging to the class of drug substances normally denoted NSAIDs, but other drug substances having a low solubility in acidic medium and/or a pK_a below about 5.5 may as well be suitable for use in a composition according to the invention.

Moreover, patients suffering from acute pain, mild to moderate pain and/or inflammatory conditions and/or related conditions very often require a dosage and a formulation which enable a fast onset of the therapeutic effect of the NSAID substances. The release from the dosage form must be safe, predictable and reliable. Furthermore, from a technical point of view, the release rate and the release pattern of the active drug substance from the composition should not significantly change during the shelf-life of the composition. A change in the release rate and/or release pattern may have a significant impact on the *in vivo* performance of the composition.

When testing prior art compositions intended for rapid release of the active drug substance (see e.g. Japanese patent No. 33491/90) the present inventors have revealed problems with respect to the release rate obtained and the robustness of the tablets. Thus, the development of a pharmaceutical composition which is suitable for rapid release of the active substance seems surprisingly to be a balance of on the one hand to obtain a composition which is sufficient robust to withstand normal handling (i.e. to have a sufficient mechanical strength) and on the other hand to enable a fast release and dissolution of the active drug substance in an acidic aqueous medium.

Thus, the purpose of the present invention is to provide a pharmaceutical composition for oral use which is useful for a fast delivery of an active drug substance to the circulatory system upon administration.

In one aspect, the invention relates to a quick release pharmaceutical composition for oral administration comprising a therapeutically and/or prophylactically active substance which has a solubility of at the most about 0.1 % w/v in 0.1 N hydrochloric acid at room temperature,

the composition being based on a powder comprising the therapeutically and/or prophylactically active substance and having such a particle size that - when the powder is subjected to a sieve analysis - then at least about 90% w/w such as, e.g. at least about 92% w/w, at least about 94% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of the particles passes through sieve 180 μm, the powder being contacted with an aqueous medium to form a particulate composition, which has such a particle size that - when the particulate composition is subjected to a sieve analysis - then at least about

50% w/w such as, e.g., at least about 55% w/w. at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w of the particles passes through sieve 180 μm, and

the composition - when tested in accordance with the dissolution method I defined herein employing 0.07 N hydrochloric acid as dissolution medium - releases at least about 50% w/w of the active substance within the first 20 min of the test.

In another aspect the invention relates to a quick release pharmaceutical composition for oral administration comprising a therapeutically and/or prophylactically active substance which has a solubility of at the most 0.1 % w/v in 0.1 N hydrochloric acid at room temperature,

the composition being in the form of a particulate composition or being based on a particulate composition which is obtained by contacting a powder comprising the therapeutically and/or prophylactically active substance with an aqueous medium in such a manner that the mean particle size of the particles of the particulate composition is at the most about 100% larger than the mean particle size of the powder before contact with the aqueous medium, and

the composition - when tested in accordance with the dissolution method I defined herein employing 0.07 N hydrochloric acid as dissolution medium - releases at least about 50% w/w of the active substance within the first 20 min of the test.

In preferred embodiments, the composition releases at least 55% w/w such as, e.g., at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of the total active drug substance present in the composition within the first 20 min of the test.

In another aspect the invention relates to a method for the preparation of a composition according to the invention, the method comprising the steps of

i) mixing the therapeutically and/or prophylactically active substance with a) an alkaline substance, b) a filler having binding properties, and, optionally, c) other pharmaceutically acceptable excipients to obtain a powder mixture,

ii) contacting the thus obtained powder mixture with an aqueous medium to obtain a wet powder,

iii) drying the thus obtained wet powder at a temperature above room temperature until the water content in the powder is at the most about 5% w/w determined as described herein, to obtain a first particulate mixture,

iv) sieving the thus obtained first particulate mixture,

v) optionally, adding any further pharmaceutically acceptable excipients to obtain a second particulate mixture,

vi) optionally, compressing the thus obtained second particulate mixture into tablets, and

vii) optionally, coating the thus obtained tablets.

In still further aspects the invention relates to a method for treatment and/or prophylaxis of acute pain and/or mild or moderate pain comprising administering to a patient an effective amount of a therapeutically and/or prophylactically active drug substance in the form a quick release composition according to the invention.

As mentioned above, the solubility of the therapeutically and/or prophylactically active substance in 0.1 N hydrochloric acid at room temperature is at the most about 0.1% w/v such as, e.g., at the most about 0.05% w/v, at the most about 0.01% w/v, at the most about 0.009% w/v, at the most about 0.008% w/v, at the most about 0.007% w/v, at the most about 0.006% w/v, at the most about 0,005% w/v, at the most about 0,004% w/v, at the most about 0.003% w/v, at the most about 0.002 % w/v or at the most about 0.001% w/v.

Since the solubility of the therapeutically and/or prophylactically active substance such as, e.g., lornoxicam is < 1 mg /100 ml in 0.1 N HCl (aqueous solution of 0.1 N hydrochloric acid) the present inventors have found that incorporation of e.g. an NSAID substance in free form or in the form of a traditional formulation does not give the desired quick release under acidic conditions to enable a fast onset of the therapeutic effect *in vivo*.

Furthermore, irrespective of the solubility under acidic conditions, a composition containing an active drug substance which has a very low dissolution rate in 0.1 N or 0.07 N HCl may also present problems with respect to obtaining a quick release and dissolution of the active drug substance. Accordingly, compositions according to the invention may as well contain a therapeutically and/or prophylactically active substance which – when tested by solubility method I described herein – has such a dissolution rate that it allows an amount of at the most 50% w/w of the active substance to be dissolved within the first 20 min of the test.

A quick release of an active drug substance (such as, e.g., an NSAID substance) will, however, take place under acidic conditions provided that the drug substance is presented in a formulation wherein specific means has been used in order to manipulate the release rate so that the release becomes much faster compared to a traditional composition. Thus, the present inventors have found it necessary to adjust the release rate from a traditional composition when the active drug substance either has i) a very low solubility in 0.1 N hydrochloric acid, ii) a very low solubility rate, or iii) has a pK_a below about 5.5 such as, e.g., at the most about 5.3, at the most about 5.2, at the most about 5.0 such as, e.g., in a range of from about 3.4 to about 5.0, in a range of from about 4.0 to about 5.0. Thus, a fast release composition must be manipulated with respect to release in order to achieve a suitable fast release rate.

The present inventors have surprisingly found that in order to obtain a quick release composition containing active drug substances like the ones described above it is necessary to subject the active drug substance to contact with an alkaline substance under certain conditions. Furthermore, the success of the manufacture, i.e. a tablet that fulfils the general requirements of tablets, depends not only on a sole addition of e.g. sodium hydrogencarbonate (as described in Japanese patent No. 33491/90, Taisho) but also on the following parameters:

1. Contact conditions for the active drug substance and an alkaline substance (contact time, energy input and contact medium)
2. Inclusion of a substance denoted "a filler having binding properties"
3. The mean particle size of the filler having binding properties
4. The mean particle size or the particle size (as obtained from a sieve analysis) of the particulate material obtained after contacting the active drug substance and the alkaline substance with an aqueous medium and before any manufacture of the composition into e.g. tablets
5. The porosity of the particles obtained after contacting the active drug substance and the alkaline substance with an aqueous medium and before any manufacture of the composition into e.g. tablets. The present inventors have found that in certain cases it is possible to obtain suitable release characteristics even if the particle size is not as small as claimed. In those cases, however, the porosity of the particles has been sufficiently high to allow a quick release or alternatively, the hardness of the particles is low.

In the experimental section herein is shown the influence of various process parameters on the properties of the resulting composition. The overall conclusion from the experiments is that in order to obtain a quick release composition it is of utmost importance to control conditions under which the contact between the active drug substance and the alkaline substance takes place. Furthermore, it is demonstrated that in order to obtain a composition with favourable shelf-life it seems necessary that the contact takes place during the manufacturing of the composition (see Example 12 which shows that when the contact between the active drug substance and the alkaline substance has taken place before manufacturing then a decreased shelf-life is obtained). Further investigations have shown that a suitable release is only obtained when the particle size of the particulate material obtained after contact between the active drug substance and the alkaline substance is controlled. (However, as explained above, the particle size requirement can be less stringent if the porosity of the particulate material is increased or if the hardness of the particles is decreased) In other words, it is of utmost importance with respect to the release of the active substance to ensure that the contact *in situ* between the active drug substance and the alkaline substance takes place under controlled conditions. The contact is performed by adding an aqueous medium to a powder mixture comprising the active drug substance and the alkaline substance and, optionally the filler having binding properties and other pharmaceutically acceptable

excipients. The addition of such a medium is performed by the same procedures as if the powder mixture is subjected to a wet granulation process. However, the present inventors have found that the application of the aqueous medium and the process involved must be controlled in such a manner that the resulting particulate mixture is not a traditional granulate, i.e. agglomerates built up of particles of the substances employed. Normally, during a granulation process the particle size is increased by a factor of at least 1.5 and a 200-500% increase may be observed. However, if agglomerates are formed to a major extent, the mean particle size of the particulate mixture will become so large that it has a negative impact on the release rate.

Furthermore, the constitution of the aqueous medium is an important and critical factor (see below).

As a consequence of the above-mentioned formulation requirements, the present inventors have found that the manufacture of a composition according to the invention – even if a wetting step is included – is to be regarded as a process suitable for dry granulation and/or dry compression. It is contemplated that the balance between the qualities of the excipients and the aqueous treatment of the active substance and the alkaline substance is very important in order to obtain a suitable result with respect to both obtaining a quick release and a proper, substantially robust composition. It is believed that a mere effervescent tablet containing e.g. the active substance and sodium hydrogen carbonate will not lead to a controlled quick release because the carbon dioxide formed when such a tablet is dissolved in a glass of water will lead to a quick disintegration but not a quick dissolution. Most likely, the disintegration is so quick that the individual components (e.g. the active substance and the alkaline substance) have no substantial influence on one another. By subjecting the active substance and the alkaline substance to a controlled aqueous treatment, the formation of carbon dioxide during this treatment is believed to take place to some extent but the gas formation is not exhausted. Thus, when the tablet disintegrates in the stomach the remaining carbon dioxide is formed which allows a more ideal disintegration of the tablet and, consequently, gives rise to a local condition in the stomach which is favourable for quick dissolution of the active substance. A local increase in the pH value in the microenvironment of the particles is thus contemplated.

A composition according to the invention may be in the form of a solid composition such as in the form of a particulate composition or in the form of a unit dosage composition such as, e.g., a tablet, a capsule, a sachet or the like.

As mentioned above, the process with respect to the preparation of a composition according to the invention has to be controlled. Thus, it is important that the active drug substance is brought into contact with an alkaline substance. The alkaline substance may be an antacid or an antacid-like substance such as, e.g., sodium hydrogen carbonate, sodium carbonate, potassium carbonate, magnesium carbonate, magnesium hydroxide or magnesium metasilicate aluminate or mixtures thereof. The reaction medium is typically a solvent comprising water and an organic solvent. The organic solvent is a solvent which is miscible with water such as, e.g., a branched or unbranched lower (C_1-C_5) aliphatic alcohol like, e.g., ethanol, methanol, isopropanol, 1-propanol, 1-butanol, 2- butanol, tert. butanol , 1- pentanol, 2-pentanol, 3-pentanol, iso-pentanol and tert. pentanol and mixtures thereof.

The concentration of the organic solvent in the solvent employed is normally from about 0% v/v to about 95% v/v such as, e.g., from about 10% v/v to about 90% v/v, from about 10% v/v to about 80% v/v, from about 15% v/v to about 70% v/v, from about 15% v/v to about 60% v/v, from about 20% v/v to about 50% v/v, from about 20% v/v to about 40% v/v, from about 25% v/v to about 30% v/v such as, e.g. about 25% v/v.

An especially suitable organic solvent is ethanol in a concentration from about 0% v/v to about 95% v/v. The present inventors have found that a contact medium, i.e. an aqueous medium, comprising water and ethanol in a volume ratio of from about 1:50 to about 1:1 is suitable, preferably the ratio is from about 1:10 to about 1: 1 such as, e.g. 1:2 or 1:3. Such an aqueous medium may only contain water and ethanol or it may contain other solvents as well.

The contact is generally carried out without any external heating, but of course heating may be employed to speed up the process. The contact performed may result in a formation of a conjugate, an adduct or a salt or a partial salt but investigations are on-going in order to clarify this specific question. Without being limited in any way, it is presently believed that the conjugate or adduct formed may be in the form of a salt or

complex formed by a reaction between the therapeutically and/or prophylactically active substance and the alkaline substance employed in process step i) above.

If the active drug substance and the alkaline substance is processed under conditions where an aqueous contact between the two components does not take place (i.e. under anhydrous conditions) then the present inventors have found that the resulting composition does not fulfil the requirements herein with respect to the release the active drug substance from the composition.

The mean particle size of the antacid-like substance employed in compositions according to the invention (as raw material) is normally at the most about 250 μm, such as at the most about 225 μm, at the most about 200 μm, at the most about 175 μm, at the most about 150 μm, at the most about 145 μm, at the most about 140 μm, at the most about 135 μm, at the most about 130 μm such as, e.g., in a range of from about 20 μm to about 250 μm, in a range of from about 40 μm to about 200 μm, in a range of from about 60 μm to about 175 μm, in a range from about 80 μm to about 150 μm or in a range of from about 100 μm to about 120 μm.

Besides the employment of an alkaline substance in order to enable a suitable contact with the active drug substance, another important ingredient in a composition according to the invention is an ingredient which imparts the necessary mechanical strength to the composition to enable normal handling and, optionally, conventional coating of the composition. In the present context, such an ingredient is denoted "a filler having binding properties". As demonstrated in the Examples herein compositions without such an ingredient or compositions including such an ingredient but having an inappropriate particle size seem to be compositions which are too soft, i.e. have such a poor mechanical strength (friability and crushing strength) that they will not withstand the handling tablets normally have to withstand in order to be used by patients.

Examples of a suitable filler having binding properties for use in compositions according to the invention is, e.g., lactose (such as, e.g., Tabletose®, Pharmatose®), sugar derivatives (such as, e.g., mannitol, sorbitol), calcium carbonate ($CaCO_3$), tricalcium phosphate ($Ca_5(PO_4)_3OH$), calcium hydrogen phosphate ($CaHPO_4$) (such as, e.g., Di-Cafos®, Di-Tab®, Emcompress® or Pharmacompress®), or the like and/or mixtures thereof.

In the experimental section herein calcium hydrogen phosphate has been employed as an example of a filler having binding properties and the results show that the mechanical strength of the tablets prepared is dependant on the particle size of the calcium hydrogen phosphate employed. Too small or too large a particle size will result in tablets which are too soft to withstand normal handling by patients.

Accordingly, the filler having binding properties as raw material has normally a mean particle size of at the most about 140 μm, such as, e.g., at the most about 130 μm, at the most about 120 μm, at the most about 110 μm, at the most about 100 μm, at the most about 90 μm, at the most about 80 μm, at the most about 70 μm, at the most about 60 μm, at the most about 50 μm, at the most about 40 μm, at the most about 35 μm, at the most about 30 μm or at the most about 25 μm such as, e.g., in a range of from about 10 μm to about 80 μm. or in a range of from about 10 to about 65 μm such as e.g. 15-55 μm.

In accordance with the discussion above relating to the particle size, the process step ii) above in a process for the preparation of a composition according to the invention is performed in a conventional high shear mixer employing an energy input which is sufficient to enable a contact to take place between the therapeutically and/or prophylactically active substance and the alkaline substance employed in step i) but at the same time is sufficiently low to avoid formation of a large amount of agglomerates during the mixing.

Thus, in a composition according to the invention, the mean particle size of the particles of the particulate mixture obtained after contact between the active drug substance and the alkaline substance (including any other ingredients present such as, e.g. a filler having binding properties) is at the most about 100% larger than the mean particle size of the powder mixture before the reaction in an aqueous medium. More specifically, the mean particle size of the particle of the particulate composition is at the most 90% such as, e.g., about 80%, about 75%, about 70%, about 65%, about 60%, about 55% or about 50% larger than the mean particle size of the powder mixture before the reaction in an aqueous medium.

The particle size of the particulate mixture is also expressed by means of results obtained from a sieve analysis, namely that at least about 50% w/w such as, e.g., at least about 55% w/w. at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at

least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w of the particles passes through sieve 180 μm. Before the contact with the aqueous medium, the particle size of the powder is also expressed by means of results obtained from a sieve analysis, namely that at least about 90% w/w such as, e.g. at least about 92% w/w, at least about 94% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of the particles passes through sieve 180 μm.

With respect to the mean particle size of the particles of the particulate composition obtained after contact of between the active drug substance with the alkaline substance (including any other ingredients present such as, e.g. a filler having binding properties) it is at the most about 250 μm, such as, e.g. at the most about 240 μm, at the most about 230 μm, at the most about 220 μm, at the most about 210 μm, at the most about 200 μm, at the most about 190 μm, at the most about 180 μm, at the most about 175 μm, at the most about 150 μm, at the most about 125 μm, at the most about 100 μm, at the most about 90 μm, at the most about 80 μm or at the most about 75 μm, whenever appropriate, after a reaction in an aqueous medium.

As mentioned above, a composition according to the invention has such a mechanical strength that it can be subjected to normal handling and coating in conventional coating apparatus without breakage or otherwise rupture. Therefore, a composition according to the invention in the form of tablets having a diameter of 9.5 mm– when subjected to a crushing strength test in accordance with Ph. Eur. - has a crushing strength of at least about 50 N such as, e.g., at least about 60 N, at least about 70 N, at least about 80 N such as, e.g., in a range from about 60 to about 130 N, in a range from about 70 to about 120 N or in a range of from about 75 to about 110 N such as from about 80 to about 100 N. With respect to tablets having other diameters than 9.5 mm, a person skilled in the art will know which crushing strength values become relevant.

An important ingredient with respect to imparting the desired mechanical strength to a composition according to the invention (if the composition is in the form of a tablet) is as mentioned above the filler having binding properties. Therefore, a composition according to the invention - when tested as a composition without the filler having binding properties in the crushing strength apparatus according to Ph. Eur. - is contemplated to have a

crushing strength of less than about 45 N such as, e.g., less than about 30 N, less than about 25 N, less than about 20 N, less than about 15 N or less than about 10 N.

In order i) to avoid any substantial degradation of the active drug substance employed in a composition according to the invention and ii) to enable a substantially constant release rate of the active drug substance from a composition according to the invention in the life span of the composition, water content in the composition is at the most about 5% w/w such as, e.g., at the most about 4% w/w, at the most about 3%, at the most about 2% w/w, at the most about 1.5% w/w, at the most about 1.3% w/w, at the most about 1.1% w/w, at the most about 1.0% w/w or at the most about 0.9% w/w determined by a LOD (loss on drying) method (IR dryer, 30 min at 70 °C).

Definitions of selected terms used herein

The term "modified release composition" used in the present context is defined as a composition from which the release of the drug differs from that of a traditional composition. The release rate is in other words controlled and it is possible to manipulate the release rate by e.g. changing the formulation parameters. The term "modified" is often used in the sense of prolonged, but the term is not restricted to an extended or prolonged effect; the term "modified" may as well cover the situation where the release rate is manipulated in such a manner that a quicker release than normally expected is obtained. Thus, in the present context the terms "quick" , "fast" and "enhanced" release as well as "controlled", "delayed", "sustained", prolonged", "extended" and other synonyms well known to a person skilled in the art are covered by the term "modified", but with respect to the present invention, the term "modified release" is to be understood as a "quick release", "fast release" or "enhanced release".

The term modified release in the present context refers to a composition which can be coated or uncoated and prepared by using pharmaceutically acceptable excipients and/or specific procedures which separately or together are designed to modify the rate or the place at which the active ingredient or ingredients are released (Ph. Eur. 97).

The terms "quick release", "fast release" or "enhanced release" in the present context refer to a modified release composition of which the release of the active ingredient and its subsequent absorption are fast. More specifically, the terms "quick

release", "fast release" or "enhanced release" mean that for a composition – when subjected to a dissolution method I described herein – at least about 50% w/w of the active substance is dissolved within the first 20 min of the test.

The term "dosage unit" in the present context refers to one single unit, e.g. a capsule, tablet, a sachet or any other relevant dosage form known within the art. A dosage unit may represent a plurality of individual units which in accordance with the general state of the art may be in the form of a capsule, a tablet, a sachet, etc.

The term "bioavailability" designates the rate and extent to which the drug is absorbed from the modified release composition.

The terms "NSAIDs" or "NSAID substances" are used herein to designate a group of drugs that belongs to non-steroid anti-inflammatory drug substances and pharmaceutically acceptable salts, prodrugs and/or complexes thereof as well as mixtures thereof.

The therapeutic classes mentioned herein are in accordance with the ATC (Anatomical Therapeutic Chemical) classification system.

Active drug substances

In the following are given examples of active drug substances which may be incorporated in a composition according to the invention. A majority of the active drug substances mentioned are weak acids, i.e. substances which have a pK_a value below about 5.5 such as, e.g., in a range of from about 3.0 to about 5.5 or in a range of from about 4.0 to about 5.0. In this connection it can be mentioned that the pK_a value for lornoxicam is about 4.7, for naproxen about 4.2, for indometacin about 4.5 and for acetylsalicylic acid about 3.5. Moreover, active drug substances like those mentioned above (i.e. weak acids having a pK_a value of at the most about 5.5 or about 5.0) generally have a poor solubility in media having a pH below the pK_a value; as an example the solubility of lornoxicam at a pH corresponding to 0.1 N HCl is less than about 1 mg/100 ml at room temperature and active drug substances like acetylsalicylic acid, indometacin and naproxen are regarded as substances which are practically insoluble in water and 0.1 N HCl at room temperature. From the discussion relating to solubility and availability of the active drug substance in

order to get access to the circulatory system it is should be appreciated that the release (dissolution) of the active drug substance from the composition should be quick under acidic conditions, e.g., in 0.1 N HCl even if the active drug substance has a very low solubility in this medium.

Relevant examples of active drug substances suitable for use in compositions according to the invention are in general weakly acidic substances such as, e.g., paracetamol and/or NSAID substances like

- aminoarylcarboxylic acid derivatives like e. g. enfenamic acid, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, morniflumate, niflumic acid, and tolfenamic acid,
- arylacetic acid derivatives like e.g. aceclofenac, acemetacin, amfenac, bromfenac, cimmetacin, diclofenac, etodolac, fentiazac, glucametacin, indomethacin, lonazolac, metiavinic acid, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, and zomepirac,
- arylcarboxylic acids like e.g. ketorolac and tinoridine,
- arylpropionic acid derivatives like e. g. alminoprofen, bermoprofen, carprofen, dexibuprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen, ibuproxam, ketoprofen, loxoprofen, naproxen, oxaprozin, pranoprofen, protizinic acid, and tiaprofenic acid,
- pyrazoles like e.g. epirizole,
- pyrazolones like e.g. benzpiperylon, mofebutazone, oxyphenbutazone, phenylbutazone, and ramifenazone,
- salicylic acid derivatives like e.g. acetaminosalol, acetylsalicylic acid, benorylate, eterisalate, fendosal, imidazole salicylate, lysine acetylsalicylate, morpholine salicylate, parsalmide, salamidacetic acid and salsalate,
- thiazinecarboxamides like a.o. ampiroxicam, droxicam, lornoxicam, meloxicam, piroxicam, and tenoxicam,
- others like bucillamine, bucolome, bumadizon, diferenpiramide, ditazol, emorfazone, nabumetone, nimesulide, proquazone and piroxicam (e.g. in the form of a betacyclodextrin complex).

From a market point especially the following NSAIDs are interesting: lornoxicam, diclofenac, nimesulide, ibuprofen, piroxicam, piroxicam (betacyclodextrin), naproxen,

ketoprofen, tenoxicam, aceclofenac, indometacin, nabumetone, acemetacin, morniflumate, meloxicam, flurbiprofen, tiaprofenic acid, proglumetacin, mefenamic acid, fenbufen, etodolac, tolfenamic acid, sulindac, phenylbutazone, fenoprofen, tolmetin, acetylsalicylic acid, dexibuprofen and pharmaceutically acceptable salts, complexes and/or prodrugs and mixtures thereof.

Other relevant active drug substances are COX-2 (COX is an abbreviation for cyclooxygenase) inhibitors like e.g. celecosib and flosulide.

At present, the most preferred drug substance is lornoxicam and pharmaceutically acceptable salts, complexes and prodrugs thereof. Lornoxicam may be present in a composition according to the invention as the sole drug substance or in combination with other drug substances.

In those cases where a quick release composition of the present invention includes an NSAID substance as the therapeutically active ingredient, the amount of the active drug substance corresponds to from 1 to about 1600 mg of by weight. Alternatively, the dosage form may contain molar equivalent amounts of pharmaceutically acceptable salts thereof. The dosage form contains an appropriate amount to provide a substantially equivalent therapeutic effect.

The active substances mentioned above may be present in a composition according to the invention as i) the only drug substance, or ii) together with at least one other active drug substance such as, e.g. an NSAID substance.

Relevant substances in this context are e.g. antidepressants, opioids, prostaglandine analogs (e.g. misoprostol), glucocorticosteroids, cytostatics (e.g. methotrexate), H_2 receptor antagonists (e.g. cimetidine, ranitidine), proton pump inhibitors (e.g. pantoprazole, omeprazole, lansoprazole), antacids, furosemid, acetaminophen (paracetamol), penicillamine, sulfasalazine and/or auranorfin, and – whenever relevant – pharmaceutically acceptable salts, complexes and/or prodrugs and mixtures thereof.

The term "antidepressant" used in the present context includes tricyclic antidepressants as well as other antidepressants and mixtures thereof. Pharmaceutically acceptable salts and/or complexes of antidepressant are also within the definition of antidepressant. Thus,

the term "antidepressant" is used here to designate a group of drugs that have, to varying degrees, antidepressive properties and/or suitable properties with respect to alleviation or treatment of neurogenic pain and/or phantom pain. In the present context the term "antidepressant" encompasses drug substances mainly from the therapeutic class N06 or from the following drug classification: Psychoanaleptics excluding anti-obesity preparations; anti-depressants/thymoanaleptics including substances used in the treatment of endogenous and exogenous depression such as, e.g., imipramine, nortriptyline, amitriptyline, oxipramol and MAO-inhibiting substances; lithium; combinations of drugs with ataractics; psychostimulants including drugs which increase the psychic and physical performance and which have a fatigue depressing, stimulating effect such as, e.g., fentyllines, fencamfamine, methylphenidate, amphetamines; pyscholeptic-psychoanaleptic combinations; nootropics [which are a class of psychoactive drugs which are claimed to have a selective action on integrative functions of the CNS. Their action is alleged to be particularly associated with intellectual function, learning and memory. Nootropics include preparations containing substances such as piracetam, pyritinol, pyrisuccideanol maleate, meclofenoxate, cyprodenate and their combinations with other substances, excluding those products with a vasodilatory action (see the therapeutic class C04A). Combinations with cardiac glycosides are classified in the therapeutic class C01A]; and neurotonics and other miscellaneous products including products which are not classified above such as single or combination products containing bisibutiamin, deanol and derivatives, GABA, GABOB, N-acetyl asparaginic acid glutaminic acid and salts, kavain, phospholipid, succinodinitrate.

The presently most interesting drug substances belong to the tricyclic antidepressants. Relevant examples of antidepressants are: tricyclic antidepressants such as, e.g. dibenzazepine derivatives like carpipramine, clomipramine, desipramine, imipramine, imipraminoxide, imipramine pamoate, lofepramine, metapramine, opipramol, quinupramine, trimipramine; dibenzocycloheptene derivatives like amitriptyline, amitriptyline and chlordiazepoxide, amitriptyline and medazepram, amitriptyline and pridinol, amitriptyline and perphenazine, amitriptylinoxide, butriptyline, cyclobenzaprine, demexiptiline, nortriptyline, nortriptyline and diazepam, nortriptyline and perphenazine, nortriptyline and fluphenazine, nortriptyline and flupentixol, noxiptilin, protriptyline; dibenzoxepine derivatives like doxepin; and other tricyclic anti-depressants like adinazolam, amoxapine, dibenzepin, dimetacrine, dosulepin, dosulepin and diazepam, dothiepin, fluacizine (fluoracyzine, toracizin), iprindole, maprotiline, melitracen,

melitracene and flupentixol, pizotyline, propizepine, and tianeptine; other antidepressants like 5-hydroxytryptophan, ademetionine, amfebutamone, amfebutamone hydrochloride, amineptine, amineptine hydrochloride, amisulpride, fluoxetine hydrochloride, fluoxetine, hypericin, lithium carbonate, sertraline hydrochloride, sertraline, St John's wort dry extract, trimipramine maleate, citalopram, citalopram hydrobromide, clomipramine chloride, clomipramine hydrochloride, d-phenylalanine, demexiptiline, demexiptiline hydrochloride, dimethacrine tartrate, dothiepin, dothiepin hydrochloride, doxepin, fluphenazine hydrochloride, fluvoxamine, fluvoxamine hydrogen maleate, fluvoxamine maleate, ginkgo biloba, indalpine, isocarboxazide, johanniskrauttrockenestrakt, 1-tryptophan, lithium citrate, lithium sulfate, lofepramine, maprotiline, maprotiline hydrochloride, maprotiline mesilate, medifoxamine, metaprimine fumarate, mianserin, moclobemide, nitroxazepine hydrochloride, nomifensine, nomifensine maleate, nomifensin hydrogenmaleat, oxitriptan, paroxetine, paraoxetine hydrochloride, phenelzine, phenelzine sulfate, piracetam, pirlindole, pivagabine, prolintane hydrochloride, propizepine hydrochloride, protriptyline hydrochloride, quinupramine, remoxipride hydrochloride, rubidium chloride, setiptiline maleate, tianeptine sodium, trazodone hydrochloride, venlafaxine hydrochloride, maprotiline, toloxatone, tranylcypromine, trazodone, trazodone hydrochloride, viloxazine, viloxazine hydrochloride, zimelidine, zimelidine dihydrochloride.

At present, the most interesting antidepressant drug substances for use in a composition according to the invention are amitriptyline and/or imipramine and pharmaceutically acceptable salts, complexes and prodrugs thereof. Amitriptyline and/or imipramine may be present in a composition according to the present invention either as the sole drug substance or in combination with other drug substances. Amitriptyline is a very interesting drug candidate with respect to preventing and/or treating neurogenic pains and phantom pains.

The term "opioid" is used here to designate a group of drugs that are, to varying degrees, opium- or morphine-like in their properties. The term includes natural and synthetic opioids as well as active metabolites such as morphine-6-glucuronide and morphine-3-glucuronide, and mixtures of opioids. Pharmaceutically acceptable salts and/or complexes of opioids are also within the definition of opioids.

Further relevant examples of opioids for use in compositions according to the invention include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide,

buprenorphine butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, heroin, hydrocondone, hydromorphone, hydroxypethidine, isomethadone, dextropropoxyphene, ketobemidone, levallorphan, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicormorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, salts thereof, mixtures of any of the foregoing, mixed μ-agonists/antagonists, μ- and/or κ-agonists, combinations of the above, and the like.

Within the scope of the invention is of course that more than one active drug substance may be present in a composition, e.g. more than one NSAID substance and/or drug substances within the same or different therapeutic classes. Specific relevant therapeutic classes are M01A (NSAIDs), R05D, N02 (analgesics), N2A (opioids) and N2B (non-narcotic analgesics).

Dosage

In general, the dosage of the active drug substance present in a composition according to the invention depends *inter alia* on the specific drug substance, the age and condition of the patient and of the disease to be treated.

Compositions according to the invention will generally contain an amount of the active drug substance which enables a sufficient therapeutic and/or prophylactic response.

In order to illustrate the broad ranges of suitable doses, the recommended daily doses for selected NSAID substances is listed in the following:

Aceclofenac: 200 mg
Diclofenac: 100 mg
Etodolac: 400 mg

Fenbufen: 900 mg
Fenoprofen: 1.5 g
Flurbiprofen: 200 mg
Ibuprofen: 1.6 g
Indometacin: 100 mg
Ketoprofen: 200 mg
Meloxicam: 15 mg
Nabumeton: 1 g
Naproxen: 750 mg
Piroxicam: 20 mg
Sulindac: 300 mg
Tenoxicam: 20 mg
Tiaprofenic acid: 600 mg
Tolfenamic acid: 400 mg
Tolmetin: 800 mg

The amount of e.g. an NSAID substance in a quick release composition according to the invention may be selected so that is corresponds to about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 8 mg, 10 mg, 12 mg, 16 mg, 20 mg, 24 mg, 25 mg, 30 mg, 32 mg, 50 mg, 60 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1 g, 1.1 g, 1.2 g, 1.3 g or 1.6 g of NSAID substance which are dosages generally known in the art.

A composition according to the invention may be produced in different series of dosage forms of e.g. 4 mg, 8 mg, 12 mg, 16 mg, 24 mg, 32 mg etc., each of the series having individual properties resulting from the design of modified release of the composition. Any desired total dosage can then be selected from the relevant dosage forms within each of the series.

The preferred dosage form according to the invention is in the form of a capsule, tablet, sachet etc. The size of the dosage form is adapted to the amount of the active drug substance contained in the composition.

The above suggested dosage amounts should not be regarded as a limitation of the scope of the invention as it is obvious for the skilled person that any desired amount of the

active drug substance may be applied and is only limited by the size of the composition and the type of the active drug substance.

Pharmaceutically acceptable excipients

Apart from the active drug substance in the composition, a pharmaceutical composition according to the invention may further comprise pharmaceutically acceptable excipients.

In the present context, the term "pharmaceutically acceptable excipient" is intended to denote any material which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se*. A pharmaceutically acceptable excipient may be added to the active drug substance with the purpose of making it possible to obtain a pharmaceutical formulation which has acceptable technical properties. Although a pharmaceutically acceptable excipient may have some influence on the release of the active drug substance, materials useful for obtaining modified release are not included in this definition.

Fillers/diluents/binders may be incorporated such as sucrose, sorbitol, mannitol, lactose (e.g., spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose or Fast-Floc®), microcrystalline cellulose (e.g., various grades of Avicel®, such as Avicel® PH101, Avicel® PH102 or Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tai® and Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low-substituted) (e.g. L-HPC-CH31, L-HPC-LH11, LH 22, LH 21, LH 20, LH 32, LH 31, LH30), dextrins, maltodextrins (e.g. Lodex® 5 and Lodex® 10), starches or modified starches (including potato starch, maize starch and rice starch), sodium chloride, sodium phosphate, calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate), calcium sulfate, calcium carbonate. In pharmaceutical formulations according to the present invention, especially microcrystalline cellulose, L-hydroxypropylcellulose, dextrins, maltodextrins, starches and modified starches have proved to be well suited.

Disintegrants may be used such as cellulose derivatives, including microcrystalline cellulose, low-substituted hydroxypropyl cellulose (e.g. LH 22, LH 21, LH 20, LH 32, LH 31, LH30); starches, including potato starch; croscarmellose sodium (i.e. cross-linked carboxymethylcellulose sodium salt; e.g. Ac-Di-Sol®); alginic acid or alginates; insoluble

polyvinylpyrrolidone (e.g. Polyvidon® CL, Polyvidon® CL-M, Kollidon® CL, Polyplasdone® XL, Polyplasdone® XL-10); sodium carboxymethyl starch (e.g. Primogel® and Explotab®).

Glidants and lubricants may be incorporated such as stearic acid, metallic stearates, talc, waxes and glycerides with high melting temperatures, colloidal silica, sodium stearyl fumarate, polyethylenglycols and alkyl sulphates.

Surfactants may be employed such as non-ionic (e.g., polysorbate 20, polysorbate 21, polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85, polysorbate 120, sorbitane monoisostearate, sorbitanmonolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan sesquioleate, sorbitan trioleate, glyceryl monooleate and polyvinylalkohol), anionic (e.g., docusate sodium and sodium lauryl sulphate) and cationic (e.g., benzalkonium chloride, benzethonium chloride and cetrimide) or mixtures thereof.

Other appropriate pharmaceutically acceptable excipients may include colorants, flavouring agents, and buffering agents.

A coating may also be applied on a composition according to the invention provided that the coating does not substantially retard the release of the active drug substance from the composition. Typically, a film coating may be employed.

Manufacturing processes

As discussed above, the invention also relates to a method for preparing a composition according to the invention. The method comprising the steps of

i) mixing the therapeutically and/or prophylactically active substance with a) an alkaline substance, b) a filler having binding properties, and, optionally, c) other pharmaceutically acceptable excipients to obtain a powder mixture,

ii) contacting the thus obtained powder mixture with an aqueous medium to obtain a wet powder,

iii) drying the thus obtained wet powder at a temperature above room temperature until the water content in the powder is at the most about 5% w/w determined as described herein, to obtain a first particulate mixture,

iv) sieving the thus obtained first particulate mixture,

v) optionally, adding any further pharmaceutically acceptable excipients to obtain a second particulate mixture,

vi) optionally, compressing the thus obtained second particulate mixture into tablets, and

vii) optionally, coating the thus obtained tablets.

The individual steps of the method are performed in apparatus which are suitable for the specific type of process step. It is of course advantageous to performed more than one step in the same apparatus provided that the critical conditions can be controlled in the desired manner.

With respect to step i), the most critical parameter is the particle size of the starting material, cf. the discussion above, especially the particle size of the filler having binding properties.

Step ii) is a very important step and the conditions under which this step is carried out are very critical. Most important is it that in this step the powder is subjected to not a granulation process but a wetting process resulting in a particulate material in which the individual particles of the powder mixture are brought into contact and held together by binding forces which are established by the energy input given during step ii) The present inventors have made investigations which show that A) if a normal granulation process is employed, i.e. a process which results in the formation of agglomerates, or B) if a direct compression (see Example 20b) procedure is employed, i.e. a process in which step ii) is irrelevant because no wetting of the powder blend takes place, then the final composition does not fulfil the requirements with respect to quick release. However, as reported in the experimental section herein the use of the correct conditions may lead to a composition

from which almost 100% w/w of the active substance (at least 90-95% w/w) is released *in vitro* within the first 10 min of the test employing Dissolution method I as described below.

The mechanism which is believed to take place in step ii) is to bring the active substance and the alkaline substance in close contact and at the same time utilise conditions which are favourable with respect to building up a composition which has optimal disintegration and dissolution properties. To this end, it is believed that employment of an alkaline substance which is able to produce gas, carbon dioxide, upon contact with water (or an aqueous medium having a pH below 7) is acceptable as a certain production of gas during the wetting procedure facilitates the necessary controlled disintegration of the final compostion, i.e. avoiding a too fast disintegration due to an excessive amount of gas production when the final composition disintegrates. To this end, the inventors have performed experiments in which the active substance and the alkaline substance have been subjected to a treatment with an aqueous medium and subsequently dried and then the particulate material obtained in this manner has been employed in step i) of the method described above. However, this procedure does not lead to a satisfactory result and the composition obtained has a unacceptable shelf-life, i.e. the aqueous pre-treatment of the active substance with the alkaline substance seems to have a negative influence on the chemical stability of the active substance itself.

The critical parameters in step ii) are the contact medium, the contact time and the energy input (i.e. the energy added to the powder mixture to build up the particulate material). The particle size of the resulting particulate material is a very important parameter, cf. the discussion above, but as mentioned above it is possible successfully to obtain suitable composition even if the particle size of the particulate material is larger than the sizes claimed if the particles either are soft or have an increased porosity.

The contact medium is not used as a granulation medium, e.g. no water-soluble binders is present in the medium. Typically the medium is an aqueous medium having a composition as described hereinbefore. A preferred medium is a medium containing ethanol and water and wherein the concentration of ethanol in the solvent is from about 0% v/v to about 95% v/v such as, e.g., from about 10% v/v to about 90% v/v, from about 10% v/v to about 80% v/v, from about 15% v/v to about 70% v/v, from about 15% v/v to about 60% v/v, from about 20% v/v to about 50% v/v, from about 20% v/v to about 40% v/v, from about 25% v/v to about 35% v/v such as, e.g. about 33.3% v/v. An especially suitable aqueous

medium is a medium containing ethanol and water in a volume ratio of from about 1:10 to about 1:1 such as from about 1:3 to about 1:1.5, e.g. 1:2.

With respect to the energy supply during step ii) the present inventors have found that the use of a mixer of the type high speed impeller is suitable.

The energy supplied during step ii) may advantageously be added discontinuous, i.e. with intervals of wet-massing and wet-resting (i.e. intervals in which the aqueous medium is added to the powder during mixing and intervals in which no adding of aqueous medium takes place and no mixing takes place as exemplified in Example 16).

As a starting point of determining the necessary energy supply when either changing the batch size or the apparatus, the swept volume is a guidance.

The swept volume is related to the energy input and is defined in the following way:

The vertical swept volume out by one impeller blade at each revolution is calculated by dividing the blade area into vertical segments. Based on this volume and the impeller speed, the volume swept out by the blades per second is determined relative to the volume of the product or the volume of the bowl.

Moreover, it is important that step ii) is performed in a suitable apparatus which enables an energy input which a) is sufficient to bringing the particles in contact with the aqueous medium without substantially deteriorate the stability of the final composition and/or b) is sufficient to bringing the therapeutically and/or prophylactically active substance and the alkaline substance in contact with the aqueous medium without negatively influencing the release rate of the active substance from the final composition.

As discussed above, step ii) is typically performed in a conventional high shear mixer employing an energy input which is sufficient to enable a contact to take place between the therapeutically and/or prophylactically active substance and the alkaline substance employed in step i) but at the same time is sufficiently low to avoid formation of a large amount of agglomerates during the mixing.

The mean particle size of the particles of the first particulate mixture is at the most about 100% larger than the mean particle size of the powder mixture from step i) before subjecting the powder mixture to the reaction in the aqueous medium employed in step ii).

More specifically, the mean particle size of the particle of the first particulate mixture is at the most 90% such as, e.g., about 80%, about 75%, about 70%, about 65%, about 60%, about 55% or about 50% larger than the mean particle size of the powder mixture from step i) before subjecting the powder mixture to the reaction in an aqueous medium employed in step ii).

The particle size is also expressed by results of a sieve analysis and then the following sizes are relevant:

The powder obtained in step i) has such a particle size that - when the powder is subjected to a sieve analysis - then at least about 90% w/w such as, e.g. at least about 92% w/w, at least about 94% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of the particles passes through sieve 180 μm, and the first particulate mixture obtained in step iii) has such a particle size that - when the particulate composition is subjected to a sieve analysis - then at least about 50% w/w such as, e.g., at least about 55% w/w. at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w of the particles passes through sieve 180 μm.

Typically, the mean particle size of the particles of the first particulate mixture is at the most about 250 μm, such as, e.g. at the most about 240 μm, at the most about 230 μm, at the most about 220 μm, at the most about 210 μm, at the most about 200 μm, at the most about 190 μm, at the most about 180 μm, at the most about 175 μm, at the most about 150 μm, at the most about 125 μm, at the most about 100 μm, at the most about 90 μm, at the most about 80 μm or at the most about 75 μm.

Step iii) in which the wet particulate material is dried is of course also important in order to obtain a proper shelf-life of the product. The remaining steps are steps well known in the art of pharmaceutical formulation and a person skilled in the art knows hand-books in which further details are found.

In the following examples, the invention is further disclosed.

MATERIALS AND METHODS

Materials employed in the compositions which were investigated in the course of development of the present invention were as given in the following. In those cases where reference is given to an official pharmacopoeia, the reference is to the current edition of the stated pharmacopoeia.

The following abbreviations are used:

Ph. Eur.:	European Pharmacopoeia
USP/NF:	United States Pharmacopoeia National Formulary
DLS:	Dansk Lægemiddelstandard

Materials	Quality	Manufacturer
Cellulosum microcristallinum (Avicel PH 101)	Ph.Eur.	FMC
Dibasic Calcium Phosphate, Anhydrous (Calcium hydrogen phosphate)	USPNF	Kyowa
Sodium bicarbonate	USPNF	Kirsch
Hydroxypropylcellulose (HPC L fine)	Ph. Eur.	Nippon Soda
Low-substituted Hydroxy Propyl Cellulose	USPNF	Shin-Etsu
Calcium stearate	Ph.Eur.	Akcros Chemicals
Ethanol, 96 %	DLS	Danisco
Aqua Purificata	Ph. Eur.	
Macrogol 6000 (polyethylene glycol)	Ph. Eur.	BASF
Hydroxypropylmethylcellulose (Pharmacoat 603)	USP	Shin-Etsu
Hydroxypropylmethylcellulose (Pharmacoat 606W)	USP	Shin-Etsu
Magnesium stearate	Ph. Eur.	Ackros
Polyplasdone XL	USPNF	ISP

Aerosil 200	Ph. Eur.	Degussa
Talc	Ph. Eur.	Luzenac val chisone
Titanium dioxide	Ph. Eur.	Bayer
Hydroxypropylmethylcellulose 5	Ph. Eur.	Dow
Propylene glycol	Ph. Eur.	Arcochemie
Ibuprofen	Ph. Eur.	Albemarle S.A.
Furosemide	Ph. Eur.	Assia Chemical Industries Ltd.
Sodium lauryl sulfate		Henkel
Lornoxicam		Nycomed

DISSOLUTION METHOD I

0.07 N HCl (lornoxicam)

Lornoxicam has a very low solubility under acidic conditions such as in 0.1 or 0.07 N HCl. *Inter alia* in order to show that the relatively fast release fraction indeed releases lornoxicam at acidic pH (simulating the pH conditions in the stomach), dissolution method I is employed.

Test method

Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

Dissolution medium: 900.0 ml dissolution medium (see below)

Number of revolutions: 100 rpm

Stirrer: Paddle

Temperature of dissolution medium: 37°C ± 0.5°C

Measuring times: every 5 minutes and 20 min after the start of the test (details appear from the following examples)

Analysis method

Detection wavelength: λ = 378 nm

Measuring equipment: UV/VIS – spectrophotometer, 1 cm cuvette

Preparation of reagents

Dissolution medium: Weigh out 50.0 g of sodium chloride and measure out 141.6 ml of concentrated hydrochloric acid. Dissolve the chemicals in distilled water and dilute to 25 l with distilled water.

Standards

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 µg/ml lornoxicam were prepared. Lornoxicam is dissolved in solvent for standards (cf. below).

Standards: 20.00 ml of each of the stock solutions is added to the reference vessel (cf. below).

Solvent for standards: 1.5 % w/w aqueous sodium acetate solution : methanol (1:1)

Test procedure

900 ml of dissolution medium is filled to each of the vessels (typically three or six vessels for the product and one vessel for reference solution). The medium is heated to 37 °C $\pm$ 0.5 °C. The product to be tested (e.g. a therapeutically and/or prophylactically active substance, a particulate composition, a granulate, granules or a composition in the form of a tablet, capsule or a sachet) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindle is started, and the absorbance of the

samples and standards is measured at 378 nm with zero setting towards the dissolution medium.

The percentage dissolved is measured over a suitable time interval.

Calculation for dissolution method

Percentage dissolved was calculated with reference to an external standard in the reference vessel.

The concentration of the standard in the reference vessel is calculated by the formula below:

mg lornoxicam per 1000 ml = $\left(\frac{q_1 \bullet 20}{V} + \frac{q_2 \bullet 20}{V}\right) \bullet \frac{1000}{940}$

Where:

q_1	=	amount of standard weighed out for S_1 (mg)
q_2	=	amount of standard weighed out for S_2 (mg)
20	=	added volume of S_1 and S_2 to the reference vessel (ml)
V	=	dilution volume of the standard (ml)
940	=	volume in the reference vessel after addition of the standards (S_1 and S_2) to the vessel (ml)
1000	=	conversion factor to 1000 ml

The content of lornoxicam as percentage dissolved was calculated from the formula below:

$$\frac{abs_{sample} \bullet StA \bullet 900 \bullet x \bullet 100}{abs_{StA}\ 1000 \bullet q_{tablet} \bullet 8} \bullet \frac{n}{100}$$

Where

abs_{sample}	=	absorbance measured in each vessel containing samples
StA	=	mg lornoxicam pr 1000 ml in the vessel containing standard
900	=	volume of the medium (ml)

100	=	factor converting to percent
abs_{StA}	=	absorbance measured in vessel containing the standard
1000	=	factor converting the concentration of the standard to mg/ml
8	=	declared content (mg) in the tablet
n	=	potency of the standard (%)
100	=	factor converting to percent

Determination of dissolution rate – solubility method I

The dissolution rate of an active substance is determined using the same procedure as described under "Dissolution method I" above and with any relevant modification in the calculation method described.

Test for resistance to crushing of tablets

The test is performed in accordance with the guidelines given in Ph.Eur. 1997, pp 135-136.

The following examples are intended to illustrate specific embodiments of the present inventions but are not intended in any way to limit the invention.

EXAMPLE 1

Investigation of the influence of various process parameters on the dissolution rate of the final composition

Initial investigations by the inventors have indicated that the dissolution rate of a therapeutically and/or prophylactically active substance seems to be dependant on the manufacturing process employed. Especially, it was judged necessary to control critical parameters like e.g. i) spray pressure during the addition of reaction medium, ii) reaction time, iii) amount of reaction medium added and iv) the mixing intensity (i.e. ± employment of a chopper). Accordingly, labtrials based on a 2^4 factorial design with replication of centre points were performed.

The purpose of the trials was to investigate the influence of certain process parameters on the dissolution of the therapeutically and/or propylactically active substance from the composition obtained. The dissolution test was performed in 0.07 N hydrochloric acid employing the dissolution method I described herein and the amount of active substance released and dissolved after 20 min of the dissolution test was determined.

The factors and the levels investigated are listed below:

Factors	Lower level	High level
Spray pressure[a]	0.5 bar	2.0 bar
Reaction time[b]	2 min	9 min
Amount of medium	1440 g	1640 g
Intensity of mixing (+/- employment of chopper)	-	+[c]

[a]: the spray pressure was measured just before the inlet of air to the nozzle

[b]: excl. time for distribution of the water

[c]: the speed of the chopper was 1

The design included 20 trials as the centrepoints (with (+) or without (–) chopper) were replicated once. The composition employed throughout the trials is described in the following together with the manufacturing process employed for trial 1 (batch No. 30069733). The manufacturing process for the other trials was in accordance with trial 1 apart from the modifications which were necessary in order to test the above-mentioned process parameters (see Table 1 below).

I	Lornoxicam	80.0 g
II	Sodium hydrogen carbonate	400.0 g
III	Avicel PH 101	960.0 g
IV	Calcium hydrogen phosphate anhydrous	1104.0 g
V	L-HPC	480.0 g
VI	Hydroxy propyl cellulose	160.0 g
VII	Purified water	1230.0 g
VIII	Ethanol 99,9 %	410.0 g
IX	Calcium stearate	5.0 g*

* amount adjusted for a total of 1 kg of I-VI.

II-VI were admixed for 6 min in a Fielder intensive mixer with impeller speed I and without use of chopper. Then a 1 kg aliquot was mixed with I in a planetary mixer for 10 min. The mixture was sieved through a 0.5 mm sieve and then admixed in the Fielder to the remaining II-VI mixture.

VII + VIII were mixed and applied to the mixture (I – VI) by a 2 components nozzle with a spray pressure of 0.5 bar and with a spraying time of approx. 2 min. The impeller speed was I and the chopper speed I. When spraying was completed, the mixing was continued for 9 min at impeller speed I and chopper speed I.

The drying of the wet mixture was carried out in a Aeromatic fluid bed with an inlet air temp of 65 °C. The drying was continued for 45 min. Thereafter, the mixture was sieved through a 1.0 mm sieve and the drying process was continued with an inlet air temperature of 80 °C. When the outlet temperature reached 50 °C, after approx. 20 min, the drying was stopped.

1200 g of the thus obtained particulate mixture were sieved through a 0.7 mm sieve. IX was sieved through a 0.3 mm sieve and admixed to 1000 g of the sieved particulate mixture in a planetary mixer for 10 min.

The thus obtained particulate mixture was compressed by a Korsch rotary tabletting machine. Punches: 9.5 mm. A compound cup was used. Weight of the tablet: 320 mg.

Process parameters employed and dissolution rates obtained from compositions corresponding to trials 1-20 are shown in the following Table 1.

Table 1

2^4 factorial design with replication of centre point						
Batch No.	Trial No.	Pressure (bar)	Time (min)	Amount (g)	Chopper yes/no	Release 20 min %
30069733	1	0.5	9	1640	yes	91.85
1079732	2	2	2	1440	yes	89.88
2079732	3	0.5	9	1640	no	90.85
2079734	4	0.5	2	1440	yes	92.83
3079732	5	1.25	5.5	1540	yes	94.14
7079732	6	2	9	1640	yes	79.64
8079732	7	2	9	1640	no	84.17
8079734	8	2	2	1640	yes	88.14
9079732	9	0.5	9	1440	no	91.24
10079732	10	2	9	1440	yes	93.76
11079732	11	2	9	1440	no	95.8
14079732	12	2	2	1640	no	93.77
1479735	13	2	2	1440	no	89.49
15079732	14	1.25	5.5	1540	no	94.03
15079734	15	1.25	5.5	1540	no	92.07
16079732	16	0.5	2	1440	no	88.99
21079732	17	0.5	9	1440	yes	95.23
21079734	18	0.5	2	1640	no	93.93
22079732	19	1.25	5.5	1540	yes	94.54
22079734	20	0.5	2	1640	yes	94.25

In general the following technical properties of the tablets were obtained (uncoated cores):

Water content (LOD – 30 min at 70 °C): 1.4-2.2 %

Disintegration time (mean): 3 - 6 min.

Tablet hardness (crushing strength) (mean): 80 - 100 N

Uniformity of the mass (S_{rel}): 1 - 2%

Conclusion

As shown in Table 1 above, the dissolution of lornoxicam from the various compositions tested varies from 79% w/w to about 94% w/w (the amount dissolved has been determined after 20 min of the dissolution test employing dissolution method I described herein).

Statistical analysis showed that the following process parameters were significant or almost significant at the 5% level with respect to influence on the dissolution rate.

Spray pressure (P = 0.03)
Amount of medium (P = 0.06)
Interactions between spray pressure and amount of medium (P = 0.02)
Interactions between spray pressure and chopper (P = 0.03)
Interactions between amount of medium and reaction time (P = 0.002)
Interactions between spray pressure, reaction time and amount of medium (P = 0.04)

EXAMPLE 2

Design of lornoxicam compositions having a quick release of lornoxicam in 0.07 N hydrochloric acid

Based on the results obtained in the factorial design described in Example 1 and the aim of approaching or reaching almost a 100% w/w release after 20 min, three realistic estimates of values for the process parameters were calculated. The values of the process parameters are described in Table 2 below. The composition and manufacturing process were identical to trial 1 given in Example 1.

Table 2

Trial (Batch No.)	Nozzle	Spray pressure (bar)	Reaction time (min.*)	Amount of medium (g)	Chopper Yes/No	Release 20 min. (%)	Cellulose, microcryst. (quality)
1 (15089734)	2-component	2.2	16	1440	No	97.63	Ming Tai
2 (15089736)	2-component	0.5	2	1925	No	96.06	Ming Tai
3 (15089738)	2-component	1.6	8.5	1320	Yes	93.87	Ming Tai
4 (26089732)	2-component	2.2	16	1440	No	97.20	FMC

* Excluding the time for distribution of water

Trials Nos. 1-3 were manufactured with cellulose, microcrystalline supplied from Ming Tai. In order to investigate whether i) the results obtained with respect to the technical properties of the composition and ii) the results obtained with respect to the release of lornoxicam from the composition were influenced by employment of a specific quality of microcrystalline cellulose, another quality from another supplier (FMC) was included in trial 4 (batch No. 26089732). Trial 4 was identical to trial 1 in Table 2.

The technical properties of tablets obtained from trials 1-4 were identical to the results obtained in Example 1.

Conclusion

As shown in Table 2 a release of 98% w/w was achieved after 20 min, i.e. a significant improvement of the dissolution rates compared with those obtained in Example 1. Thus, the percentages released were approaching 100%.

Comparing the results from trial 4 (26089732 FMC) with trial 1 (15089734 Ming Tai) given in Table 2, indicate that no significant difference in release or technical properties of the compositions have been observed.

EXAMPLE 3

Investigation of the influence of the quality of sodium hydrogencarbonate employed

The labtrials described in the following were based on the employment of sodium hydrogencarbonate obtained from different suppliers.

Two identical compositions (trials corresponding to batch Nos. 23079733 and 23079735) were manufactured in order to test sodium hydrogencarbonate (mean particle size ~ 120 µm) supplied from Kirsch. Previously, sodium hydrogencarbonate (mean particle size ~ 105 µm) supplied from Tosho was used.

The manufacturing process parameters were identical to trial 5 described in Table 1 given in Example 1.

Dissolution properties of the cores

About 94% w/w for both trials (percentages dissolved after 20 min employing the dissolution method I described herein).

The technical properties were identical to those described in Example 1.

Conclusion

There is no significant difference between the release results of the 2 trials performed, i.e. the quality of sodium hydrogencarbonate employed does not seem to have any significant influence within the variations tested on the dissolution behaviour of a lornoxicam containing composition. Furthermore, the small variation with respect to mean particle size does not seem to have any important influence on the dissolution behaviour of a composition according to the invention.

EXAMPLE 4

Investigation of a process parameter (application of reaction medium) on the dissolution behaviour

The labtrial described in the following was based on the use of a 1-component nozzle.

In this trial (batch No. 27089732) a 1-component nozzle was used in order to apply the reaction medium. The composition and manufacturing process are identical to trial 1 in Example 1 apart from the following parameters:

Spray pressure: 3.5 bar
Reaction time: 16 min.
Amount of reaction medium: 1440 g
No use of chopper.

Dissolution properties of the cores

Release after 20 min was 98.3%.

The technical properties of the tablets were identical to those given in Example 1.

Conclusion

There is no significant difference in release behaviour compared with trial 4 in Example 2. Accordingly, using a 1-component nozzle in production scale should then be possible.

EXAMPLE 5

Upscaling to production scale level

Production scale trial:
One trial (batch No. of the cores: 962620) was scaled up to production scale. The composition and manufacturing process of a batch size of 250,000 tablets are described below:

(Kg/250,000 tablets)

I	Lornoxicam	2.0 kg
II	Sodium hydrogencarbonate	10.0 kg
III	Cellulose, microcrystalline PH 101	24.0 kg
IV	Calcium hydrogen phosphate anhydrous	27.6 kg
V	L-HPC	12.0 kg
VI	Hydroxy propyl cellulose	4.0 kg
VII	Calcium stearate	0.4 kg
VIII	Purified water	27.0 kg
IX	Ethanol	9.0 kg
X	Filmcoat K01187	30.3 kg

II-VI were admixed in a Diosna intensive mixer with impeller speed I and chopper speed I for 1 min. Then a 10 kg aliquot was taken out of the mixer. 5 kg of this sample was manually mixed with I. A smaller part of the remaining II-VI mixture was sieved in a Quadro Comil U 20 through a 062R sieve. Then, the I-VI mixture was sieved and added to the remaining part of the II-VI mixture followed by admixture in the Diosna to the remaining II-VI mixture. The impeller speed was I and the chopper was I for 1 min.

VIII and IX were admixed and applied to the mixture by a 1-components nozzle (Delavan ¼ BNM22X) with a spray pressure of 6.2 bar and with a spraying time of about 3 min. Impeller speed I and chopper speed I. When the spraying was completed, the reaction was continued 13 min at impeller speed I and no chopper was used.

The drying was carried out in an Aeromatic fluid bed with an inlet air temperature of about 65 °C and was continued for 45 min. Then the drying process was continued with an inlet air temperature of about 80°C. When the outlet temperature was about 42°C and RH % (over the mixture) was about 17%, the drying was terminated. The LOD of the thus obtained particulate mixture was determined to be 1.0 %.

The particulate mixture obtained was sieved in a Frewitt through a 0.71 mm sieve. VII was sieved in Quadro Comil U20 through a 062R sieve and admixed to the sieved particulate mixture in Diosna mixer for 25 sec. The impeller speed was I.

The particulate mixture was compressed into tablets by use of a Beta press rotary tabletting machine supplied by Manesty. Punches: 9.5 mm. A compound cup was used.

Technical properties of uncoated tablets

Humidity (LOD): 1.2-1.4%
Disintegration time: 1'45" - 2 min.
Tablet hardness: 80-100 N.

Dissolution properties of the cores

After 20 minutes 99.25% w/w was released (dissolution method I as described herein)

The cores were coated (batch No. of the coated tablets: 962640) with a white HPMC coat (Filmcoat K01187) in an Accela Cota 150 having 3 nozzles. Spray pressure was 6 bars as measured at the control panel and the liquid flow rate was approx. 175 g/min at the start of the process and approx. 130 g/min at the end of the process. The composition of the coat is described below:

I	Methylhydroxypropylcellulose 5	1.43 kg
II	Propyleneglycol	0.28 kg
III	Titanium dioxide	0.90 kg
IV	Talcum	0.90 kg
V	Purified water	26.70 kg

Dissolution properties of coated tablets

After 20 minutes 98.62% w/w was released (dissolution method I described herein)
Humidity (LOD): 2.4-2.6%

Conclusion

The results obtained demonstrate that almost a 100% release and dissolution of lornoxicam from lornoxicam tablets is obtainable even in a production scale.

EXAMPLE 6

Investigation on the influence of the particle size of a particulate composition on the dissolution behaviour

Labtrial of tablets (particle size of the particulate composition used to prepare tablets; above or below 212 micron).

1 particulate composition batch (batch No. 08079731) was separated into two fractions, i.e. fines (mean particle size (PS)<212 micron) and coarse material (mean particle size >212 micron). Tablets based on these two fractions (batch No. 07109731 A = <212 μm and batch No. 07109731 B = >212 μm) were manufactured.

Dissolution behaviour

20 min dissolution of tablets based on particulate composition with a PS < 212 μm: 93.1%

20 min dissolution of tablets based on particulate composition with a PS > 212 μm : 85.4%.

Conclusion

The particle size of the particulate composition employed in the tabletting process seems to have a significant influence on the release rate. Furthermore, a smaller mean particle size seems to have a better behaviour with respect to fast dissolution than a larger mean particle size.

EXAMPLE 7

Upscaling – production scale

In this trail 5 batches were prepared after the same method as described in Example 5 apart from i) the type of nozzle used for atomization of the reaction medium, ii) the amount of reaction medium and iii) the reaction time. In Example 7 a shower type to the

distribution of the medium was used which do not give a real atomization. The process parameters of these trials are shown in Table 3:

Table 3

Trial No.	Amount of medium G/10,000 tab.	Reaction time*	+/- chopper	Release 20 min
1 (972510)	1440	16 min	-	100.4 %
2 (972520)	1440	8 min	-	99.1 %
3 (972530)	1340	16 min	-	100.2 %
4 (972540)	1340	8 min	-	-
5 (972550)	1440	6 min	+	-

*: Including time for distribution of water; approx. 2 min

The technical properties were identical to the results given in Example 5.

The cores were coated as described in Example 5.

20 min dissolution of coated tablets

Coated tablets of trial 1 (972560 (batch no. of the cores: 972510)): 100.4 %
Coated tablets of trial 2 (972570 (batch No. of the cores: 972520)): 100.4 %
Coated tablets of trial 3 (972580 (batch no. of the cores: 972530)): 99.0 %
Coated tablets of trial 4 (972600 (batch No. of the cores: 972540)): 96.1 %
Coated tablets of trial 5 (972590 (batch No. of the cores: 972550)): 94.1 %

The above-given results demonstrate that the amount of coating liquid and the reaction time are critical (support the results from the labtrials described in Example1). However, the method of distribution of the reaction medium to the powder does not appear to be critical in production scale.

Conclusion

A reaction time including time for distribution of water corresponding to about 8 min seems to require at least about 1440 g of reaction medium/10,000 tablets. A reaction time including the time for distribution of water corresponding to about 6 min or below will most likely not result in a batch having a release close to 100% released after 20 min.

EXAMPLE 8

Investigation on the influence of sodium hydrogencarbonate and calcium hydrogen phosphate on the properties of the final composition

Labtrials investigating the influence of the particle size of critical excipients on the dissolution and/or technical properties were based on a 2^4 factorial design with 2 replication of the centrepoint.

The purpose of the trials was to find the effect on the technical properties of the factors and the levels listed below.

19 trials have been performed. The manufacturing process used was identical to trial 1 in Example 1, however the spray pressure was fixed at 2.2 bar, the reaction time (excluding the time for distribution of water) at 16 min and the chopper was not used.

Factors	1 µm	2 µm	3 µm	4 µm
$NaHCO_3$	40	86	122	200
$CaHPO_4$	11	25*,30	60	128

*: The batch No. of this ingredient is identical to the batch No. used in Example 1.

20 min dissolution (for batches with a satisfactory or almost satisfactory friability), particle size of $CaHPO_4$ and $NaHCO_3$ and technical properties are shown in Table 4.

Table 4

Trial No.	$NaHCO_3$ µm	$CaHPO_4$ µm	Tablet Hardness	Disintegration	Friability %	Uniformity of mass (S_{rel})	Release 20 min (%)
1(18039832)	122*	25*	92.7	6'25"	0.26/0.31	1.50	95.5
2(19039832)	86	11	44.1	5'10"	10.4/0.31	1.50	90.5
3(23039832)	122	60	6.9	1'37"	100	3.29	-
4(24039832)	122	30	73.4	4'41"	0.32/0.36	2.75	90.4
5(25039832)	200	128	48.2	4'10"	6.64/3.42	1.53	-
6(25039834)	200	11	42.1	4'22"	6.67/9.07	3.14	-
7(25039837)	86	30	92.5	5'42"	0.20/0.19	2.31	89.7
8(27039832)	40	11	48.3	4'57"	58.91/29.31	2.57	-
9(30039832)	200	30	90.1	4'13"	0.39/0.40	2.59	91.0
10(31039833)	122	30	89.4	4'57"	0.32/0.38	2.92	89.6
11(02049832)	122	11	35	3'34"	100	2.80	-
12(03049832)	40	30	77.3	4'54"	0.39/0.37	2.60	90.9
13(06049832)	40	128	24.8	3'06"	100	2.92	-
14(07049832)	200	60	17.7	1'28"	100	4.04	-
15(08049832)	122	128	20.1	2'34"	100	3.27	-
16(14049832)	122	30	78.2	4'10"	0.29/0.32	2.16	89.8
17(14049834)	40	60	6.3	1'28"	100	0.69	-
18(15049832)	86	60	3.5	1'22"	100	2.11	-
19(17049832)	86	128	28.3	2'28"	100	1.93	-

*: The batch No. of this ingredient is identical to the batch No. used in Example 1.

Anova variance analysis with respect to crushing strength and disintegration is given in the following:

Analysis of Variance – crushing strength – Type III Sums of Squares

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Main Effects					
A:CaHPO4	16613.9	4	4153.48	83.43	0.0000
B:NaHCO3	448.545	3	149.515	3.00	0.0767
Residual	547.601	11	49.7819		
TOTAL (corrected)	18128.2	18			

All F-ratios are based on residual mean square error.

The results given above are shown in Figs. 1 and 2 and show that the particle size of the calcium hydrogen phosphate employed has a significant influence on the crushing strength of the tablets. The particle size of the sodium hydrogencarbonate employed seems to have little or no influence on the crushing strength of the tablets.

Analysis of Variance - disintegration – Type III Sums of Squares

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Main Effects					
A:CaHPO4	138086.0	4	34521.5	25.97	0.0000
B:NaHCO3	3303.57	3	1101.19	0.83	0.5055
Residual	14623.8	11	1329.43		
TOTAL (corrected)	155165.0	18			

All F-ratios are based on residual mean square error.

The results given above are shown in Fig. 3 and show that the particle size of the calcium hydrogen phosphate employed has a significant influence on the disintegration time of the tablets whereas the particle size of the sodium hydrogencarbonate employed seems to have a much less pronounced influence on the disintegration time of the tablets.

Conclusion

The particle size of $CaHPO_4$ appears to have a significant effect on the technical properties (friability and disintegration time). $CaHPO_4$ having a mean particle size of approx. 11 μm, 60 μm and 128 μm does not give hard tablets but tablets with a friability % for most of them close to 100. However, the particle size of $NaHCO_3$ does not appear have a significant effect on the technical properties.

EXAMPLE 9

Water-based reaction

3 labtrials involving a reaction medium consisting solely of water were performed. The composition and manufacturing process were identical to the trials relating to the particle size in accordance with Example 8. The results of these trials are shown in Table 5.

Table 5

Trial No.	Amount of medium (g)	Amount through a 0.18 mm sieve (%)	Tablet Hardness N	Uniformity of mass (S_{rel})	Disintegration	Release 20 min.
1(20049832)	1440	92	98.6	2.70	5'01"	95.8
2(22049832)	1940	60.2	98.8	2.30	8'08"	65.8
3(23049832)	1440	91.2	96.9	2.97	5'08"	91.3

Conclusion

Trials 1 and 3 employing an amount of medium of 1440 g/10,000 tablets gave a release of about 91-95% w/w (dissolution method I as described herein). A higher amount of the medium (trial 2) gave a low release of 65.8% w/w and a longer disintegration time. The mean particle size of the particulate composition of trial 2 is larger than that of trial 1 and 3.

EXAMPLE 10

Upscaling – production scale

2 trials (batch Nos. of the cores: 020590 and 020600) were prepared in production scale. The composition and manufacturing process of the cores were identical to trial 2 in Table 3 (Example 7) (scale-up 2).

The aim of this series of batches was to improve the coating process in order to minimise the water content in the tablets after the coating (too high a water content may lead to degradation of lornoxicam).

A change in the coating process was carried out by increasing the product temperature during the coating with about 10°C, by lowering the liquid flow rate to about 80 g/min and by introducing a 1h drying after the coating has been applied.

Technical properties of the cores

Batch No.:	020590	020600
Humidity (LOD):	1.33%	1.39%
Disintegration:	2 – 4 min	2 – 3 min
Tablet hardness:	90 – 120 N	90 – 120 N

20 min dissolution of the cores

020590: 97.3%
020600: 97.9%

20 min dissolution of coated tablets

021170 (batch No. of the cores: 020590): 97.6%
020640 (batch No. of the cores: 020600): 96.8%
Humidity (LOD): 1.3-1.5%

Conclusion

The water content of the tablets has been reduced from about 2.0 or more to values below 1.5%.

The small increase in the disintegration time was due to an increase in the tablet hardness of approx. 20 N.

EXAMPLE 11

Production scale trial with water based reaction

One batch (No. 020560) based on a reaction medium consisting solely of water was prepared in production scale. The composition and manufacturing process of the cores were identical to the trials in Example 10 apart from the reaction medium, which in this example was purified water The reaction time (including time for distribution of the water; approx. 2 min) was 16 min.

Tablets were compressed as described in Example 10.

Technical properties of cores

Humidity (LOD):	1.4%
Disintegration time (min):	1'30"
Tablet hardness:	50-70 N

20 min dissolution of the cores

The coating process was carried out with identical process parameters as described in Example 10.

20 min dissolution of coated tablets

020610 (batch No. of the cores: 020560): 91% w/w
Humidity (LOD): 1.3%

Conclusion

A water-based reaction (in this case without any other solvent than water) in production scale gave a low tablet hardness. The hardness of the tablets gave some problems during the coating process. The release after 20 min seems to be lower compared to the results obtained in Example 10.

EXAMPLE 12

Investigation on the influence of the conjugate reaction conditions on the chemical degradation of lornoxicam.

The purpose of the present example was to investigate whether the reaction between an active drug substance (lornoxicam) and an alkaline substance (sodium hydrogencarbonate) suitable can be performed before any addition of other ingredients and pharmaceutically acceptable excipients without influencing the favourable stability characteristics with respect to chemical degradation of lornoxicam.

One batch (a) of tablets having the composition listed in Example 1 was manufactured as described in Example 1 using a spray pressure of 1.3 bar, a reaction time of 9 min, an impeller and chopper speed I and with an amount of reaction medium of 1440 g. The cores were film coated using the film described in the following:

Pharmacoat 603 (HPMC)	108 g
Macrogol 6000	9 g
Titanium dioxide	41 g
Talc	8 g
Purified water	374 g
Ethanol	655 g

The thus coated tablets were packed in double aluminium blister packages.

A second batch (b) of tablets having the composition listed below was manufactured in the following manner:

8 g of sodium hydrogencarbonate was dissolved in 120 g of water and mixed with a suspension of 32 g lornoxicam in 600 g of ethanol. While forming gaseous carbon dioxide, lornoxicam dissolved. 100 g of Pharmacoat 606W was added and dissolved. 212 g of sodium hydrogen carbonate was admixed and dissolved. The solution obtained was mixed with Avicel in a lab size mixer. The wet mixture was dried and then magnesium stearate and polyplasdone XL were admixed in the lab scale mixer.

Lornoxicam	32 g
Sodium hydrogencarbonate	220 g
Avicel PH 101	998 g
Pharmacoat 606W	100 g
Aerosil 200	12 g
Magnesium stearate	4 g
Polyplasdone XL	34 g

The tablets were coated with the film coating shown in the table above. The amount of dry matter applied was adjusted to the number of tablets produced.

The coated tablets were packed in sealed glass containers.

The two batches (a and b) - which both were packed in water tight packages – were exposed to room temperature for 6 month with an intermediate measurement after 3 months. In the following are given the results (degradation product HN 33144 is a degradation product of lornoxicam):

Batch	Degradation product HN 33144		Total amount of degradation product	
	% w/w of total weight		% w/w of total weight	
	3 months	6 months	3 months	6 months
a	0.1	0.2	0.2	0.2
b	0.8	0.7	2.6	2.9

Conclusion

The formation of a conjugate (e.g. a sodium salt of lornoxicam) before admixing the other tabletting excipients seems to lead to a product which has a poor stability with respect to the chemical stability of lornoxicam.

EXAMPLE 13

Production scale investigation on the influence of the particle size of calcium hydrogen phosphate on the tablet hardness

Production scale trials were carried out based on the findings in Example 8. The experiments were carried out without the addition of any therapeutically active substance.

4 trials were performed and the batches used in the trials were manufactured as described in Example 10 (batch size: 80 kg) with the only changes that calcium hydrogen phosphate was employed in qualities having a mean particle size as described below and that the therapeutically active substance, lornoxicam, was omitted from the compositions.

The mean particle sizes of the various qualities of the calcium hydrogen phosphate employed were as follows and the particle size was determined by laser light scattering:

Table 6

Trial No. (Batch No.)	Mean particle size measured (n = 2), µm	Comments	Obtained tablet hardness N (n ≥18)
1 (10023460)	30		101 – 126
2 (10023463)	56		41 – 62
3 (10023461)	17		96 – 115
4 (10023462)	33	Mixture 1:1 w/w of $CaHPO_4$ used in trial 2 (batch No. 10023463) and in trial 3 (batch No. 10023461)	92 – 108

Conclusion

The hardness of the tablets obtained from trial No. 1 (batch No. 10023460) and trial No. 2 (batch No. 10023463) are in accordance with the findings in Example 8, namely that an increase in mean particle size leads to tablets having a decrease in the tablet hardness.

From Table 6 it is also seen that it is possible to obtain an acceptable tablet hardness even if the mean particle size is as low as 17 μm (trial 3). Furthermore, an acceptable tablets hardness can be obtained by use of a mixture of different qualities of calcium hydrogen phosphate having different mean particle size as long as the resulting mean particle size has a suitable size (neither too small nor too large), cf. trial 4. The latter is obtainable even though the particle size distribution changes.

EXAMPLE 14

Production scale continuation of Example 13 including incorporation of lornoxicam in the compositions

The results of Example 13 showed that both the approx. 30 μm $CaHPO_4$ quality and the mixture of different $CaHPO_4$ qualities having a resulting mean particle size of approx. 30 μm will lead to tablets with acceptable hardness. However, the tablets prepared in Example 13 were without any therapeutically active substance. Therefore, it was tested whether the same conclusion is valid for tablets containing a therapeutically active substance such as, e.g., lornoxicam.

The following batches were produced in the same manner as described in Example 10:

1. Batch No. 10025279 containing the same type of $CaHPO_4$ as in batch No. 10023460 of Example 13.
2. Batch No. 10025280 containing the same type of $CaHPO_4$ as in batch No. 10023460 of Example 13.
3. Batch No. 10025281 containing the same type of $CaHPO_4$ as in batch No. 10023462 of Example 13.
4. Batch No. 10025282 containing the same type of $CaHPO_4$ as in batch No. 10023462 of Example 13.

The following results were obtained:

Table 7

Trial No. (Batch No.)	Tablet hardness; Uncoated tablets	20 min. dissolution data coated tablets		
	N	Mean (%)	s	n
1 (10025279)	81 – 113	87.2	1.7	6
2 (10025280)	86 – 128	89.9	0.8	6
3 (10025281)	68 – 97	85.8 85.4	1.1 1.4	6 6
4 (10025282)	87 – 110	87.5	0.5	6

s = standard deviation

n = number of tests

Conclusion

The hardness of the tablets from the above listed batches is satisfactory for all batches. This means that mixing of $CaHPO_4$ batches with different particle sizes is possible as long as the mean particle size is close to the acceptable level of approx. 30 μm. Furthermore, incorporation of lornoxicam in the compositions does not seem to have any practical influence on the tablet hardness.

EXAMPLE 15

Labscale trials - Effect of reducing particle size of the powder mixture after treatment with an aqueous medium

In labscale tablet cores were manufactured as described in Example 8 with the exception that the batch size was 4.48 kg (in Example 8 the batch size was 3.2 kg). The composition

of the individual tablets was identical to the composition given in Example 1. The batches were prepared using the following ingredients and amounts:

I	Lornoxicam	112.0 g
II	Sodium bicarbonate	560.0 g
III	Avicel PH 101	1344.0 g
IV	Calcium hydrogen phosphate anhydrous	1546.0 g
V	L-HPC	672.0 g
VI	Hydroxy propyl cellulose	224.0 g
VII	Purified water	1512.0 g
VIII	Ethanol 99,9 %	504.0 g
IX	Calcium stearate	5.0 g*

* amount adjusted for a total of 1 kilogram of I-VI, i.e. the content of calcium stearate is 5.0 g/kg.

The following results were obtained:

Table 8

Trial No. (Batch No.)	PS reduction method #	PS obtained *	Dissolution 20 min. dissolution data			Comments
		% (w/w)	Mean	s	n	
1 (16039832)	Dry sieving; 0.7 mm	54	82.3	0.2	6	
2 (17039832)	Dry sieving; 0.6 mm	71	87.8	0.2	6	Same granulate as in trial 1 (batch No. 16039832)
3 (03039932)	Wet sieving; 0.6 mm Dry sieving; 0.7 mm	66	83.6	0.7	3	
4 (03039931)	Semiwet sieving; 0.6 mm Dry sieving; 0.7	62	83.7	0.6	3	
5 (12039932)	Comill; semidry; 0.27 mm Dry sieving; 0.7 mm	97	91.2	0.7	3	Rather time consuming
6 (28059931)	Use of chopper at high speed during all of the wet massing phase	70	89.9	1.1	6	

#: Particle Size (PS) reduction method applied during or after the granulation or drying of the particulate material (dry sieving means that the reduction method is applied after

drying of the wet particulate material; wet sieving means that the reduction method is applied while the particulate material is wet and before any drying; semiwet drying means that the particulate material has almost been dried before the reduction method is applied).

*: % through sieve 180 μm

Conclusion

All particle reduction methods seem to be suitable. The comill method, however, seems to be most efficient but it is also the most time consuming.

In accordance with Example 1 the attempt in trial No. 6 (batch No. 28059931) to avoid the formation of agglomerates by vigorous use of the chopper did only moderately improve the process as agglomerates are still present and the dissolution is still fairly low.

EXAMPLE 16

Labscale trials - Effect of introducing non-continuous wet-massing

In lab scale tablet cores were manufactured as described in Example 15 with the exception that the wet massing phase has been varied. The following batches were manufactured:

Table 9

Trial No. (batch No.)	Wet massing time*	Wet massing interruption*	20 min. dissolution #			% w/w through sieve 180 µm
	min.	min.	mean	s	n	
1 (12939933)	1+1+1+1	3+3+3+3	97.1 95.3 96.5 98.0 96.5 96.5 96.2 97.2 99.1	0.6 1.3 1.3 3.7 ¤ 3.4 ¤ 0.8 ¤ 0.9 ¤ 1.4 1.4	3 3 3 3 3 3 3 3 3	72
2 (16039935)	1+1+1+1	3+3+3+3	95.3 96.4	0.4 1.4	3 3	71
3 (16039936)	1+1+1+1	3+3+3+3	93.0 94.5	3.5 0.8	3 3	70
4 (23039935)	1+1	6	81.0 86.9 85.4	1.1 1.7 2,1	3 6 6	66
5 (23039936)	1+1	30	93.4 96.7 96.7 94.8 96.5 95.4	0.4 0.8 0.6 ¤ 2.4 ¤ 2.1 ¤ 1.4 ¤	3 3 3 3 3 3	67
6 (26039932)	2+2+2+2	2+2+2+2	92.7 93.5	1.4 0.2	6 3	80
7 (26039931)	2+2+2+2 $	2+2+2+2	89.3 91.6	1.6 0.7	6 3	75
8 (12049940)	1+1+1	15+15	97.6 97.2 94.9	1.8 1.5 1.2	6 6 3	69

*: the "wet massing time" and "wet massing interruption" are to be understood in the following way. Wet massing time: 1+1+1+1 and wet massing interruption 3+3+3+3 means that the granulate has been produced by the following method: 1 min wet massing

followed by 3 min interruption followed by 1 min wet massing followed by 3 min interruption and so on.

#: When more than one mean value is shown, the analysis have been repeated on tablets from the same trial No.

¤: The data have not been corrected for variation in tablet mass

$: Rpm of impeller only half the value of the other experiments. Actual value used in trial 26039931: approx. 140 rpm.

Conclusion

As can be seen from the above listed data then the introduction of periods of no agitation during the wet massing phase gives dissolution data that clearly are above what could be achieved by milling the dry granulate as described in Example 15.

However the use of periods of no agitation must be adjusted neither to have too much nor too little agitation, i.e. energy input. As an example, in trial No. 4 (batch No. 23039935) it is clear that a too short overall wet massing has been employed (the dissolution results are fairly low), whereas in trial No. 7 (batch No. 26039931) too much agitation might have been used. Therefore the dissolution data for trials Nos. 4 and 7 are not as high as those obtained from trial No. 1 (batch No.12039933).

EXAMPLE 17

Labscale trials to test the set-up in Example 16 but employing a smaller batch size

Lab scale batches were manufactured as in Example 16 with the exception that the batch size has been lowered to 3.2 kg in order to test the influence of the batch size. This batch size of 3.2 kg gives the exact same composition as in Example 8. In fact batch Nos. 18039832, 24039832, 31039833 and 14049832 are from Example 8 and are quoted here again to facilitate a comparison of the data.

The following results were obtained:

Table 10

Trial No. (batch No.)	Wet massing time*	Wet massing interruption*	20 min. dissolution #			% w/w through sieve 180 μm after drying
	min.	min.	mean	s	n	
1 (18039832)	16	0	95.5	0.5	6	
2 (24039832)	16	0	90.4	0.6	6	
3 (31039833)	16	0	89.6	0.8	6	
4 (14049832)	16	0	89.8	1.1	6	
5 (29049932)	1+1+1	15+15	95.4 94.3 93.6	2.2 1.8 0.2	6 3 3	68
6 (28049931)	1+1+1+1	3+3+3+3	98.4 98 9.,9	1.3 1.6 0.7	6 3 3	63

*: the "wet massing time" and "wet massing interruption" are to be understood in the following way. Wet massing time: 1+1+1+1 and wet massing interruption 3+3+3+3 means that the granulate has been produced by the following method: 1 min wet massing followed by 3 min interruption followed by 1 min wet massing followed by 3 min interruption and so on.

#: When more than one mean value is shown analysis have been repeated on tablets from the same trial No.

Conclusion

The conclusion from Example 16 is also valid for the trial of Example 17 even though the batch size in Example 17 is lower. There is a marked benefit with respect to the obtained dissolution results in using the interval wet massing set up described above.

Furthermore it is interesting to note that of all of the batches from Examples 16 and 17 with different interruptions of the wet massing phase no batch has a very fine particle size. This indicates that the particle size of the particulate material is not the only parameter to influence the dissolution rate.

EXAMPLE 18

Lab scale trials with Ibuprofen as the therapeutically active substance

In lab scale, 3 types of tablet cores were manufactured. The *first type* (batch No. 10059932) was manufactured as described in Example 8 with the exception that lornoxicam has been substituted with ibuprofen. Therefore, the composition was as follows:

I	Ibuprofen	80.0 g
II	Sodium bicarbonate	400.0 g
III	Avicel PH 101	960.0 g
IV	Calcium hydrogen phosphate anhydrous	1104.0 g
V	L-HPC	480.0 g
VI	Hydroxy propyl cellulose	160.0 g
VII	Purified water	1080.0 g
VIII	Ethanol 99,9 %	360.0 g
IX	Calcium stearate	5.0 g/kg*

* amount adjusted for a total of 1 kilo of I-VI.

The same way of manufacturing but excluding the wet massing phase, that is manufacturing the tablets by direct compression, was used for the *second type* (batch No.07069934) of tablet cores.

The *third type* (batch No. 07069933) of tablets was manufactured in the same manner as the second type, that is by direct compression, with the exception that the sodium hydrogencarbonate was omitted.

The following results were for each dissolution test based on the measurement on 15 tablets with a declared amount of Ibuprofen of 120 mg. The dissolution method used is the following:

Test Method

Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7. The measurements were performed using an Perkin-Elmer spectrophotometer Lambda 15.

Glass fibre filter: Whatmann GF/F

Dissolution medium: 900 ml dissolution medium. (see below)

Number of revolutions: 50 rpm.

Temperature of dissolution medium: 37°C ± 0.5°C.

Measuring times: At 10, 20, 30 and 60 min. (and 180 min.)

Detection UV: 221 nm

Preparation of reagents:

Dissolution medium: Weigh out 50.0 g of sodium chloride and measure out 141.6 ml of concentrated hydrochloric acid. Dissolve the chemicals in distilled water and dilute to 25 l with distilled water.

Standards:

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 1000 µg/ml Ibuprofen was prepared. Ibuprofen was dissolved in dissolution medium.

Standard: Each of the stock solutions was diluted to two standards with dissolution medium: E.g. 2.00 ml was diluted to 50.00 ml and 3.00 ml was diluted to 50.00 ml, or 2.00 ml was diluted to 50.00 ml and 4.00 ml was diluted to 50.00 ml with dissolution medium.

Test procedure

900 ml of dissolution medium is filled to each of the vessels (typically three or six vessels for the product). The medium is heated to 37°C ± 0.5°C. The product to be tested (e.g. therapeutically and/or prophylactically active substance, a particulate composition, a granulate, granules or a composition in the form of a tablet, capsules or a sachet) is placed in the vessel.
A samples volume of e.g. 10 ml is extracted and filtered at the defined times.
Samples and standards were diluted with ethanol to a suitable concentration (e.g. a 25 times dilution) before measuring.

Calculation for the dissolution method.

Percentage dissolved was calculated with reference to a standard of Ibuprofen.

Calculate the quantity (y_{10}, y_{20}, y_{30} and y_{60}) of Ibuprofen dissolved in per cent of the stated content in each of the tablets using the following expressions.

10 min.

$$y_1 = \frac{abs_{sample} \cdot stA}{abs_{std}} \cdot \frac{n \cdot 900 \cdot 100}{100 \cdot x}$$

20 min.

$$z_{20} = \frac{abs_{sample} \cdot stA}{abs_{std}} \cdot \frac{n \cdot (900 - v) \cdot 100}{100 \cdot x}$$

$$y_{20} = z_{20} + y_{10} \cdot \frac{v}{900}$$

30 min.

$$z_{30} = \frac{abs_{sample} \cdot stA}{abs_{std}} \cdot \frac{n \cdot (900-2v) \cdot 100}{100 \cdot x}$$

$$y_{30} = z_{30} + y_{10} \cdot \frac{v}{900} + y_{20} \cdot \frac{v}{900-v}$$

60 min.

$$z_{60} = \frac{abs_{sample} \cdot stA}{abs_{std}} \cdot \frac{n \cdot (900-3v) \cdot 100}{100 \cdot x}$$

$$y_{60} = z_{60} + y_{10} \cdot \frac{v}{900} + y_{20} \cdot \frac{v}{900-v} + y_{30} \cdot \frac{v}{900-2v}$$

Where

stA	=	Concentration of the standard in mg/ml.
Abs_{sample}	=	Absorption of the sample
Abs_{std}	=	Absorption of the standard
n	=	Potency of the standard in percent
v	=	sample amount in ml
x	=	stated content

The results obtained are the following:

Time	Batch No. 10059932		Batch No. 10059932		Batch No. 07069934		Batch No. 07069933	
	n = 2		n = 3		n = 2		n = 2	
	x	s	x	s	x	s	x	S
10 min	63.0	5.8	64.5	4.4	39.6	1.8	22.8	0.6
20 min	65.1	6.7	62.6	1.2	43.6	0.6	26.7	1.3
30 min	61.3	0.4	62.4	1.4	43.4	1.8	28.7	1.0
60 min	56.2	2.7	60.2	0.8	40.2	0.6	30.4	0.1
180			43.2	6.1				

Conclusion

From the data shown above it is evident that the first formulation type, that is the approach of Example 1, markedly improves the dissolution rate compared to a direct compression, irrespective of whether $NaHCO_3$ is present. However, the addition of $NaHCO_3$ in a direct compression has some effect on the dissolution rate.

EXAMPLE 19

Lab scale trials with furosemid as the therapeutically active substance

In lab scale, 3 types of tablet cores were manufactured. The *first type* (batch No. 06059932) was manufactured as described in Example 8 with the exception that lornoxicam has been substituted with furosemid. Therefore, the composition was as follows:

I	Furosemid	80.0 g
II	Sodium bicarbonate	400.0 g
III	Avicel PH 101	960.0 g
IV	Calcium hydrogen phosphate anhydrous	1104.0 g
V	L-HPC	480.0 g
VI	Hydroxy propyl cellulose	160.0 g

VII	Purified water	1080.0 g
VIII	Ethanol 99,9 %	360.0 g
IX	Calcium stearate	5.0 g/kg*

* amount adjusted for a total of 1 kilo of I-VI

The same way of manufacturing but excluding the wet massing phase, that is manufacturing the tablets by direct compression, was used for the *second type* (batch No. 04069934) of tablet cores.

The *third type* (batch No. 04069932) of tablets was manufactured as the second type, that is by direct compression, with the exception that sodium hydrogencarbonate was omitted.

The results given below are results for each dissolution test performed and based on a measurement on 1 tablet with a declared amount of furosemid of 8 mg. The dissolution method used is dissolution method I, only are the revolutions of the paddle changed to 50 rpm and the wavelength used is 274 nm. The substance used for standard is furosemide, the concentrations being identical to that of lornoxicam.

The following results were obtained:

Time	Batch No. 06059932		Batch No. 04069934		Batch No. 04069932	
	n = 2		n = 2		n = 2	
	x	s	x	s	x	s
10 min	102.4	1.4	90.2	2.6	73.8	0.2
20 min	104.7	1.8	92.3	0.3	86.0	1.4
30 min	104.5	1.0	93.9	0.9	93.1	0.7
60 min	105.1	1.2	96.7	0.1	102.2	0.7
80 min	104.3	1.2	97.3	0.3	105.1	0.6
100 min	104.3	1.3	97.5	0.1	106.8	0.4

If these data are adjusted so that the end release after 100 min equals 100 % the following data is obtained:

Time	Batch No. 06059932		Batch No. 04069934		Batch No. 04069932	
	n = 2		n = 2		n = 2	
	Org	Adj.	Org	Adj.	Org	Adj.
10 min	102.4	**98.2**	90.2	**92.5**	73.8	**69.1**
20 min	104.7	**100.4**	92.3	**94.7**	86	**80.5**
30 min	104.5	**100.2**	93.9	**96.3**	93.1	**87.2**
60 min	105.1	**100.9**	96.7	**99.2**	102.2	**95.7**
80 min	104.3	**100.0**	97.3	**99.8**	105.1	**98.4**
100 min	104.3	**100.0**	97.5	**100.0**	106.8	**100.0**

Org: = original data

Adj: = adjusted data

Conclusion

From the data given above it is seen that the initial release after 10 and 20 min is markedly influenced by the kind of formulation. This means that the addition of $NaHCO_3$ gives a markedly quicker dissolution rate. The formulation of type 1 seems to be the most effective indicating that the wet massing step is advantageous.

EXAMPLE 20

Lab scale trials - Investigation on the influence on the dissolution rate by adding sodium lauryl sulphate to lornoxicam containing compositions.

In lab scale the effect of sodium lauryl sulfate was investigated by

a) granulating with a formulation in which $NaHCO_3$ has been substituted by sodium lauryl sulfate or

b) direct compression of the formulation of Example 8 with the addition of sodium lauryl sulphate.

The actual formulation of trial a) and b) are shown below:

	Trial a; batch No. 18069932 {gram}	Trial b; batch No. 17069932 {gram}
Lornoxicam	80	80
Sodium bicarbonate	-	400
Sodium lauryl sulphate	32	32
Avicel PH 101	960	960
Calcium hydrogen phosphate anhydrous	1104	1104
L-HPC	480	480
Hydroxy propyl cellulose	160	160
Purified water	955,5	-
Ethanol 99,9 %	318,5	-
Calcium stearate	5 g/kg*	5 g/kg*

*: adjusted for 1 kg of particulate material

The composition of trial a was manufactured as described in Example 8) and the composition of trial b was manufactured by direct compression (i.e. omitting the wet massing phase).

The results obtained were the following:

Time [min]	Trial a, batch No. 17069932 n = 3		Trial b, batch No 18069932 n = 3	
	x	s	x	s
10	25.1	1.1	23.0	0.5
20	28.2	0.6	28.0	0.2
60	30.9	0.5	32.2	0.1
120	32.0	0.6	33.9	0.1

Conclusion

From the results given above it is seen that the addition of a surface active agent like sodium lauryl sulphate does not lead to a quick release of lornoxicam. The same result is seen in the case where sodium hydrogencarbonate as well as sodium lauryl sulphate are present in the composition.

CLAIMS

1. A quick release pharmaceutical composition for oral administration comprising a therapeutically and/or prophylactically active substance which has a solubility of at the most about 0.1 % w/v in 0.1 N hydrochloric acid at room temperature,

the composition being based on a powder comprising the therapeutically and/or prophylactically active substance and having such a particle size that - when the powder is subjected to a sieve analysis - then at least about 90% w/w such as, e.g. at least about 92% w/w, at least about 94% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of the particles passes through sieve 180 μm, the powder being contacted with an aqueous medium to form a particulate composition, which has such a particle size that - when the particulate composition is subjected to a sieve analysis - then at least about 50% w/w such as, e.g., at least about 55% w/w. at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w of the particles passes through sieve 180 μm, and

the composition - when tested in accordance with the dissolution method I defined herein employing 0.07 N hydrochloric acid as dissolution medium - releases at least about 50% w/w of the active substance within the first 20 min of the test.

2. A quick release pharmaceutical composition for oral administration comprising a therapeutically and/or prophylactically active substance which has a solubility of at the most 0.1 % w/v in 0.1 N hydrochloric acid at room temperature,

the composition being in the form of a particulate composition or being based on a particulate composition which is obtained by contacting a powder comprising the therapeutically and/or prophylactically active substance with an aqueous medium in such a manner that the mean particle size of the particles of the particulate composition is at the most about 100% larger than the mean particle size of the powder before contact with the aqueous medium, and

the composition - when tested in accordance with the dissolution method I defined herein employing 0.07 N hydrochloric acid as dissolution medium - releases at least about 50% w/w of the active substance within the first 20 min of the test.

3. A quick release pharmaceutical composition for oral administration comprising a therapeutically and/or prophylactically active substance which has a pK_a value of at the most about 5.5, such as, e.g., at the most about 5.3, at the most about 5.2, at the most about 5.0 such as ,e.g., in a range of from about 3.4 to about 5.0 or in a range of from about 4.0 to about 5.0,

the composition being based on a powder comprising the therapeutically and/or prophylactically active substance and having such a particle size that - when the powder is subjected to a sieve analysis - then at least about 90% w/w such as, e.g. at least about 92% w/w, at least about 94% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of the particles passes through sieve 180 μm, the powder being contacted with an aqueous medium to form a particulate composition, which has such a particle size that - when the particulate composition is subjected to a sieve analysis - then at least about 50% w/w such as, e.g., at least about 55% w/w. at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w of the particles passes through sieve 180 μm, and

the composition - when tested in accordance with the dissolution method I defined herein - releases at least about 50% w/w of the active substance within the first 20 min of the test.

4. A quick release pharmaceutical composition for oral administration comprising a therapeutically and/or prophylactically active substance which has a pK_a value of at the most about 5.5, such as, e.g., at the most about 5.3, at the most about 5.2, at the most about 5.0 such as ,e.g., in a range of from about 3.4 to about 5.0 or in a range of from about 4.0 to about 5.0,

the composition being in the form of a particulate composition or being based on a particulate composition which is obtained by contacting a powder comprising the

therapeutically and/or prophylactically active substance with an aqueous medium in such a manner that the mean particle size of the particles of the particulate composition is at the most about 100% larger than the mean particle size of the powder before contact with the aqueous medium, and

the composition - when tested in accordance with the dissolution method I defined herein - releases at least about 50% w/w of the active substance within the first 20 min of the test.

5. A composition according to any one of the preceding claims, wherein the composition – when subjected to dissolution method I as defined herein employing 0.07 N hydrochloric acid as dissolution medium – releases at least 55% w/w such as, e.g., at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of total amount of active substance present in the composition within the first 20 min of the test.

6. A composition according to any one of the preceding claims wherein the solubility of the therapeutically and/or prophylactically active substance in 0.1 N hydrochloric acid at room temperature is at the most about 0.05% w/v such as at the most about 0.01% w/v, at the most about 0.009% w/v, at the most about 0.008% w/v, at the most about 0.007% w/v, at the most about 0.006% w/v, at the most about 0.005% w/v, at the most about 0.004% w/v, at the most about 0.003% w/v, at the most about 0.002 % w/v or at the most about 0.001% w/v.

7. A composition according to any one of the preceding claims, wherein the therapeutically and/or prophylactically active substance – when tested by solubility method I described herein – has such a dissolution rate that it allows an amount of at the most 50% w/w of the active substance to be dissolved within the first 20 min of the test.

8. A composition according to any one of the preceding claims, wherein the composition is in the form of a solid composition.

9. A composition according to any one of the preceding claims, wherein the composition is in the form of a particulate composition.

10. A composition according to any one of the preceding claims in the form of a unit dosage form.

11. A composition according to any one of the preceding claims, wherein the aqueous medium comprises water and an organic solvent.

12. A composition according to any one of the preceding claims, wherein the mean particle size of the particles of the particulate composition is at the most about 250 μm, such as, e.g. at the most about 240 μm, at the most about 230 μm, at the most about 220 μm, at the most about 210 μm, at the most about 200 μm, at the most about 190 μm, at the most about 180 μm, at the most about 175 μm, at the most about 150 μm, at the most about 125 μm, at the most about 100 μm, at the most about 90 μm, at the most about 80 μm or at least at the most about 75 μm, whenever appropriate, after contact with an aqueous medium.

13. A composition according to any one of the preceding claims further comprising at least one pharmaceutically acceptable excipient.

14. A composition according to claim 13, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, fillers and diluents.

15. A composition according to claim 14, wherein the composition comprises a filler having binding properties.

16. A composition according to claim 15, wherein the filler having binding properties is, e.g., lactose (such as, e.g., Tabletose®, Pharmatose®), sugar derivatives (such as, e.g., mannitol, sorbitol), calcium carbonate ($CaCO_3$), tricalcium phosphate ($Ca_5(PO_4)_3OH$), calcium hydrogen phosphate ($CaHPO_4$) (such as, e.g., Di-Cafos®, Di-Tab®, Emcompress® or Pharmacompress®), or the like and/or mixtures thereof.

17. A composition according to claim 16, wherein the filler having binding properties is calcium hydrogen phosphate.

18. A composition according to any one of claims 15-17, wherein the filler having binding properties as raw material has a mean particle size of at the most about 140 μm, such as, e.g., at the most about 130 μm, at the most about 120 μm, at the most about 110 μm, at the most about 100 μm, at the most about 90 μm, at the most about 80 μm, at the most about 70 μm, at the most about 60 μm, at the most about 50 μm, at the most about 40 μm, at the most about 35 μm, at the most about 30 μm or at the most about 25 μm such as, e.g., in a range of from about 10 μm to about 80 μm or in a range of from about 15 μm to about 55 μm..

19. A composition according to any one of the preceding claims further comprising an alkaline substance such as, e.g., an antacid or an antacid-like substance.

20. A composition according to claim 19, wherein the alkaline substance is an antacid or an antacid-like substance such as, e.g., sodium hydrogen carbonate, magnesium carbonate, magnesium hydroxide or magnesium metasilicate aluminate or mixtures thereof.

21. A composition according to claim 19 or 20, wherein the mean particle size of the antacid-like substance as raw material is at the most about 250 μm, such as at the most about 225 μm, at the most about 200 μm, at the most about 175 μm, at the most about 150 μm, at the most about 145 μm, at the most about 140 μm, at the most about 135 μm, at the most about 130 μm such as, e.g., in a range of from about 20 μm to about 250 μm, in a range of from about 40 μm to about 200 μm, in a range of from about 60 μm to about 175 μm, in a range from about 80 μm to about 150 μm or in a range of from about 100 μm to about 120 μm.

22. A composition according to any one of the preceding claims, wherein a particulate composition further has been processed to obtain a composition in the form of tablets, capsules or sachets.

23. A composition according to any one of the preceding claims in the form of tablets.

24. A composition according to claim 23 obtainable by compressing a powder comprising the therapeutically and/or prophylactically active substance and at least one pharmaceutically acceptable excipient into tablets.

25. A composition according to any of claims 22-24, wherein the composition has such a mechanical strength as to enable handling and coating in a conventional coating apparatus.

26. A composition according to claim 25, wherein the composition – when subjected to a crushing strength test in accordance with Ph. Eur. - has a crushing strength of at least about 50 N such as, e.g., at least about 60 N, at least about 70 N, at least about 80 N such as, e.g., in a range from about 50 N to about 150 N, in a range of from about 60 N to about 130 N, in a range from about 70 N to about 120 N or in a range of from about 75 N to about 110 N such as from about 80 to about 100 N.

27. A composition according to any one of claims 22-26 comprising a first pharmaceutically acceptable excipient which imparts a suitable robustness to the composition to enable handling and, if desired, coating in a coating apparatus.

28. A composition according to claim 27, wherein the first pharmaceutically acceptable excipient is a filler having binding properties.

29. A composition according to any one of claims 26-28, wherein the composition - when tested as a composition without the first pharmaceutically acceptable excipient in the crushing strength apparatus according to Ph. Eur. - has a crushing strength of less than about 45 N such as, e.g., less than about 30 N, less than about 25 N, less than about 20 N, less than about 15 N or less than about 10 N.

30. A composition according to claim 28, wherein the filler having binding properties is, e.g., lactose (such as, e.g., Tabletose®, Pharmatose®), sugar derivatives (such as, e.g., mannitol, sorbitol), calcium carbonate ($CaCO_3$), tricalcium phosphate ($Ca_5(PO_4)_3OH$), calcium hydrogen phosphate ($CaHPO_4$) (such as, e.g., Di-Cafos®, Di-Tab®, Emcompress® or Pharmacompress®), or the like and/or mixtures thereof.

31. A composition according to any one of the preceding claims, wherein the therapeutically and/or prophylactically active substance is a non-steroid anti-inflammatory drug substance (NSAID substance).

32. A composition according to any one of the preceding claims, wherein the therapeutically and/or prophylactically active substance is selected from the group consisting of lornoxicam, diclofenac, nimesulide, ibuprofen, piroxicam, piroxicam (betacyclodextrin), naproxen, ketoprofen, tenoxicam, aceclofenac, indometacin, nabumetone, acemetacin, morniflumate, meloxicam, flurbiprofen, tiaprofenic acid, proglumetacin, mefenamic acid, fenbufen, etodolac, tolfenamic acid, sulindac, phenylbutazone, fenoprofen, tolmetin, acetylsalicylic acid, dexibuprofen, paracetamol, and pharmaceutically acceptable salts, complexes and/or prodrugs thereof and mixtures thereof.

33. A composition according to any one of the preceding claims, wherein the therapeutically and/or prophylactically active substance is lornoxicam or a pharmaceutically acceptable salt, complex or prodrug thereof.

34. A composition according to any one of the preceding claims, wherein the therapeutically and/or prophylactically active substance is present in the composition in an amount which is sufficient to give an enhanced onset of the effect.

35. A composition according to any one of the preceding claims comprising a further active drug substance.

36. A composition according to claim 35, wherein the further active drug substance is an antidepressant, an opioid, a prostaglandine analogue (e.g. misoprostol), a glucocorticosteroid, a cytostaticum (e.g. methotrexate), a H_2 receptor antagonist (e.g. cimetidine, ranitidine), a proton pump inhibitor (e.g. pantoprazole, omeprazole, lansoprazole) and/or an antacidum.

37. A composition according to claim 35, wherein the further active drug substance is paracetamol, penicillamine, sulfasalazine and/or auranorfin.

38. A composition according to any one of the preceding claims in unit dosage form, wherein the unit dosage of the composition comprises from about 1 to about 32 mg of the therapeutically and/or prophylactically active substance.

39. A composition according to any one of claims 1-37 in unit dosage form, wherein the unit dosage comprises from about 1 mg to about 1.6 g such as from about 1 mg to about 1.2 g of the therapeutically and/or prophylactically active substance.

40. A composition according to any one of claims 1-37 in unit dosage form, wherein the unit dosage comprises from about 50 mg to about 1.1 g of the therapeutically and/or prophylactically active substance.

41. A composition according to any one of claims 1-37 in unit dosage form, wherein a unit dosage comprises from about 100 mg to about 1.0 g of the therapeutically and/or prophylactically active substance.

42. A composition according to any one of claims 1-37 in unit dosage form, wherein a unit dosage comprises from about 200 mg to about 900 mg of the therapeutically and/or prophylactically active substance.

43. A composition according to any one of claims 1-37 in unit dosage form, wherein a unit dosage comprises from about 300 mg to about 800 mg of the therapeutically and/or prophylactically active substance.

44. A composition according to any one of the preceding claims, wherein the therapeutically and/or prophylactically active substance is lornoxicam and a unit dosage of the composition contains 4, 8, 12, 16, 20, 24, 28, 32 or 36 mg of lornoxicam.

45. A composition according to any one of the preceding claims, wherein the water content in the composition is at the most about 5% w/w such as, e.g., at the most about 4% w/w, at the most about 3%, at the most about 2% w/w, at the most about 1.5% w/w, at the most about 1.3% w/w, at the most about 1.1% w/w or at the most about 0.9% w/w determined by the LOD (loss on drying) method described herein.

46. A composition according to any one of the preceding claims comprising sodium hydrogen carbonate.

47. A composition according to any one of the preceding claims comprising calcium hydrogen phosphate.

48. A composition according to any one of the preceding claims, wherein the composition is coated with a coat which does not substantially retard the release of the therapeutically and/or prophylactically active substance from the composition.

49. A composition according to any one of the preceding claims, wherein the composition is coated with a film coating.

50. A method for the preparation of a composition according to any one of the preceding claims, the method comprising the steps of

i) mixing the therapeutically and/or prophylactically active substance with a) an alkaline substance, b) a filler having binding properties, and, optionally, c) other pharmaceutically acceptable excipients to obtain a powder mixture,

ii) contacting the thus obtained powder mixture with an aqueous medium to obtain a wet powder,

iii) drying the thus obtained wet powder at a temperature above room temperature until the water content in the powder is at the most about 5% w/w determined as described herein, to obtain a first particulate mixture,

iv) sieving the thus obtained first particulate mixture,

v) optionally, adding any further pharmaceutically acceptable excipients to obtain a second particulate mixture,

vi) optionally, compressing the thus obtained second particulate mixture into tablets, and

vii) optionally, coating the thus obtained tablets.

51. A method according to claim 50, wherein step ii) is performed in a suitable apparatus which enables an energy input which is sufficient to bringing the particles in contact with the aqueous medium without substantially deteriorate the stability of the final composition.

52. A method according to claim 50, wherein step ii) is performed in a suitable apparatus which enables an energy input which is sufficient to bringing the therapeutically and/or prophylactically active substance and the alkaline substance in contact with the aqueous medium without negatively influencing the release rate of the active substance from the final composition.

53. A method according to claim 51or 52, wherein the energy input is provided discontinuous.

54. A method according to any one of claims 50-53, wherein step ii) is performed in intervals of wet-massing and wet-resting.

55. A method according to any one of claims 50-54, wherein the alkaline substance employed in step i) is an antacid-like substance such as, e.g., sodium hydrogen carbonate, magnesium carbonate, magnesium hydroxide or magnesium metasilicate aluminate or mixtures thereof.

56. A method according to any one of claims 50-55, wherein the filler having binding properties is, e.g., lactose (such as, e.g., Tabletose®, Pharmatose®), sugar derivatives (such as, e.g., mannitol, sorbitol), calcium carbonate ($CaCO_3$), tricalcium phosphate ($Ca_5(PO_4)_3OH$), calcium hydrogen phosphate ($CaHPO_4$) (such as, e.g., Di-Cafos®, Di-Tab®, Emcompress® or Pharmacompress®), or the like and/or mixtures thereof.

57. A method according to any one of claims 50-56, wherein the aqueous medium employed in step ii) is a solvent comprising water and an organic solvent.

58. A method according to claim 57, wherein the organic solvent is a solvent which is miscible with water such as, e.g., a branched or unbranched lower (C_1-C_5) aliphatic alcohol like, e.g., ethanol, methanol, isopropanol, 1-propanol, 1-butanol, 2-butanol, iso-

butanol, tert. butanol and 1-pentanol, 2-pentanol, 3-pentanol, iso-pentanol and tert. pentanol and mixtures thereof.

59. A method according to claim 58, wherein the concentration of the organic solvent in the solvent is from about 0% v/v to about 95% v/v such as, e.g., from about 10% v/v to about 90% v/v, from about 10% v/v to about 80% v/v, from about 15% v/v to about 70% v/v, from about 15% v/v to about 60% v/v, from about 20% v/v to about 50% v/v, from about 20% v/v to about 40% v/v, from about 25% v/v to about 35% v/v such as, e.g. about 33.3% v/v.

60. A method according to any one of claims 50-59, wherein step ii) is performed in a conventional high shear mixer employing an energy input which is sufficient to enable a contact to take place between the therapeutically and/or prophylactically active substance and the alkaline substance employed in step i) but at the same time is sufficiently low to avoid formation of a large amount of agglomerates during the mixing.

61. A method according to any one of claims 50-60, wherein the mean particle size of the particles of the first particulate mixture is at the most about 100% larger than the mean particle size of the powder mixture from step i) before subjecting the powder mixture to the reaction in the aqueous medium employed in step ii).

62. A method according to claim 61, wherein the mean particle size of the particle of the first particulate mixture is at the most 90% such as, e.g., about 80%, about 75%, about 70%, about 65%, about 60%, about 55% or about 50% larger than the mean particle size of the powder mixture from step i) before subjecting the powder mixture to the reaction in an aqueous medium employed in step ii).

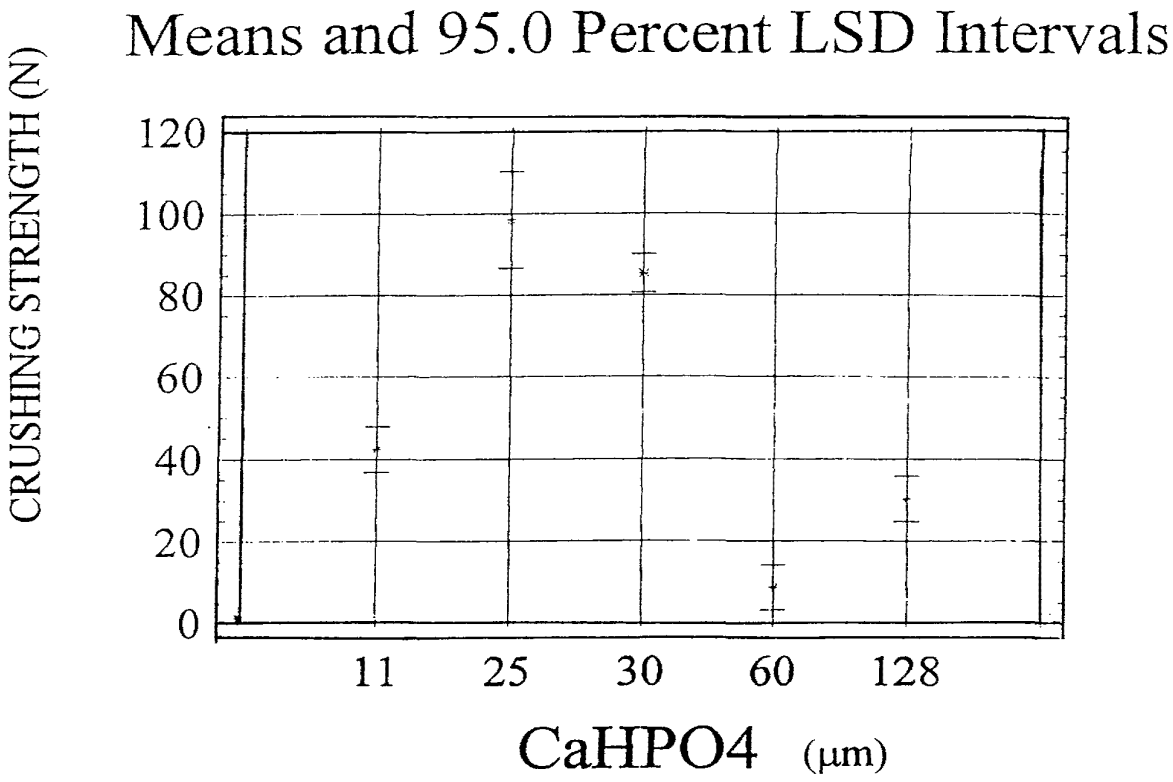
63. A method according to any one of claims 50-62, wherein the powder obtained in step i) has such a particle size that - when the powder is subjected to a sieve analysis - then at least about 90% w/w such as, e.g. at least about 92% w/w, at least about 94% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of the particles passes through sieve 180 μm, and the first particulate mixture obtained in step iii) has such a particle size that - when the particulate composition is subjected to a sieve analysis - then at least about 50% w/w such as, e.g., at least about 55% w/w. at least about 60% w/w, at least

about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w of the particles passes through sieve 180 μm.

64. A method according to any one of claims 50-63, wherein the mean particle size of the particles of the first particulate mixture is at the most about 250 μm, such as, e.g. at the most about 240 μm, at the most about 230 μm, at the most about 220 μm, at the most about 210 μm, at the most about 200 μm, at the most about 190 μm, at the most about 180 μm, at the most about 175 μm, at the most about 150 μm, at the most about 125 μm, at the most about 100 μm, at the most about 90 μm, at the most about 80 μm or at the most about 75 μm.

65. A method for treatment and/or prophylaxis of acute pain and/or mild or moderate pain comprising administering to a patient an effective amount of a therapeutically and/or prophylactically active substance in the form a quick release composition according to any one of claims 1-49.

66. A method for fast relief of acute pain comprising administering to a patient in need thereof an effective amount of a therapeutically and/or prophylactically active substance in the form a quick release composition according to any one of claims 1-49.


Means and 95.0 Percent LSD Intervals
CRUSHING STRENGTH (N)
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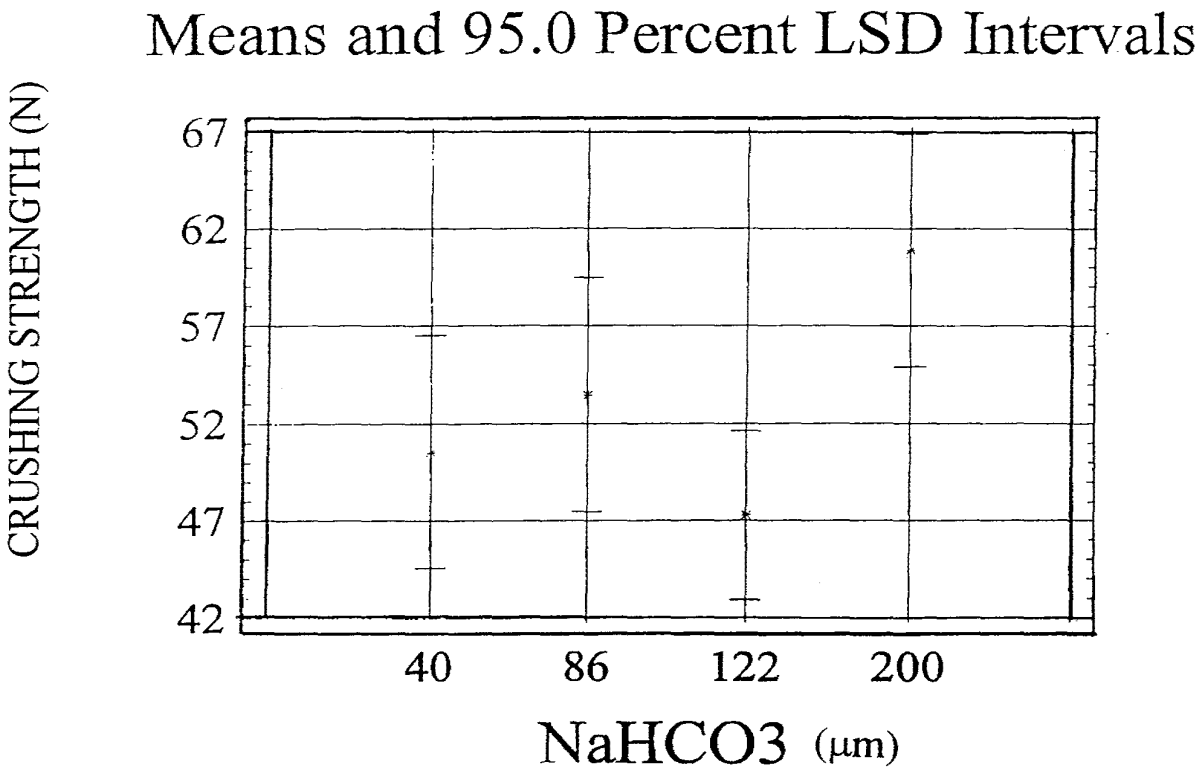
100
80
60
40
20
0
11
25
30
60
128
CaHPO4 (µm)

Fig. 1


Means and 95.0 Percent LSD Intervals
CRUSHING STRENGTH (N)
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57
52
47
42
40
86
122
200
NaHCO3 (µm)

Fig. 2

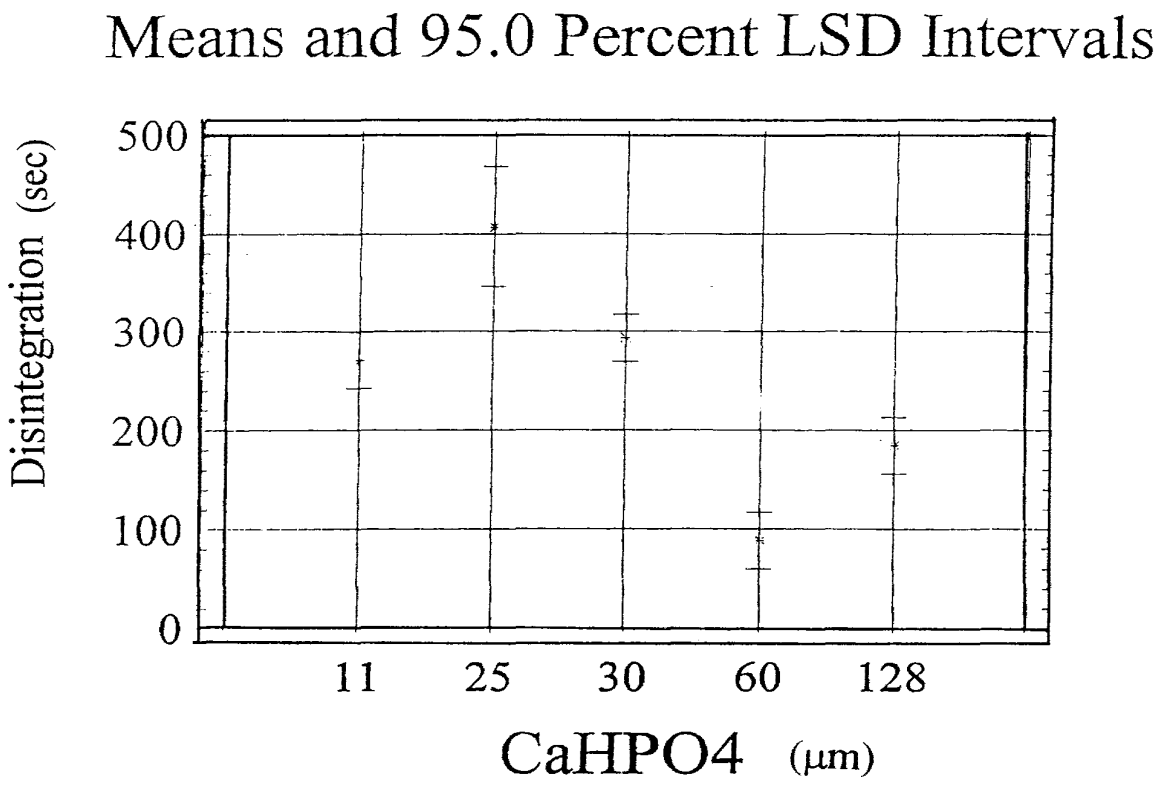
Means and 95.0 Percent LSD Intervals
Disintegration (sec)
500
400
300
200
100
0
11
25
30
60
128
CaHPO4 (μm)

Fig. 3

INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/DK 99/00480

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K9/20

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)
IPC 7 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 14839 A (SOUTH AFRICAN DRUGGISTS LIMITED) 23 May 1996 (1996-05-23) the whole document	1-66
A	WO 95 32737 A (SOUTH AFRICAN DRUGGISTS LIMITED) 7 December 1995 (1995-12-07) the whole document	1-66

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

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 February 2000	10/02/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Ventura Amat, A

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INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/DK 99/00480

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 116, no. 10, 9 March 1992 (1992-03-09) Columbus, Ohio, US; abstract no. 91424, NEMOTO, MASAMI ET AL: "Solid preparations with accelerating absorption of oxicam-type anti-inflammatory agents for internal use" XP002095848 abstract & JP 03 240729 A (TAISHO PHARMACEUTICAL CO., LTD., JAPAN)	1-66

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 99/00480

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 65-66 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int onal Application No
PCT/DK 99/00480

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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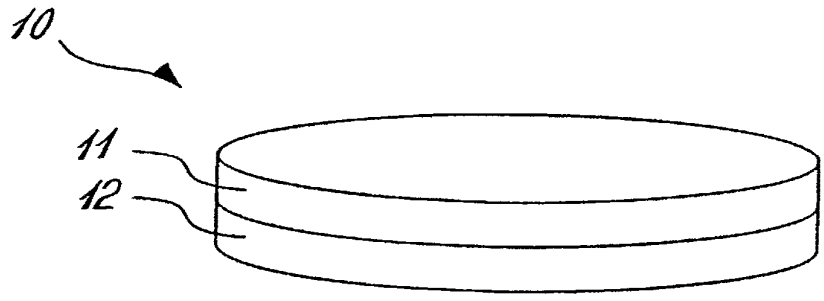
(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: STABILIZED PHARMACEUTICAL COMPOSITION OF A NONSTEROIDAL ANTI-INFLAMMATORY AGENT AND A PROSTAGLANDIN

(57) Abstract



A pharmaceutical composition is provided for the oral administration of an NSAID and a prostaglandin. The composition is a solid dosage form wherein the NSAID is enterically coated and the prostaglandin is present along with an effective stabilizing amount of a prostaglandin stabilizing agent such as hydroxypropyl methylcellulose or polyvinylpyrrolidone. Exemplary dosage forms are bilayer tablets in which the prostaglandin is misoprostol and the NSAID is diclofenac, piroxicam, or a pharmaceutically acceptable salt thereof. Methods for using the composition to treat NSAID-responsive conditions, disorders and diseases are provided as well.

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STABILIZED PHARMACEUTICAL COMPOSITION OF A NONSTEROIDAL ANTI-INFLAMMATORY AGENT AND A PROSTAGLANDIN

TECHNICAL FIELD

This invention relates generally to pharmaceutical compositions, and more particularly relates to a pharmaceutical composition containing a combination of a nonsteroidal anti-inflammatory drug (NSAID) and a prostaglandin.

BACKGROUND ART

Nonsteroidal anti-inflammatory agents such as diclofenac, difenpiramide, fenbufen, flufenamic acid, ibuprofen, indomethacin, ketoprofen, meclofenamate sodium, mefenamic acid, nabumetone, naproxen, piroxicam, suprofen and tiaprofenic acid, are widely used to relieve mild to moderate pain, for fever, and to treat inflammatory conditions. Sodium diclofenac, for example, is particularly effective for relief of musculoskeletal and joint disorders such as rheumatoid arthritis, an autoimmune disease, osteoarthritis and ankylosing spondilitis; peri-acicular disorders such as bursitis and tendinitis; soft-tissue disorders such as sprains and strains, and other painful conditions such as renal colic, acute gout, dysmenorrhoea, and for relieving pain following some surgical disorders. The NSAIDs are non-habit forming drugs and thus offer a significant advantage over traditional opioid-based drugs; furthermore, as NSAIDs are by definition "nonsteroidal," the side effects commonly associated with oral administration of steroids are avoided as well. However, it is recognized that NSAIDs also exhibit some undesirable side effects, particularly at high dosages and/or with chronic oral administration. Generally, high dosages and chronic use of NSAIDs are associated with problems such as gastrointestinal and duodenal bleeding, ulceration and perforation.

In view of the advantages of NSAIDs over opioid-based drugs and steroidal agents, steps have been undertaken to minimize the drugs' adverse effects. In one approach, NSAIDs have been administered locally, such as by injection, by topical administration of, for example, an ointment or cream, by use of a transdermal patch, or by an inhalation device. Although local administration is desirable, administration of an effective amount of the active agent is difficult or inconvenient. In another approach to reduce the adverse effects of NSAIDs, the agents are ingested after food or milk, or are taken in combination with antacids, histamine H_2-receptor antagonists, omeprazole, or sucralefate.

In yet another approach to reduce the undesirable gastrointestinal effects resulting from the oral administration of NSAIDs, the agents have been co-administered with some prostaglandins, particularly "E-series" prostaglandins such as PGE_1, PGE_2, misoprostol, and derivatives thereof; see, e.g., U.S. Patent Nos. 3,781,429 to Partridge, 3,927,213 to Lippman, 3,928,588 to Robert, and 5,015,481 to Franz et al. Administration of a prostaglandin with an NSAID has been shown to reduce the ulcerogenicity of the NSAID. However, prostaglandins are unstable compounds and degrade readily in the presence of NSAIDs, thus requiring a stabilizing agent such as hydroxypropyl methylcellulose (HPMC) or polyvinylpyrrolidone (PVP) which can, in turn, lessen the activity of an NSAID. See, for example, U.S. Patent No. 4,301,146 to Sanvordeker, which discloses prostaglandin E-type compounds stabilized with hydroxypropyl methylcellulose or polyvinylpyrrolidone before being pressed into tablets, U.S. Patent No. 3,954,787 to Monkhouse, which discloses that lyophilized compositions of prostaglandin E and sodium chloride, cyclodextrin or polyvinylpyrrolidone are stable, and U.S. Patent No. 5,015,481 to Franz et al., which discusses the destabilization of prostaglandins in the presence of the NSAIDs diclofenac and piroxicam.

There is, accordingly, a need in the art to provide a composition for administering an NSAID wherein the undesirable gastrointestinal side effects of the drug are minimized but wherein the drug's therapeutic effectiveness is maintained. The present invention is addressed to the aforementioned need in the art and provides a stabilized pharmaceutical composition of an NSAID and a prostaglandin, i.e., a composition in which the prostaglandin is stabilized and the efficacy of the NSAID is maintained.

DISCLOSURE OF THE INVENTION

Accordingly, it is a primary object of the invention to provide a stabilized pharmaceutical composition for oral administration of an NSAID and a prostaglandin.

It is another object of the invention to provide such a composition wherein the NSAID is enterically coated.

It is yet another object of the invention to provide such a composition that additionally includes a prostaglandin-stabilizing agent.

It is still another object of the invention to provide such a composition in which the enterically coated NSAID and the prostaglandin are present in discrete regions of the composition, such as in a bilayer tablet wherein the enterically coated NSAID is present in a first layer and the prostaglandin and the prostaglandin stabilizing agent are present in a second layer.

Another object of the invention is to provide a method for treating a patient with an NSAID-responsive condition, disease or disorder, wherein the method comprises administering an NSAID to the patient in a stabilized pharmaceutical composition as provided herein.

Still another object of the invention is to provide a method for reducing the undesirable gastrointestinal side effects associated with the oral administration of an NSAID, wherein the method comprises co-administering a prostaglandin with the NSAID in a stabilized pharmaceutical composition as provided herein.

Additional objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following, or may be learned by practice of the invention.

In one embodiment, the first layer of the bilayer tablet comprises an enterically coated nonsteroidal anti-inflammatory agent, and the second layer comprises a prostaglandin and a stabilizing agent.

In another embodiment, a method of treating a patient is provided for carrying out the present therapeutic method comprising administering to the patient a pharmaceutical composition bilayer tablet as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1 and 2 are schematic representations of dosage forms of the invention.

MODES FOR CARRYING OUT THE INVENTION

Overview and Definitions:

Before describing the present invention in detail, it is to be understood that this invention is not limited to particular drugs or drug delivery systems, as such 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 be limiting.

It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmacologically active agent" includes a combination of two or more pharmacologically active agents, reference to "a stabilizer" includes combinations of two or more stabilizers, reference to "a prostaglandin" includes combinations of two or more prostaglandins, and the like.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

The terms "active agent," "drug" and "pharmacologically active agent" are used interchangeably herein to refer to a chemical material or compound which, when administered to an organism (human or animal) induces a desired pharmacologic effect. Included are derivatives and analogs of those compounds or classes of compounds specifically mentioned which also induce the desired pharmacologic effect.

An "enterically coated" drug or tablet refers to a drug or tablet that is coated with a substance--i.e., with an "enteric coating"--that remains intact in the stomach but dissolves and releases the drug once the small intestine is reached.

By "pharmaceutically acceptable carrier" or "pharmaceutically acceptable vehicle" are meant materials that are suitable for oral administration and not biologically or otherwise undesirable, i.e., that may be administered to an individual along with an active agent

without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

Similarly, a "pharmaceutically acceptable" salt, ester or other derivative of an active agent as provided herein is a salt, ester or other derivative which is not biologically or otherwise undesirable.

"Stabilizing agents" as used herein refer to compounds that lower the rate at which the prostaglandins degrade, particularly in an oral pharmaceutical formulation, in the presence of an NSAID, and under environmental conditions of storage.

By "incompatible," as in two drugs that are "incompatible" with respect to each other is meant that in close physical proximity a first drug may have a deleterious effect on the physical or chemical stability of a second drug, and/or vice versa.

By the terms "effective amount" or "therapeutically effective amount" of an agent as provided herein are meant a nontoxic but sufficient amount of the agent to provide the desired therapeutic effect. As will be pointed out below, the exact amount required will vary from subject to subject, depending on the age, weight, and general condition of the subject, the severity of the condition being treated, and the like. Thus, it is not possible to specify an exact "effective amount." However, an appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using only routine experimentation.

By a "pharmacologically acceptable" compound is meant a material which is not biologically or otherwise undesirable, i.e., the material may be administered to an individual along with the selected active agent without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. Similarly, a "pharmacologically acceptable" salt or a "pharmacologically acceptable" ester of a compound as provided herein is a salt or ester which is not biologically or otherwise undesirable.

The invention, as noted above, is in one embodiment a stabilized pharmaceutical composition for administration of an NSAID and a prostaglandin, wherein the NSAID is enterically coated. Preferably, the composition is comprised of two discrete regions, wherein the enterically coated NSAID is present in a first region and the prostaglandin is present in a second region, along with a prostaglandin-stabilizing agent; an exemplary such

composition is a bilayer tablet as shown in Figure 1. The tablet **10** can have any geometric shape, although a generally oval shape is shown. The tablet **10** includes a first layer **11** and an adjacent second layer **12**; alternatively, as shown in Figure 2, the tablet can comprise a first region **13** adjacent to a second region **14**.

The invention is not limited with respect to the selected NSAID; the stabilized compositions of the invention can contain any NSAID, NSAID derivative, or combination of NSAIDs. Typical NSAIDs include, but are not limited to, acetylsalicylic acid, apazone, diclofenac, difenpiramide, diflunisal, etodolac, fenbufen, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, suprofen, tiaprofenic acid and tolmetin. Pharmaceutically acceptable analogs of such NSAIDs are suitable as well, particularly pharmaceutically acceptable salts. Diclofenac, piroxicam and their salts (e.g., diclofenac sodium) are particularly preferred.

The NSAID is present in the composition in a therapeutically effective amount; preferably, the composition is in unit dosage form. The amount of NSAID administered will, of course, be dependent on the age, weight, and general condition of the subject, the severity of the condition being treated, and the judgment of the prescribing physician. Suitable therapeutic amounts will be known to those skilled in the art and/or are described in the pertinent reference texts and literature. For diclofenac sodium, for example, a therapeutic dose is typically in the range of approximately 25 mg to about 75 mg per tablet, optimally about 50 mg per tablet. The therapeutic dosing range for a tablet containing piroxicam is about 5 mg to about 50 mg per tablet, optimally about 20 mg per tablet, while the therapeutic dosing range for a tablet containing naproxen is about 250 mg to 750 mg per tablet.

The NSAID is enterically coated within the stabilized composition of the invention. Generally, the enteric coating comprises a polymeric material that prevents NSAID release in the low pH environment of the stomach but that ionizes at a slightly higher pH, typically a pH of 4 or 5, and thus dissolves sufficiently in the small intestines to gradually release the active agent therein. Accordingly, among the most effective enteric coating materials are polyacids having a pK_a in the range of about 3 to 5. Suitable enteric coating materials include, but are not limited to, polymerized gelatin, shellac, methacrylic acid copolymer type C NF, cellulose butyrate phthalate, cellulose hydrogen phthalate, cellulose proprionate

phthalate, polyvinyl acetate phthalate (PVAP), cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate, dioxypropyl methylcellulose succinate, carboxymethyl ethylcellulose (CMEC), hydroxypropyl methylcellulose acetate succinate (HPMCAS), and acrylic acid polymers and copolymers, preferably formed from methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate with copolymers of acrylic and methacrylic acid esters (Eudragit NE, Eudragit RL, Eudragit RS) particularly preferred.

The NSAID-containing region or layer can also contain various excipients, as is well known in the pharmaceutical art, provided such excipients do not exhibit a destabilizing effect on any components in the composition. Thus, excipients such as binders, bulking agents, diluents, disintegrants, lubricants, fillers, carriers, and the like can be combined with the NSAID in the core. For solid compositions, diluents are typically necessary to increase the bulk of a tablet so that a practical size is provided for compression. Suitable diluents include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch and powdered sugar. Binders are used to impart cohesive qualities to a tablet formulation, and thus ensure that a tablet remains intact after compression. Suitable binder materials include, but are not limited to, starch (including corn starch and pregelatinized starch), gelatin, sugars (including sucrose, glucose, dextrose and lactose), polyethylene glycol, waxes, and natural and synthetic gums, e.g., acacia sodium alginate, polyvinylpyrrolidone, cellulosic polymers (including hydroxypropyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, hydroxyethyl cellulose, and the like), and Veegum. Lubricants are used to facilitate tablet manufacture; examples of suitable lubricants include, for example, magnesium stearate, calcium stearate, and stearic acid, and are preferably present at no more than approximately 1 wt.% relative to tablet weight. Disintegrants are used to facilitate tablet disintegration or "breakup" after administration, and are generally starches, clays, celluloses, algins, gums or crosslinked polymers. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc. If desired, flavoring, coloring and/or sweetening agents may be added as well. Other optional components for incorporation into an oral formulation herein include, but are not limited to, preservatives, suspending agents, thickening agents,

and the like. Fillers include, for example, insoluble materials such as silicon dioxide, titanium oxide, alumina, talc, kaolin, powdered cellulose, microcrystalline cellulose, and the like, as well as soluble materials such as mannitol, urea, sucrose, lactose, dextrose, sodium chloride, sorbitol, and the like.

The second region or layer of the composition contains a prostaglandin to reduce or eliminate the undesirable side effects of the NSAID following oral administration. Thus, preferred prostaglandins are those which are effective in this regard, i.e. are typically "anti-ulcerogenic." The prostaglandin is selected from the group consisting of naturally occurring prostaglandins, derivatives of naturally occurring prostaglandins such as hydrolyzable lower alkyl esters thereof, synthetic prostaglandins and semisynthetic prostaglandins.

The "naturally occurring" prostaglandins useful in conjunction with the present invention are PGE_0, PGE_1, PGA_1, PGB_1, $PGF_{1\alpha}$, 19-hydroxy-PGA_1, 19-hydroxy-PGB_1, PGE_2, PGA_2, PGB_2, 19-hydroxy-PGA_2, 19-hydroxy-PGB_2, PGE_3, $PGF_{3\alpha}$ and PGI_2. The term "synthetic prostaglandin derivatives" is intended to encompass known or unknown compounds related to the aforementioned naturally occurring prostaglandins that are chemically synthesized using starting materials other than one of the naturally occurring prostaglandins. The term "semisynthetic prostaglandin derivatives" refers to known or unknown compounds related to the aforementioned naturally occurring prostaglandins and that are synthesized therefrom. Synthetic and semisynthetic prostaglandins include, but are not limited to, carboprost tromethamine, dinoprost tromethamine, dinoprostone, lipoprost, gemeprost, metenoprost, sulprostone and tiaprost. The preferred prostaglandin is misoprostol, present in an amount of about 50 to 500 μg per tablet, more preferably about 100 to 200 μg per tablet. Misoprostol is released immediately in the gastrointestinal tract, and produces its gastric anti-secretory effect thereby effectively reducing and/or eliminating the ulcerogenocity of the NSAID.

The region or layer of the present pharmaceutical composition containing the prostaglandin also contains a prostaglandin stabilizing agent such as hydroxypropyl methylcellulose or polyvinylpyrrolidone, as disclosed in U.S. Patent No. 4,301,146 to Sanvordeker. Other stabilizing agents include, but are not limited to: cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose phthalate, microcrystalline cellulose and carboxymethylcellulose sodium;

and vinyl polymers and copolymers such as polyvinyl acetate, polyvinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymers. The stabilizing agent is present in an amount effective to provide the desired stabilizing effect; generally, this means that the ratio of prostaglandin to the prostaglandin stabilizing agent is at least about 1:500 w/w, more preferably about 1:99 w/w.

The prostaglandin-containing region or layer can also contain various excipients, as discussed with respect to the NSAID-containing region or layer, i.e., excipients that do not exhibit a destabilizing effect and include, for example, binders, bulking agents, diluents, disintegrants, lubricants, fillers, carriers, and the like.

The active agents in the present composition, i.e., both the NSAID and the prostaglandin, may be administered in the form of a pharmacologically acceptable salt, ester, amide, prodrug or analog or as a combination thereof. Salts, esters, amides, prodrugs and analogs of the active agents may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry and described, for example, by J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," 4th Ed. (New York: Wiley-Interscience, 1992). For example, basic addition salts are prepared from the neutral drug using conventional means, involving reaction of one or more of the active agent's free hydroxyl groups with a suitable base. Generally, the neutral form of the drug is dissolved in a polar organic solvent such as methanol or ethanol and the base is added thereto. The resulting salt either precipitates or may be brought out of solution by addition of a less polar solvent. Suitable bases for forming basic addition salts include, but are not limited to, inorganic bases such as sodium hydroxide, potassium hydroxide, ammonium hydroxide, calcium hydroxide, trimethylamine, or the like. Preparation of esters involves functionalization of hydroxyl groups which may be present within the molecular structure of the drug. The esters are typically acyl-substituted derivatives of free alcohol groups, i.e., moieties which are derived from carboxylic acids of the formula RCOOH where R is alkyl, and preferably is lower alkyl. Esters can be reconverted to the free acids, if desired, by using conventional hydrogenolysis or hydrolysis procedures. Preparation of amides and prodrugs can be carried out in an analogous manner. Other derivatives and analogs of the active agents may be prepared using standard techniques known to those skilled in the art of synthetic organic chemistry, or may be deduced by reference to the pertinent literature.

Before incorporation into a dosage form, the NSAID is preferably provided in a particulate form suitable for processing. Preferred types of particles are selected from the group consisting of granules, pellets, seeds and microspheres. Granules may be prepared by any art-known process. It is preferred, however, that the granules be prepared by processes such as high shear granulation, low shear granulation or fluid-bed granulation provided with top spray. Pellets or seeds can be prepared by techniques known to those skilled in the art, for example, by using a fluid-bed granulator provided with a rotor-disc. Microspheres can be prepared by any art known process with preparation by spray drying preferred.

Once in particulate form, the NSAID is enterically coated. Although any art-known process may be used, it is preferred that the enteric coating process be accomplished by utilizing either a fluid-bed coater provided with a top spray or a fluid-bed Wurster coater with a bottom spray. The resulting enterically coated particles should have a particle size in the range of about 20 μm to 1500 μm, preferably in the range of about 50 μm to 300 μm.

Before incorporation into the dosage form, the prostaglandin should be separately stabilized with the stabilizing agent. Suitable stabilization procedures are well known to those skilled in the art.

One preferred dosage form of the present invention is a bilayer tablet. Bilayer tablets as shown in Figures 1 and 2 provide several manufacturing advantages. The bilayer tablet is made in a single step compression, thereby eliminating the operations of prior methods involving first compressing one of the actives as a core tablet and subsequently coating the core, and additionally eliminating the concomitant steps of in-process and quality controls for manufacturing two different tablets. Thus, the bilayer tablet is easier and more economical to manufacture than prior compositions that separate a first drug and a second drug into physically discrete regions of a single dosage form.

A preferred method for forming tablets herein is by direct compression of the enterically coated NSAID and prostaglandin, optionally in combination with diluents, binders, lubricants, disintegrants, colorants or the like. As an alternative to direct compression, compressed tablets can be prepared using wet-granulation or dry-granulation processes. Tablets may also be molded rather than compressed, starting with a moist material containing a suitable water-soluble lubricant. Preferred tablets herein are manufactured using compression rather than molding, however.

In an alternative embodiment, the enterically coated NSAID and the stabilized prostaglandin are mixed into a single granulation, and the admixture is compressed into a tablet or filled into a capsule. In the admixture, there is a random possibility of the NSAID and the prostaglandin coming into contact with each other. However, the enteric coating on the NSAID granules provides a physical barrier between the NSAID and the prostaglandin, thereby minimizing direct physical contact between the two active agents. Capsule materials may be either hard or soft, and are preferably sealed, such as with gelatin bands or the like. Tablets and capsules for oral use will generally include one or more commonly used excipients as discussed earlier herein.

For administration of the dosage form, i.e., the tablet or capsule containing the enterically coated NSAID and the stabilized prostaglandin, a total weight in the range of approximately 100 mg to 1000 mg is used. The dosage form is orally administered to a patient suffering from a condition for which an NSAID would typically be indicated, including, but not limited to: alleviation of pain, e.g., arthritic pain, lumbosacral pain, musculo-skeletal pain, pain associated with a sore throat, and the like; treatment of inflammatory conditions and diseases such as osteoarthritis and rheumatoid arthritis; and treatment of psoriasis.

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the foregoing description as well as the examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

EXAMPLE 1

A misoprostol-HPMC complex 1% was made by mixing misoprostol with HPMC in a ratio of 1:99. Misoprostol, an oily, viscous liquid was stabilized as a solid dispersion using hydroxypropyl methycellulose as substrate and spraying misoprostol from an alcoholic solution in a fluid-bed granulator. The granules so obtained were mixed with excipients as described in Example 2.

EXAMPLE 2

The granules of the misoprostol-HPMC complex prepared in Example 1 were mixed with the following excipients.

Ingredient	mg per 200 mg
Misoprostol-HPMC Complex 1%	20.0
Microcrystalline Cellulose PH 102	141.8
Crospovidone XL	8.0
Microcrystalline Cellulose PH 102	29.0
Hydrogenated Castor Oil Powder	0.8
Colloidal Silicon Dioxide	0.4

The blend so obtained was used in the preparation of the bilayer tablets as described in Examples 5 and 6 below.

EXAMPLE 3

A blend of enterically coated granules of diclofenac was prepared as follows.

Ingredient	mg per 200 mg
Granulation I	
Diclofenac Sodium	50.0
Lactose Hydrous Spray Dried	15.0
Microcrystalline Cellulose PH 102	16.0
Starch (Corn) Tablet White	9.0
Povidone PVK-30	4.0
Granulation II	
Methacrylic Acid Copolymer Type C	5.4
Triacetin	0.54
Antifoam 1520-US	0.06
Microcrystalline Cellulose PH 102	98
Hydrogenated Castor Oil Powder	2

In the first step, granulation I was prepared by blending diclofenac sodium with lactose hydrous spray dried, microcrystalline cellulose PH 102, starch (corn) tablet white, and an aqueous solution of Povidone PVK-30 in a fluid-bed granulator. The granules so obtained were enteric coated in a fluid-bed granulator by the application of an enteric dispersion system containing methacrylic acid copolymer type C, NF, triacetin, and antifoam 1520-US. The enterically coated diclofenac granules were then blended with microcrystalline cellulose PH 102 and hydrogenated castor oil powder.

EXAMPLE 4

A second composition of the diclofenac layer for the pharmaceutical delivery system of bilayer tablet was prepared consisting of enterically coated granules of diclofenac. The tablet had the following composition, and the excipients were blended according to Example 3.

Ingredients	**mg per 200 mg**
Granulation I	
Diclofenac Sodium	50.0
Lactose Hydrous Spray Dried	15.0
Microcrystalline Cellulose PH 102	18.0
Starch (Corn) Tablet White	9.0
Povidone PVK-30	4.0
Granulation II	
Methacrylic Acid Copolymer Type C	2.70
Triacetin	0.27
Antifoam 1520-US	0.03
Hydrogenated Castor Oil Powder	1.0

EXAMPLE 5

A bilayer tablet was prepared containing a misoprostol solid dispersion and enterically coated granules of diclofenac. The enterically coated NSAID prepared in Example 3 was first placed in the tablet press, followed by the misoprostol blend prepared in Example 2. The tableting mechanism was then actuated to give a bilayer tablet.

EXAMPLE 6

The misoprostol blend, prepared in Example 2, is mixed with the diclofenac blend prepared in either Example 3 or Example 4. The admixture so obtained is compressed into a tablet, or is filled into a capsule shell.

CLAIMS:

1. A solid pharmaceutical composition for oral administration, comprising:
a therapeutically effective amount of a nonsteroidal anti-inflammatory drug (NSAID) coated with an enteric coating material;
an effective anti-ulcerogenic amount of a prostaglandin; and
an effective stabilizing amount of a prostaglandin stabilizing agent.

2. The composition of claim 1, comprising a dosage form having two discrete regions, wherein the enterically coated NSAID is present in the first of said two regions and the prostaglandin and prostaglandin stabilizing agent are present in the second of said two regions.

3. The composition of claim 2, comprising a bilayer tablet.

4. The composition of claim 2, comprising a capsule.

5. The composition of claim 1, comprising an admixture of the enterically coated NSAID, prostaglandin and prostaglandin stabilizing agent.

6. The composition of claim 5, in the form of a tablet.

7. The composition of any one of claims 1 to 6, wherein the NSAID is selected from the group consisting of acetylsalicylic acid, apazone, diclofenac, difenpiramide, diflunisal, etodolac, fenbufen, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, suprofen, tiaprofenic acid, tolmetin, pharmaceutically acceptable salts thereof, and combinations of any of the foregoing.

8. The composition of claim 7, wherein the NSAID is diclofenac or a pharmaceutically acceptable salt thereof.

9. The composition of claim 8, wherein the NSAID is diclofenac.

10. The composition of claim 8, wherein the NSAID is diclofenac sodium.

11. The composition of claim 7, wherein the NSAID is piroxicam.

12. The composition of any one of claims 1 to 11, wherein the prostaglandin is selected from the group consisting of misoprostol, PGE_0, PGE_1, PGA_1, PGB_1, PGF_1, 19-hydroxy-PGA_1, 19-hydroxy-PGB_1, PGE_2, PGA_2, PGB_2, 19-hydroxy-PGA_2, 19-hydroxy-PGB_2, PGE_3, PGF_3, PGI_2, carboprost tromethamine, dinoprost tromethamine, gemeprost, metenoprost, sulprostone, tiaprost and combinations thereof.

13. The composition of claim 12, wherein the prostaglandin is misoprostol.

14. The composition of any one of claims 1 to 13, wherein the prostaglandin stabilizing agent is selected from the group consisting of hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, microcrystalline cellulose, carboxymethylcellulose sodium, polyvinylpyrrolidone, polyvinyl acetate, polyvinylacetate phthalate, and vinylacetate crotonic acid copolymer, and combinations thereof.

15. The composition of claim 14, wherein the stabilizing agent is hydroxypropyl methylcellulose.

16. The composition of claim 14, wherein the stabilizing agent is polyvinylpyrrolidone.

17. The composition of any one of claims 1 to 16, wherein the NSAID is in particulate form.

18. The composition of claim 17, wherein the particulate form is selected from the group consisting of granules, pellets, seeds and microspheres.

19. The composition of claim 17, wherein the NSAID has a particle size in the range of about 20 μm to 1500 μm.

20. The composition of claim 19, wherein the particle size is in the range of about 50 μm to about 300 μm.

21. The composition of any one of claims 1 to 20, wherein the total weight of the composition is in the range of approximately about 100 mg to about 1000 mg.

22. The composition of claim 21, wherein the amount of prostaglandin is in the range of approximately about 5 μg to about 500 μg.

23. A bilayer tablet for oral administration of a nonsteroidal anti-inflammatory drug (NSAID), comprising:
(a) a first layer containing a therapeutically effective amount of an enterically coated NSAID selected from the group consisting of acetylsalicylic acid, apazone, diclofenac, difenpiramide, diflunisal, etodolac, fenbufen, flufenamic acid,

flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, suprofen, tiaprofenic acid, tolmetin, pharmaceutically acceptable salts thereof, and combinations of any of the foregoing; and

(b) a second layer containing an effective anti-ulcerogenic amount of a prostaglandin selected from the group consisting of misoprostol, PGE_0, PGE_1, PGA_1, PGB_1, PGF_1, 19-hydroxy-PGA_1, 19-hydroxy-PGB_1, PGE_2, PGA_2, PGB_2, 19-hydroxy-PGA_2, 19-hydroxy-PGB_2, PGE_3, PGF_3, PGI_2, carboprost tromethamine, dinoprost tromethamine, gemeprost, metenoprost, sulprostone, tiaprost and combinations thereof, and an effective stabilizing amount of a prostaglandin stabilizing agent selected from the group consisting of hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, microcrystalline cellulose, carboxymethylcellulose sodium, polyvinylpyrrolidone, polyvinyl acetate, polyvinylacetate phthalate, and vinylacetate crotonic acid copolymer, and combinations thereof.

24. A bilayer tablet for oral administration of a nonsteroidal anti-inflammatory drug (NSAID), comprising:

(a) a first layer containing a therapeutically effective amount of an enterically coated NSAID selected from the group consisting of diclofenac, piroxicam, naproxen and pharmaceutically acceptable salts thereof; and

(b) a second layer containing an effective anti-ulcerogenic amount of misoprostol and an effective stabilizing amount of a prostaglandin stabilizing agent selected from the group consisting of hydroxypropyl methylcellulose and polyvinylpyrrolidone.

25. The tablet of claim 24, having a total weight in the range of approximately 100 mg to 1000 mg.

26. The tablet of claim 25, containing approximately 25 mg to 75 mg diclofenac.

27. The tablet of claim 25, containing approximately 5 mg to 50 mg piroxicam.

28. The tablet of claim 25, containing approximately 250 mg to 750 mg naproxen.

29. The tablet of claim 25, containing approximately 100 μg to 200 μg misoprostol.

30. A tablet comprising an admixture of (a) a therapeutically effective amount of an enterically coated NSAID selected from the group consisting of diclofenac, piroxicam and pharmaceutically acceptable salts thereof; (b) an effective anti-ulcerogenic amount of misoprostol; and (c) an effective stabilizing amount of a prostaglandin stabilizing agent selected from the group consisting of hydroxypropyl methyl cellulose and polyvinylpyrrolidone.

31. A method for treating a patient suffering from a condition, disease or disorder that is responsive to an NSAID, comprising orally administering to the patient the pharmaceutical composition of any one of claims 1 to 22 or the tablet of any one of claims 23 to 30.

32. The method of claim 31, wherein the composition or tablet is administered twice daily.

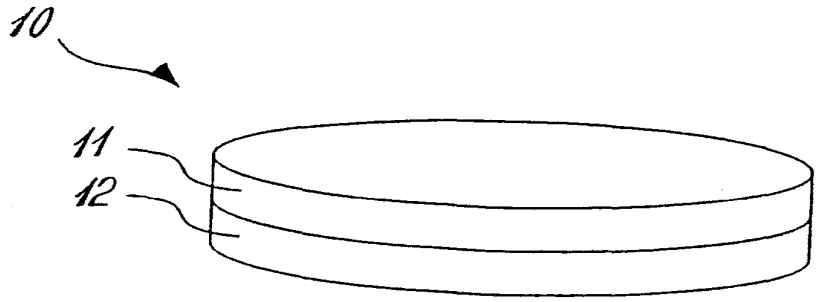

Figure 1

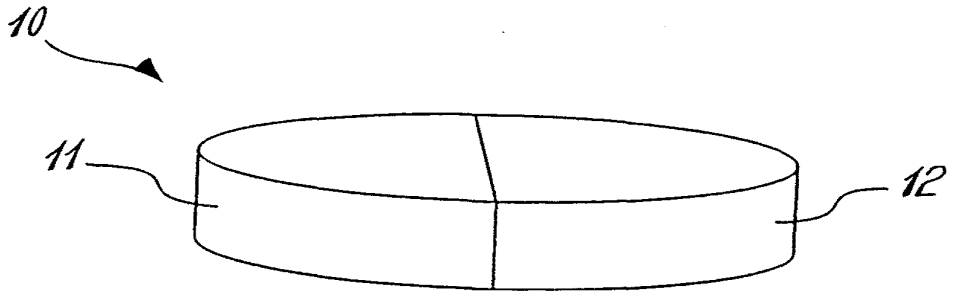

Figure 2

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/CA 00/00301

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/557 A61K9/20 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)
IPC 7 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)
WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 16895 A (G. D. SEARLE) 14 November 1991 (1991-11-14) claims 1-3,7-11 examples 2-9 ---	1,2, 4-16,21, 22,30-32
P,X	WO 00 01368 A (NORTON HEALTHCARE) 13 January 2000 (2000-01-13) claims 1,3,5,16,19,24,26 page 2, paragraph 3 page 3, paragraph 3 page 4, paragraph 1 page 5; example 3 --- -/--	1-3,5-32

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

[X] Patent family members are listed in 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
29 June 2000	06/07/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

2

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/CA 00/00301

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 65496 A (SHERMAN, BERNARD CHARLES) 23 December 1999 (1999-12-23) claims 1-3 page 5; examples 1-4	1,2, 5-15,21, 22,31,32
E	WO 00 15200 A (NORTON HEALTHCARE) 23 March 2000 (2000-03-23) claims 1-3,7,8,16 page 5; examples 1,2	1,2, 4-15, 17-22
A	WO 99 12524 A (NYCOMED DANMARK) 18 March 1999 (1999-03-18) the whole document	1-32

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/CA 00/00301

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9116895 A	14-11-1991	AT 121625 T	15-05-1995
		AU 7876491 A	27-11-1991
		CA 2082944 A,C	04-11-1991
		DE 69109286 D	01-06-1995
		DE 69109286 T	28-09-1995
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		GR 3015939 T	31-07-1995
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WO 0015200 A	23-03-2000	AU 5750799 A	03-04-2000
WO 9912524 A	18-03-1999	AU 9062998 A	29-03-1999
		NO 20001290 A	28-04-2000

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(19) World Intellectual Property Organization
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(25) Filing Language: English

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(74) Agent: **WITTEKIND, Raymond, R.**; Frommer Lawrence & Haug LLP, 745 Fifth Avenue, New York, NY 10151 (US).

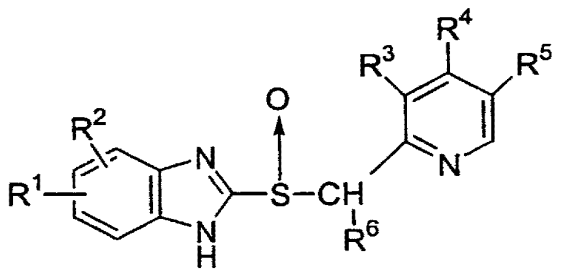
(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *With amended claims.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: STABILIZED COMPOSITION BASED ON PYRIDINYL-SULFINYL-BENZIMIDAZOLES AND PROCESS



(I)

(57) Abstract: A novel composition comprising a compound of formula(I) wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl, and ethyl; and R^3 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula (II) R^7CO_2M where in R^7 is an organic radical and M is a cation, a pharmaceutical formulation containing the composition, methods of preventing or reducing ulceration of the gastrointestinal tract by anti-inflammatory agents using the composition, and methods of stabilizing the composition are described.

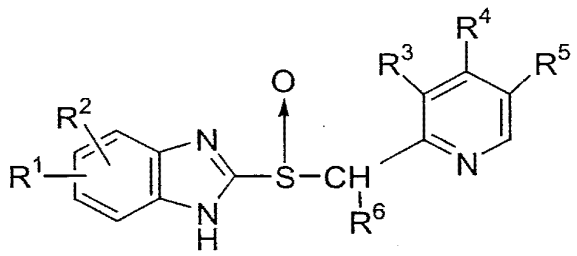
WO 00/71122 A1

STABILIZED COMPOSITION BASED ON PYRIDINYL-SULFINYL-BENZIMIDAZOLES AND PROCESS

Anti-inflammatory agents, notably agents characterized by the presence of a carboxylic acid group, suffer from a serious side effect, namely, ulceration of the gastrointestinal tract, when administered orally. For example, naproxen, 2-(6-methoxy-2-naphthyl)propionic acid, which is marketed as Naprosyn® in the United States, causes severe ulceration of the stomach and duodenum. Substituted 2-(2-benzimidazolyl)pyridines are known to inhibit gastric acid secretion in mammals, including man. One such compound, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, omeprazole, which is marketed under the brand name Losec®, is a potent inhibitor of gastric acid secretion and thereby useful for the treatment of peptic ulcer disease. Like the aforementioned anti-inflammatory agents, the 2-(2-benzimidazolyl)pyridines, particularly omeprazole, suffer from a serious defect, namely, instability under physiological conditions. It would thus be desirable to take advantage of the anti-inflammatory properties of the organic carboxylic acids, and at the same time, the gastric acid inhibiting properties of the 2-(2-benzimidazolyl)pyridines, while enhancing the stability of the gastric acid inhibitor. By so doing, a stabilized composition for the treatment of inflammatory disease conditions such as osteoarthritis and rheumatoid arthritis, without the attendant ulceration of the gastrointestinal tract would be available for treatment of inflammation. It has now been found that this goal is achieved when a composition of a 2-(2-benzimidazolyl)pyridines and a salt of an anti-inflammatory organic acid is administered to a patient suffering from inflammatory disease, the salt of the organic

acid ameliorating the inflammation and stabilizing the antiulcerogenic 2(-2-benzimidazolyl)pyridine.

The present invention relates to a composition comprising a compound of



I

formula I

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; and R^3 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula II

$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical and M is a cation, useful for the treatment of inflammation with concomitant prevention or reduction of the ulceration of the gastrointestinal tract, and stabilization of the antiulceration compound of formula I. The present invention also relates to a pharmaceutical formulation containing the composition and a method of preparing the formulation.

Subgeneric to the composition are compositions wherein:

(a) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is hydrogen; and R^3, R^4 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy and ethoxy; or a pharmaceutically acceptable addition salt thereof;

(b) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; R^3 is methyl; R^4 is methoxy; and R^5 is methyl; or a pharmaceutically acceptable acid addition salt thereof;

(c) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; R^3 is hydrogen; R^4 is methoxy; and R^5 is methyl, or R^3 is methyl, R^4 is methoxy and R^5 is hydrogen; or a pharmaceutically acceptable acid addition salt thereof;

(d) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; $R^3$and R^5 are selected from the group consisting of hydrogen and methoxy; or a pharmaceutically acceptable acid addition salt thereof;

(e) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and

alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and $R^3$and R^5 are methyl; and R^4 is hydrogen; or a pharmaceutically acceptable acid addition salt thereof;

(f) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; $R^3$and R^5 are hydrogen; and R^4 is ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof.

(g) R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; R^3, R^4 and R^5 are methyl; or a pharmaceutically acceptable acid addition salt thereof; and

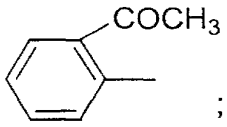
(h) A composition according to claim 1 wherein R^1 is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethoxy ; R^2 is hydrogen or methyl; R^6 is hydrogen, methyl or ethyl; $R^3$and R^5 are methyl; and R^4 is methoxy, or in which R^1 is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethyl; R^2 is hydrogen, methyl or ethyl; R^4 is methoxy ; and R^3 is methyl R^5 is hydrogen, or R^3 is hydrogen and R^5 is methyl, or a pharmaceutically acceptable acid addition salt thereof.

Preferred compositions are those wherein a compound of the formula I is selected from the group consisting of 2-[2-(4-methoxy)pyridinylmethysulfinyl]-5-acetyl-6-methyl)-benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-4,6-dimethyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-

acetyl-6-methyl)benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-ethoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3-methyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinylbenzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridylmethysulfinyl]-(5-chloro)benzimidazole, or a pharmaceutically acceptable addition salt thereof.

More preferred is one wherein R^1 is hydrogen; R^2 is methoxy; R^3 and R^5 are methyl; R^4 is methoxy; and R^6 is hydrogen which is 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

Also subgeneric thereto are compositions where the organic radical is selected from the group consisting of:

(a) 

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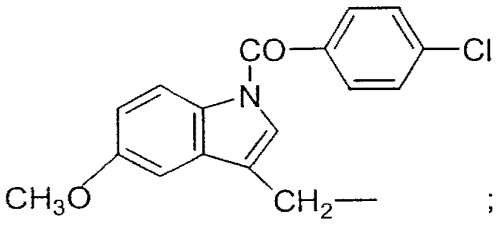
(b) 

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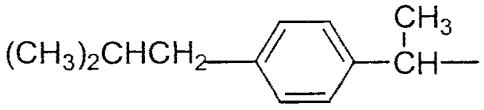
(c) 

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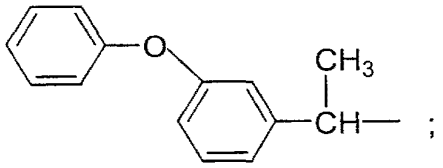
(d) 

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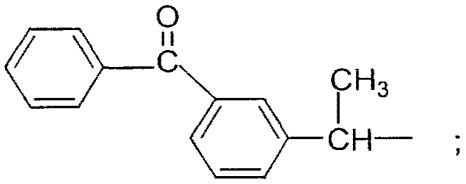
(e) 

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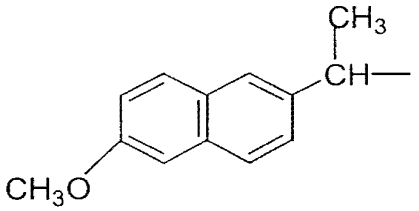
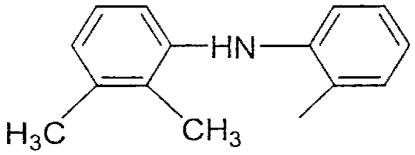
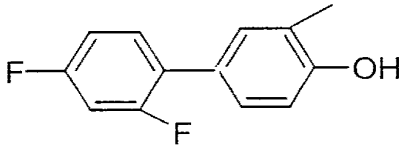
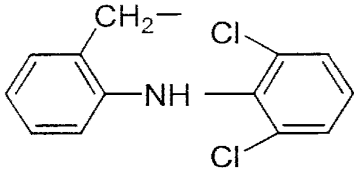
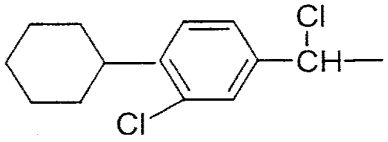
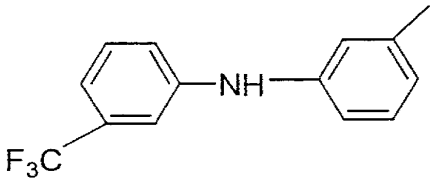
(f)  ;

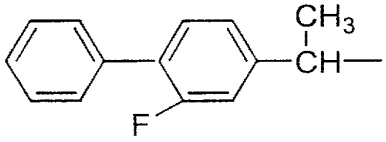
(g)  ;

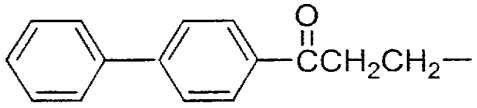
(h)  ;

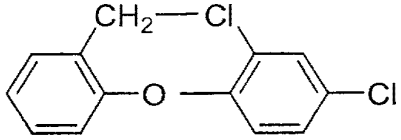
(i)  ;

(j)  ;

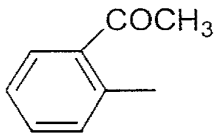
(k)  ;

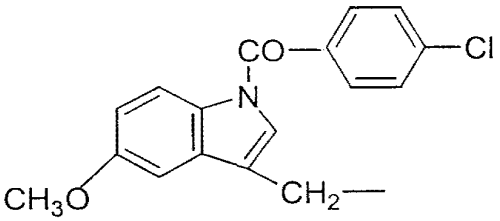
(l)  ;

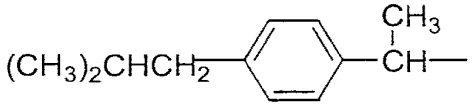
(m)  ;

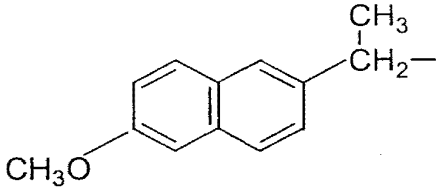
(n)  ;

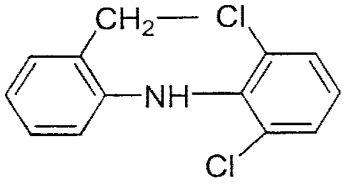
Compositions wherein the organic radical is selected from the group consisting of:

(o)  ;

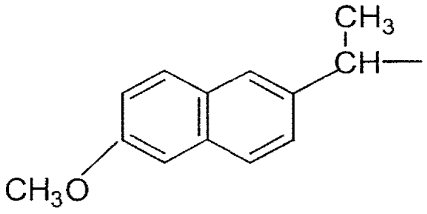
(p)  ;

(q)  ;

(r)  ; and

(s)  are more preferred.

A most preferred composition is one wherein the organic radical is

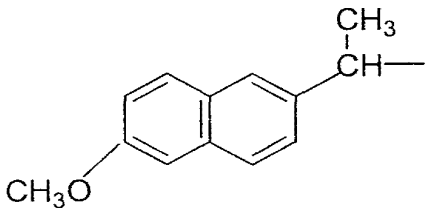


Also subgeneric thereto are:

(a) a composition wherein M is sodium, potassium, magnesium, calcium, or aluminum; and

(b) a composition wherein M is sodium.

A most preferred composition is one wherein R^1 is hydrogen; R^2 is methoxy; R^3 and R^5 are methyl; R^4 is methoxy; R^6 is hydrogen; R^7 is



and M is sodium.

As used through the specification and appended claims, the term "alkyl" refers to a straight or branched chain hydrocarbon radical containing no unsaturation and having 1 to 10 carbon atoms. Examples of alkyl groups are methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 1-pentyl, 3-hexyl, 4-heptyl, 2-octyl, 3-nonyl, 4-decyl and the like. The term "alkanol" refers to a compound formed by a combination of an alkyl group and hydroxy radical. Examples of alkanols are methanol, ethanol, 1- and 2-propanol, 2,2-dimethylethanol, hexanol, octanol, decanol and the like. The term "alkanoic acid" refers to a compound formed by combination of a carboxyl group with a hydrogen atom or alkyl group. Examples of alkanoic acids are formic acid, acetic acid, propanoic acid, 2,2-dimethylacetic acid, hexanoic acid, octanoic acid, decanoic acid and the like. The term "halogen" refers to a member of the family fluorine, chlorine, bromine, or iodine. The term "alkanoyl" refers to the radical formed by removal of the hydroxyl function from an alkanoic acid. Examples of alkanoyl groups are formyl, acetyl, propionyl, 2,2-dimethylacetyl, hexanoyl, octanoyl, decanoyl and the

like. The term "lower" as applied to any of the aforementioned groups refers to a group having a carbon skeleton containing up to an including 8 carbon atoms.

The compounds of the present invention which lack an element of symmetry exist as optical antipodes may be prepared from the corresponding racemic forms by standard optical resolution techniques, involving, for example, the separation of diastereomeric salts of those instant compounds characterized by the presence of a carboxylic acid group and an optically active base, or by synthesis from optically active precursors.

The present invention comprehends all optical isomers and racemic forms thereof and all geometric isomers of the compounds disclosed and claimed herein. The formulas of the compounds shown herein are intended to encompass all possible geometric and optical isomers of the compounds so depicted.

The 2-(2-benzimidazolyl)pyridines and the methods of preparation thereof are described in U.S. Patent 4,255,431 granted March 10, 1981 to U.K. Junggren and S.E. Sjöstrand, as is their antisecretory inhibitory properties.

The organic carboxylic acids and their anti-inflammatory properties, as well as their ulcerogenic effects are described in U.K. Patent Application GB 2 105 193 A.

The salts of the organic carboxylic acids are known or are prepared by conventional methods, for example, treatment of a carboxylic acid with an alkali metal or alkaline earth metal in a suitable solvent such as alkanol, e.g., methanol, ethanol, 2-propanol, and the like, and aqueous combinations thereof.

The stabilization of a 2-(2-benzimidizolyl)pyridine by a salt of an organic carboxylic acid in an aqueous medium is demonstrated in a conventional assay. In the

assay, the 2-(2-benzimidazolyl)pyridine is dissolved in water and the stability thereof is determined and compared to that of a solution of a 2-(2-benzimidazolyl)pyridine and a salt of an organic acid in water.

In a specific assay, omeprazole (10 mg) is dissolved in water (100 ml) at room temperature, and samples are removed periodically and assayed for omeprazole by high performance liquid chromatography on a column of Hypersil (250 x 4.6 mm) using 0.02 Mammonium acetate buffer: acetonitrile (65:35). The pressence of omeprazole is detected by ultraviolet spectroscopy at a wavelength of 235 nm.

The results are shown in the table:

Time, hr	Omeprazole in water, %	Omeprazole+Naproxen Na in water, %
0	100	100
2	95.8	97.7
19	69.8	94.9

Effective quantities of the compositions of the invention may be administered to a patient by any of the various methods, for example, orally as in capsule or tablets, parenterally in the form of sterile solutions or suspensions, and in some cases intravenously in the form of sterile solutions. The free base final products, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable acid addition salts for purposes of stability, convenience of crystallization, increased solubility and the like.

The active compositions of the present invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets. For the purpose of oral

therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, suppositories, chewing gum and the like. These preparations should contain at least 0.5% of active compositions, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0-300 milligrams of active compound.

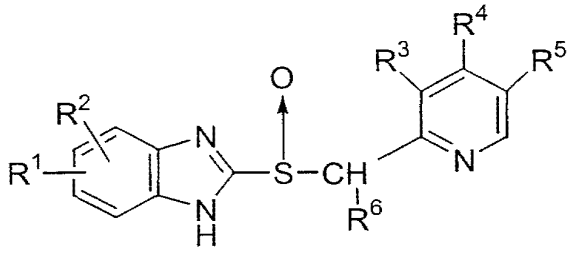
The tablets, pills, capsules, troches, suppositories and the like may also contain the following ingredients: a binder such as microcystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, cornstarch and the like; a lubricant such as magnesium stearate or Sterotex; a glidant such as colloidal silicon dioxide; and a sweetening agent and certain preservatives, dyes, coloring and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the active composition of the invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of active compound, but may be varied between 0.5 and about 30% of the weight thereof. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present inventions are

prepared so that a parenteral dosage unit contains between 0.5 to 100 milligrams of active compound.

The solutions or suspensions may also include the following components: a steril diluent such as water for injection, saline solution, fixed oils, polyethylene gylcols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in disposable syringes or multiple dose vials made of glass or plastic.

Included among pharmaceutical formulations are stabilized pharmaceutical unit dosage forms comprising a core (a) comprising a compound of formula I



I

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 and R^5 are the same or different and are each selected from the group consisting of

hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and

a compound of formula II

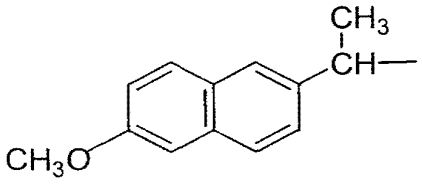
$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical and M is a cation;

(b) a first coating of the core comprising at least one layer of a polymeric coating; and

(c) a second coating comprising an enteric coating.

Preferred stabilized pharmaceutical unit dosage forms are those wherein the compound of formula I comprises compounds wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carbethoxy, alkoxy and alkanoyl; R^6 is hydrogen; and R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy; and ethoxy; or a pharmaceutically acceptable acid addition salt thereof and the compound of formula II wherein the organic radical is selected from the group consisting of



wherein M is sodium, potassium, calcium, barium or aluminum.

More preferred stabilized pharmaceutical unit dosage forms are those wherein the compound of formula I is 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-

(5-methoxy)benzimidazole and the compound of formula II is sodium 2-(6-methoxy-2-napthyl)propionic acid.

The stabilized pharmaceutical dosage forms of the present invention are formulated by granulating a mixture of the compounds of formulas I and II. Pharmaceutically acceptable excipients, for example, fillers, binders and lubricants may be included in the granulation for the purpose of facilitating the granulation and improving the acceptance of the ultimate tablet. Among fillers there may be mentioned hydroxyalkylcellulose, particularly hydroxypropylcellulose. Among binders there may be mentioned polyvinylpyrolidine. Among lubricants there may be mentioned talc and magnesium.

The granulate is first coated with at least one layer of a polymeric coating, for example a hydroxyalkylalkylcellulose, polyethylene glycol and a pigment coating, particularly a coating containing hydroxypropylmethylcellulose. The coated granulate is then coated with an enteric coating comprising a methacrylic acid copolymer. Among methacrylic acid copolymers there may be mentioned methacrylic acid ethyl acrylate copolymer.

The granulation is carried out in conventional equipment using a solvent such as 2-propanol, and the granulate is dried prior to the next operation, i.e., coating the granulate. The first coating is applied by granulating the dried granulate with, for example, hydroxypropylmethylcellulose, polyethylene, pigment, preferably in aqueous suspension, also in conventional equipment, followed by drying, i.e., removing the solvent by evaporation under conventional conditions. The dried coated granulate is then coated with a methacrylic acid copolymer, particularly methacrylic

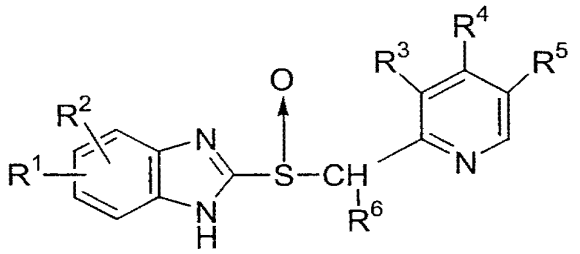
acid ethyl acrylate copolymer to yield the stabilized pharmaceutical dosage form in pellet form.

The granulation and coating steps are generally performed under conventional conditions. In one such granulation and coating procedure, 2-[2-(3,5-dimetyl-4-methoxy)-pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole (omeprazole) (20 mg/tablet), sodium 2-(6-methoxy-2-naphthyl) propionic acid (naproxen sodium) (550 mg/tablet), hydroxypropylcellulose (30 mg), polyvinylpyrrolidone (30 mg/tablet), talc (5.0 mg/tablet), and magnesium stearate (5.0 mg/tablet)is granulated in 2-propanol, dried, and the dried granulate is first coated with hydroxypropylmethylcellulose, polyethylene glycol, pigment (9mg/tablet), the coated granulate dried and granulated with a methacrylic acid ethyl acrylate copolymer in aqueous suspension and dried to form the tablet.

The tablets are stable in the solid form over a reasonably long period of time, showing no significant change in the omeprazole titer. At a temperature of 40°C and relative humidity of 75%, enteric coated tablets of omeprazole and naproxen sodium, prepared as described above, are stable over a period of three months. After three months, the omeprazole titer was determined to be 96.9%, relative to the initial amount, by high performance liquid chromatography.

What is claimed is:

1. A composition comprising a compound of formula I



I

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula II

$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical and M is a cation.

2. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carboethoxy, alkoxy, and alkanoyl, R^6 is hydrogen; and R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy and ethoxy; or a pharmaceutically acceptable addition salt thereof.

3. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; R^3 is methyl; R^4 is methoxy; and R^5 is methyl; or a pharmaceutically acceptable acid addition salt thereof.

4. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; and R^3 is hydrogen; R^4 is methoxy; and R^5 is methyl or R^3 is methyl, R^4 is methoxy and R^5 is hydrogen; or a pharmaceutically acceptable acid addition salt thereof.

5. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl, and ethyl, $R^3$and R^5 are hydrogen and methoxy; or a pharmaceutically acceptable acid addition salt thereof.

6. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy, and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl; and $R^3$and R^5 are methyl; and R^4 is hydrogen; or a pharmaceutically acceptable acid addition salt thereof.

7. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl,

halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; $R^3$and R^5 are hydrogen; and R^4 is ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof.

8. A composition according to claim 1 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, alkoxy and alkanoyl, R^6 is selected from the group consisting of hydrogen, methyl and ethyl; R^3, R^4 and R^5 are methyl; or a pharmaceutically acceptable acid addition salt thereof.

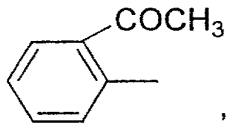
9. A composition according to claim 1 wherein R^1 is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carbethoxy or carbomethoxy ; R^2 is hydrogen or methyl; R^6 is hydrogen, methyl or ethyl; $R^3$and R^5 are methyl; and R^4 is methoxy, or in which R^1 is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethyl; R^2 is hydrogen, methyl or ethyl; R^4 is methoxy ; and R^3 is methyl and R^5 is hydrogen or R^3 is hydrogen and R^5 is methyl, or a pharmaceutically acceptable acid addition salt thereof.

10. A composition according to claim 1 wherein a compound of the formula I is selected from the group consisting of 2-[2-(4-methoxy)pyridinylmethysulfinyl]-5-acetyl-6-methyl)benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-4,6-dimethyl)-benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl-6-methyl)-benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole, 2-[2-(4-ethoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)-benzimidazole, 2-[2-

(3-methyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)-pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)-pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethysulfinyl]-(5-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethysulfinylbenzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethysulfinyl]-(5-chloro)benzimidazole, or a pharmaceutically acceptable addition salt thereof.

11. A composition according to claim 10 wherein R^1 is hydrogen; R^2 is methoxy; R^3 and R^5 are methyl; R^4 is methoxy; and R^6 is hydrogen which is 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

12. A composition according to claim 1 wherein the organic radical is selected from the group consisting of:



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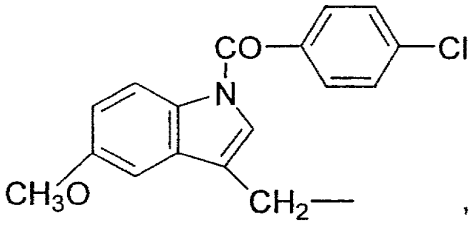

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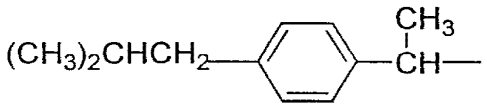

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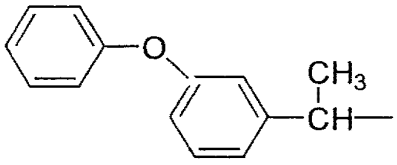

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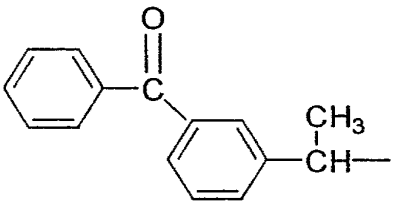

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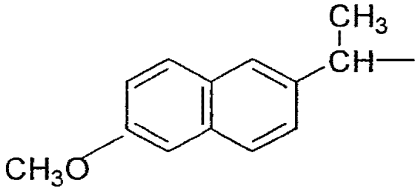

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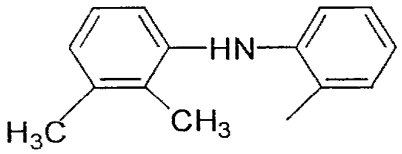

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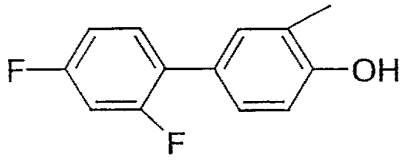

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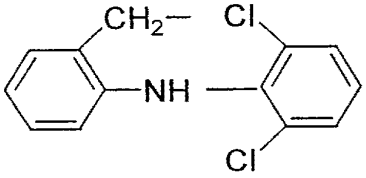

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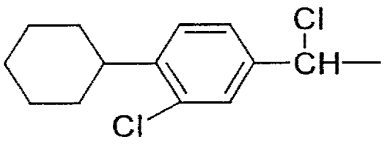

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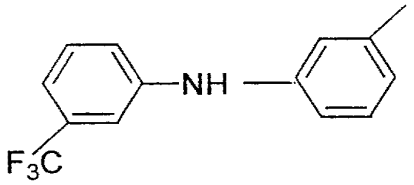

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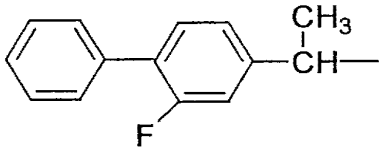

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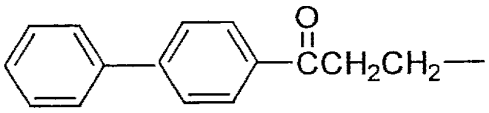

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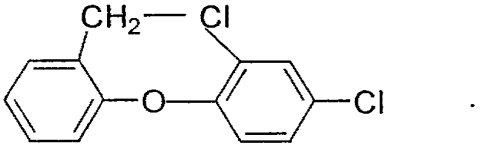

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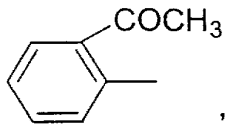
13. A composition according to claim 12 wherein the organic radical is selected from the group consisting of:



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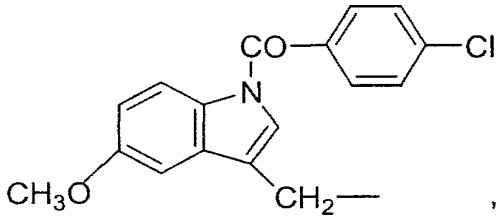

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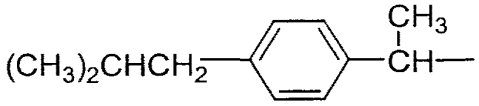
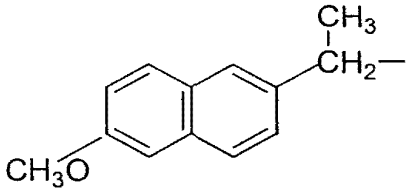
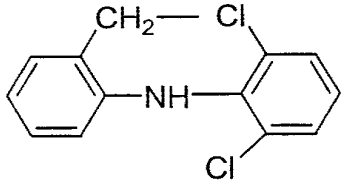




and



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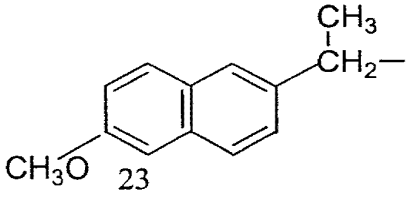
14. The composition according to claim 13 wherein the organic radical is

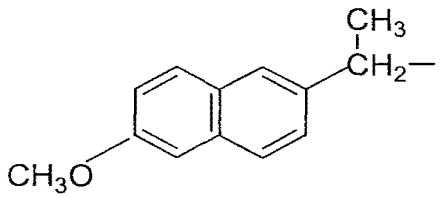


15. A compound according to claim 1 wherein M is sodium, potassium, magnesium, calcium, barium or aluminum.

16. A composition according to claim 15 wherein M is sodium, potassium, calcium, barium or aluminum.

17. A composition according to claim 16 wherein M is sodium.

18. A composition according to claim 17 wherein R^1 is hydrogen, R^2 is methoxy; R^3 and R^5 are methyl; R^4 is methoxy; R^6 is hydrogen; R^7 is



and M is sodium.

19. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 1.

20. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 2.

21. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the

gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 3.

22. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 4.

23. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 5.

24. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 6.

25. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 7.

26. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 8.

27. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 9.

28. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 10.

29. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 11.

30. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an

ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 12.

31. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 13.

32. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 14.

33. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 15.

34. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 16.

35. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 17.

36. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 18.

37. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 1.

38. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 2.

39. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an

ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 3.

40. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 4.

41. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 5.

42. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 6.

43. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 7.

44. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 8.

45. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 9.

46. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 10.

47. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 11.

48. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an

ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 12.

49. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 13.

50. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 14.

51. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 15.

52. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 16.

53. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 17.

54. A method of reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring reduction of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent reducing effective amount of a composition of claim 18.

55. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 1 and a pharmaceutically acceptable carrier therefor.

56. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 2 and a pharmaceutically acceptable carrier therefor.

57. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 3 and a pharmaceutically acceptable carrier therefor.

58. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 4 and a pharmaceutically acceptable carrier therefor.

59. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 5 and a pharmaceutically acceptable carrier therefor.

60. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 6 and a pharmaceutically acceptable carrier therefor.

61. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 7 and a pharmaceutically acceptable carrier therefor.

62. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 8 and a pharmaceutically acceptable carrier therefor.

63. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the

active ingredient a composition of claim 9 and a pharmaceutically acceptable carrier therefor.

64. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 10 and a pharmaceutically acceptable carrier therefor.

65. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract in a mammal by an anti-inflammatory agent, comprising as the active ingredient a composition of claim 11 and a pharmaceutically acceptable carrier therefor.

66. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 12 and a pharmaceutically acceptable carrier therefor.

67. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 13 and a pharmaceutically acceptable carrier therefor.

68. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 14 and a pharmaceutically acceptable carrier therefor.

69. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 15 and a pharmaceutically acceptable carrier therefor.

70. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 16 and a pharmaceutically acceptable carrier therefor.

71. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 17 and a pharmaceutically acceptable carrier therefor.

72. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 18 and a pharmaceutically acceptable carrier therefor.

73. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 1 and a pharmaceutically acceptable carrier therefor.

74. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the

active ingredient a composition of claim 2 and a pharmaceutically acceptable carrier therefor.

75. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 3 and a pharmaceutically acceptable carrier therefor.

76. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 4 and a pharmaceutically acceptable carrier therefor.

77. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 5 and a pharmaceutically acceptable carrier therefor.

78. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 6 and a pharmaceutically acceptable carrier therefor.

79. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 7 and a pharmaceutically acceptable carrier therefor.

80. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 8 and a pharmaceutically acceptable carrier therefor.

81. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 9 and a pharmaceutically acceptable carrier therefor.

82. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 10 and a pharmaceutically acceptable carrier therefor.

83. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 11 and a pharmaceutically acceptable carrier therefor.

84. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 12 and a pharmaceutically acceptable carrier therefor.

85. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the

active ingredient a composition of claim 13 and a pharmaceutically acceptable carrier therefor.

86. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 14 and a pharmaceutically acceptable carrier therefor.

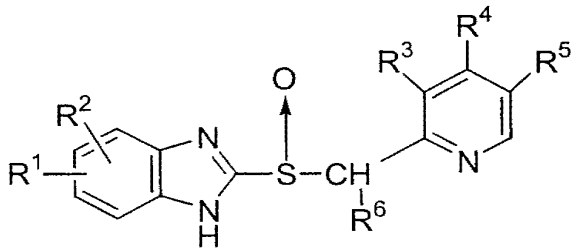
87. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 15 and a pharmaceutically acceptable carrier therefor.

88. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 16 and a pharmaceutically acceptable carrier therefor.

89. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 17 and a pharmaceutically acceptable carrier therefor.

90. A pharmaceutical formulation for reducing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 18 and a pharmaceutically acceptable carrier therefor.

91. A method of stabilizing a compound of formula I



I

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; and R^3 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof by combining the compound of formula I with a compound of formula II

$$R^7CO_2M \qquad II$$

wherein R7 is an organic radical and M is a cation to form a stabilized composition.

92. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carboethoxy, alkoxy, and alkanoyl, R^6 is hydrogen; and R^3, R^4, and R^5 are the same or different and each selected from the group consisting of hydrogen, methyl, methoxy and ethoxy; or a pharmaceutically acceptable addition salt thereof.

93. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carbethoxy, alkoxy and alkanoyl; R^6 is selected from the

group consisting of hydrogen, methyl and ethyl; R^3 is methyl; R^4 is methoxy; and R^5 is methyl; or a pharmaceutically acceptable acid addition salt thereof.

94. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; and R^3 is hydrogen, R^4 is methoxy; and R^5 is methyl, or R^3 is methyl; R^4 is methoxy and R^5 is hydrogen; or a pharmaceutically acceptable acid addition salt thereof.

95. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; $R^3$and R^5 are hydrogen and methoxy; or a pharmaceutically acceptable acid addition salt thereof.

96. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; and $R^3$and R^5 are methyl and R^4 is hydrogen; or a pharmaceutically acceptable acid addition salt thereof.

97. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; $R^3$and R^5 are hydrogen; and R^4 is

ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof.

98. A method according to claim 91 wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl; R^3, R^4 and R^5 are all methyl; or a pharmaceutically acceptable acid addition salt thereof.

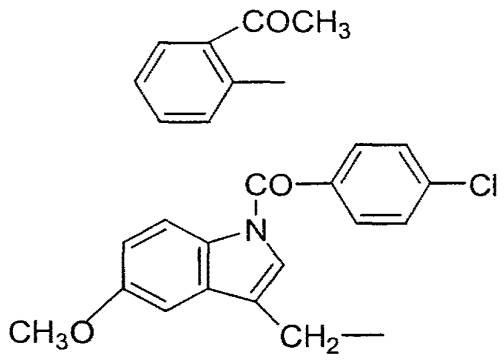
99. A method according to claim 91 wherein R^1 is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethoxy ; R^2 is hydrogen or methyl; R^6 is hydrogen, methyl or ethyl; $R^3$and R^5 are methyl; and R^4 is methoxy, or in which R^1 is hydrogen, chloro, methyl, ethyl, methoxy, acetyl, carboethoxy or carbomethyl; R^2 is hydrogen, methyl or ethyl; R^4 is methoxy ; and R^3 is methyl and R^5 is hydrogen or R^3 is hydrogen and R^5 is methoyl, or a pharmaceutically acceptable acid addition salt thereof.

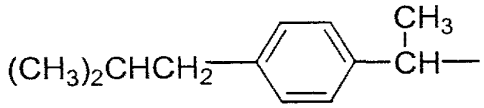
100. A method according to claim 1 wherein a compound of the formula I is selected from the group consisting of 2-[2-(4-methoxy)pyridinylmethysulfinyl]-5-acetyl-6-methyl)benzimidazole, 2-[2-(4-methoxy)pyridylmethysulfinyl]-4,6-dimethyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl-6-methyl)benzimidazole, 2-[2-(4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-ethoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3-methyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-

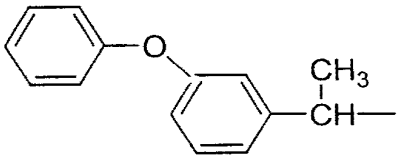
carbomethoxy-6-methyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethysulfinyl]-(5-carbomethoxy-6-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-carbomethoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-acetyl)benzimidazole, 2-[2-(4-methoxy-5-methyl)pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-methoxy)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinyl]-(5-methyl)benzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethysulfinylbenzimidazole, 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethysulfinyl]-(5-chloro)benzimidazole, or a pharmaceutically acceptable addition salt thereof.

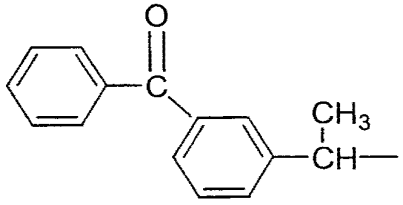
101. A method according to claim 100 wherein R^1 is hydrogen, R^2 is methoxy, R^3 and R^5 are methyl, R^4 is methoxy; and R^6 is hydrogen, which is 5-methoxy-2-[[(4-methocxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole.

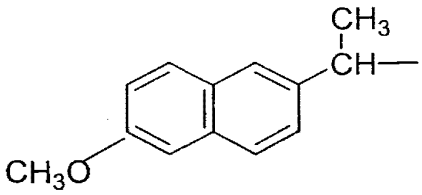
102. A method according to claim 1 wherein the organic radical selected from the group consisting of:

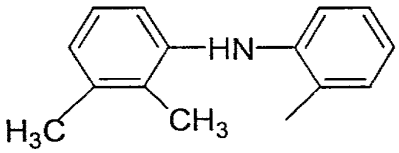


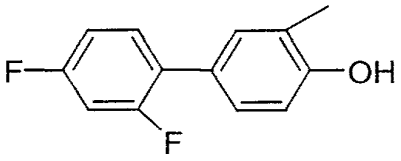


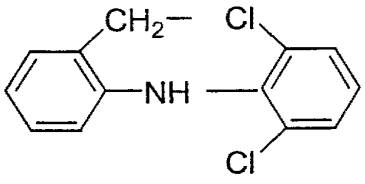


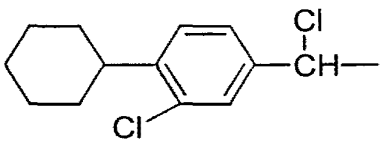


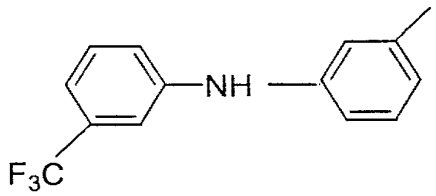


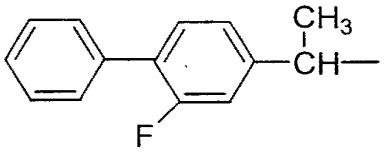


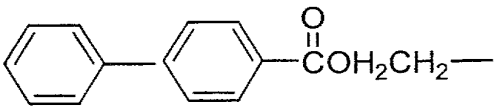


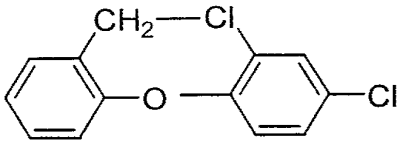




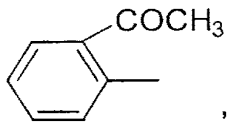




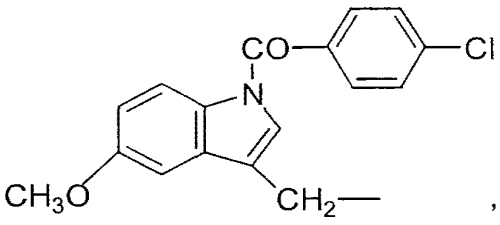




103. A method according to claim 102 wherein the organic radical is selected from the group consisting of:



,



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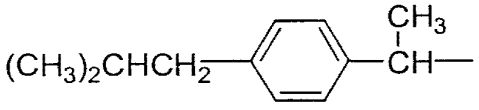
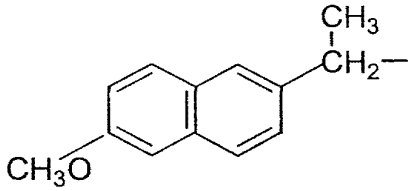
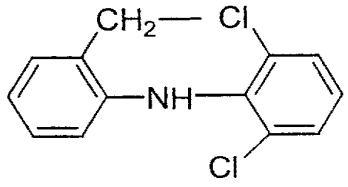


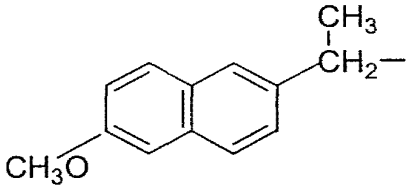


and



.

104. A method according to claim 103 wherein the organic radical is

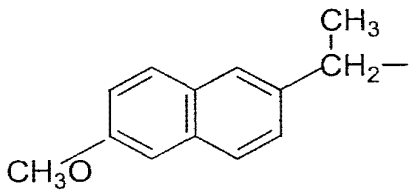


105. The method according to claim 91 wherein M is sodium, potassium, magnesium, calcium, barium or aluminum.

106. The method according to claim 105 wherein M is sodium, potassium, calcium, barium or aluminum.

107. The method according to claim 106 wherein M is sodium.

108. The method according to claim 91 wherein R^1 is hydrogen, R^2 is methoxy; R^3 and R^5 are methyl; R^4 is methoxy, R^6 is hydrogen; R^7 is



and M is sodium.

109. A method according to claim 91 wherein the compound to be stabilized of formula I is in the solid state.

110. A method according to claim 109 wherein the compound to be stabilized is in the fluid state.

111. A method according to claim 110 wherein the compound to be stabilized is in the liquid state.

112. A method according to claim 111 wherein the liquid state is a fluid state.

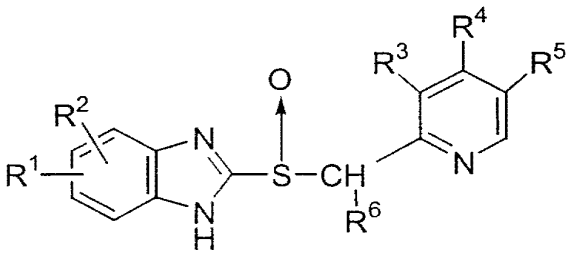
113. A method according to claim 112 wherein the fluid state is an aqueous medium.

114. A method according to claim 113 wherein the aqueous medium is the medium of the gastrointestinal tract of a mammal.

115. A method according to claim 114 wherein the aqueous medium of the gastrointestinal tract is the medium of the stomach.

116. A method according to claim 115 wherein the aqueous medium of the gastrointestinal tract is the medium of the gut.

117. A stabilized pharmaceutical unit dosage form comprising (a) a core comprising a compound of formula I



I

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof, and a compound of formula II

$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical and M is a cation;

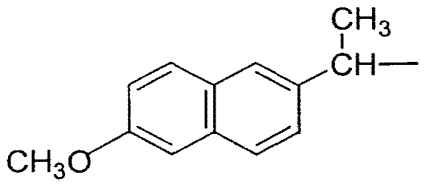
(b) a first coating of the core comprising at least one layer of a polymer coating; and

(c) a second coating comprising an enteric coating.

118. A stabilized pharmaceutical unit dosage form comprising a core according to claim 117 wherein the compound of formula I comprises compounds wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, carbomethoxy, carbethoxy, alkoxy and alkanoyl; R^6 is hydrogen; and R^3, R^4, and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy; and ethoxy; or a pharmaceutically acceptable acid addition salt thereof.

119. A stabilized pharmaceutical unit dosage form according to claim 118 wherein the compound of formula I is 2-[2-(3,5-dimethyl-4-methoxy)-pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole.

120. A stabilized pharmaceutical unit dosage form according to claim 117 wherein the organic radical of the compound of formula II is selected from the group consisting of



wherein M is sodium, potassium, calcium, barium or aluminum.

121. The stabilized pharmaceutical unit dosage form according to claim 120 wherein the compound of formula II is sodium 2-(6-methoxy-2-naphthyl)propionic acid.

122. A stabilized pharmaceutical unit dosage form according to claim 117 wherein the core comprises pharmaceutically acceptable excipients.

123. A stabilized pharmaceutical unit dosage form according to claim 122 wherein excipients comprise a filler, a binder or a lubricant.

124. A stabilized pharmaceutical unit dosage form according to claim 123, wherein the filler is a hydroxyalkylcellulose.

125. A stabilized pharmaceutical unit dosage form according to claim 124, wherein the hydroxyalkylcellulose is hydroxypropylcellulose.

126. A stabilized pharmaceutical unit dosage form according to claim 123, wherein the filler is a polyvinylpyrrolidone.

127. A stabilized pharmaceutical unit dosage form according to claim 123, wherein the lubricants are talc or magnesium stearate.

128. A stabilized pharmaceutical unit dosage form according to claim 123, wherein the polymer coating comprises a hydroxyalkylcellulose, polyethylene glycol and a pigment.

129. A stabilized pharmaceutical unit dosage form according to claim 128, wherein the hydroxyalkylcellulose is hydroxypropylmethylcellulose.

130. A stabilized pharmaceutical unit dosage form according to claim 117, wherein the enteric coating is a methacrylic acid copolymer.

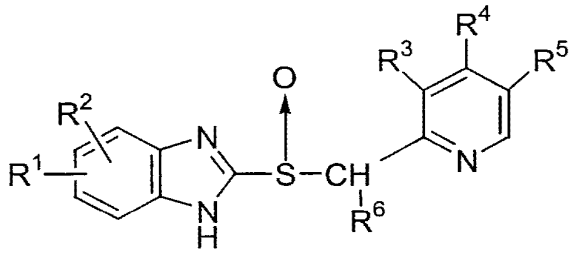
131. A stabilized pharmaceutical unit dosage form according to claim 130, wherein the methacrylic acid copolymer is a copolymer of methacrylic acid and ethyl acrylate.

132. A stabilized pharmaceutical unit dosage form according to claim 117, wherein the dosage form is a tablet.

133. A stabilized pharmaceutical unit dosage form according to claim 117, comprising 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxybenzimidazole, sodium 2-(6-methoxy-2-naphthyl)propionic acid, hydroxypropylcellusoe, polyvinylpyrrolidone, talce and magnesium stearate first coated with hydroxypropylmethylcellulose, polyethylent glycol, pigment) and enteric coated with methacrylic acid ethyl acrylate copolymer.

134. A process for the preparation of a stabilized pharmaceutical unit dosage form comprising the steps of:

(a) granulating a mixture of a compound of formula I



I

wherein R^1 and R^2 are same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, carboethoxy, alkoxy and alkanoyl; R^6 is selected from the group consisting of hydrogen, methyl and ethyl, and R^3 and R^5 are the same or different and are each selected from the group consisting of hydrogen, methyl, methoxy, ethoxy, methoxyethoxy and ethoxyethoxy; and R^4 is selected from the group consisting of methoxy, ethoxy, methoxyethoxy or ethoxyethoxy; or a pharmaceutically acceptable acid addition salt thereof,

a compound of formula II

$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical and M is a cation, a filler, a binder and a lubricant;

(b) drying the granulation of step (a)

(c) coating the dried granulation of step (b) with a first coating;

(d) drying the first coated granulation of step (c);

(e) coating the dried granulation of step (d) with an enteric coating.

135. The process for the preparation of a stabilized pharmaceutical unit dosage form according to claim 133 comprising the steps of:

(a) granulating a mixture of 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole, sodium 2-(6-methoxy-2-naphthyl)propionic acid, hydroxypropylycellulose, polyvinylpyrrolidone, talc and magnesium stearate;

(b) drying the granulate in step (a);

(c) coating the dried granulate of step (b) with a first coating comprising hydroxypropylmethylcellulose, polyethylene glycol and a pigment;

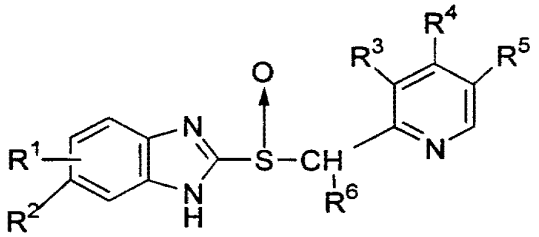
(d) drying the coated formulate from step (c); and

(e) coating the dried granulate from step (d) with an enteric coating comprising a methacrylic acid ethyl acrylate copolymer.

AMENDED CLAIMS

[received by the International Bureau 04 July 2000 (04.07.00);
original claims 1-134 replaced by new claims 135- 166 (7 pages)]

135. A composition comprising a compound of formula I



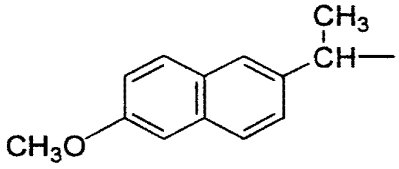
I

wherein R^1 hydrogen; R^2 is methoxy; R^6 is hydrogen; R^3 and R^5 are methyl; and R^4 is methoxy or a pharmaceutically acceptable acid addition salt thereof, and

a compound of formula II

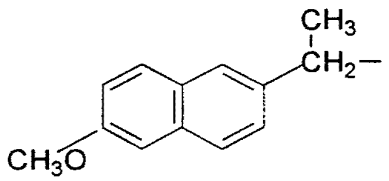
$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical selected from the group consisting of



and M is a cation selected from the group consisting of sodium potassium, magnesium, calcium, barium and aluminum.

136. A composition according to claim 135 wherein R^1 hydrogen; R^2 is methoxy; R^3 and R^5 are methyl; and R^4 is methoxy, R^6 is hydrogen; and R^7 is a group of the formula



and M is sodium.

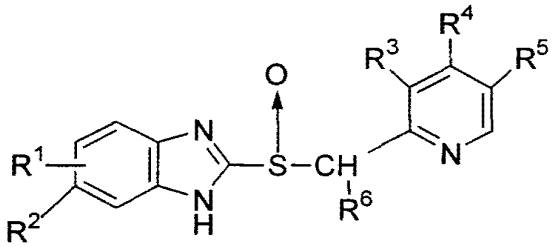
137. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 135.

138. A method of preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal requiring prevention of ulceration of the gastrointestinal tract by an anti-inflammatory agent, comprising administering an ulceration of the gastrointestinal tract by an anti-inflammatory agent preventing effective amount of a composition of claim 136.

139. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 135 and a pharmaceutically acceptable carrier therefor.

140. A pharmaceutical formulation for preventing ulceration of the gastrointestinal tract by an anti-inflammatory agent in a mammal, comprising as the active ingredient a composition of claim 136 and a pharmaceutically acceptable carrier therefor.

141. A method of stabilizing a compound of formula I



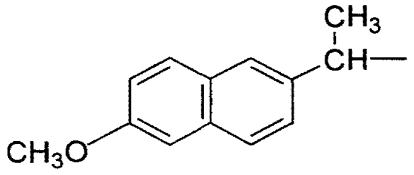
I

wherein R^1 hydrogen; R^2 is methoxy; R^6 is hydrogen; R^3 and R^5 are methyl; and R^4 is methoxy or a pharmaceutically acceptable acid addition salt thereof, and

a compound of formula II

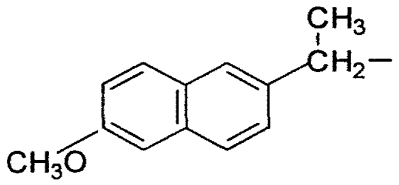
$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical selected from the group consisting of



and M is a cation selected from the group consisting of sodium potassium, magnesium, calcium, barium and aluminum.

142. The method according to claim 141 wherein R^1 is hydrogen, R^2 is methoxy; R^3 and R^5 are methyl; R^4 is methoxy, R^6 is hydrogen; R^7 is



and M is sodium.

143. A method according to claim 141 wherein the compound of formula I to be stabilized is in the solid state.

144. A method according to claim 141 wherein the compound of formula I to be stabilized is in the fluid state.

145. A method according to claim 144 wherein the compound of formula I to be stabilized is in the liquid state.

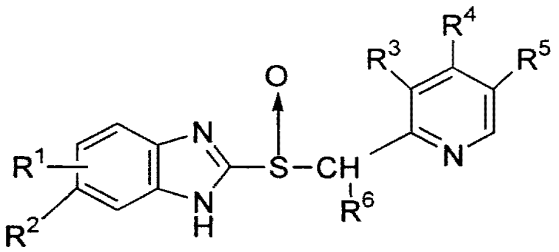
146. A method according to claim 144 wherein the fluid state is an aqueous medium.

147. A method according to claim 146 wherein the aqueous medium is the medium of the gastrointestinal tract of a mammal.

148. A method according to claim 147 wherein the aqueous medium of the gastrointestinal tract is the medium of the stomach.

149. A method according to claim 147 wherein the aqueous medium of the gastrointestinal tract is the medium of the gut.

150. A stabilized pharmaceutical unit dosage form comprising (a) a core comprising a compound of formula I



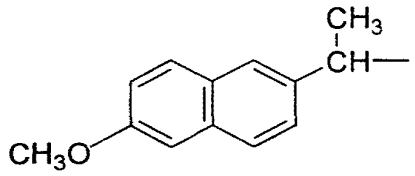
I

wherein R^1 hydrogen; R^2 is methoxy; R^6 is hydrogen; R^3 and R^5 are methyl; and R^4 is methoxy or a pharmaceutically acceptable acid addition salt thereof, and

a compound of formula II

$$R^7CO_2M \quad II$$

wherein R^7 is an organic radical selected from the group consisting of



and M is a cation selected from the group consisting of sodium, potassium, magnesium, calcium, barium and aluminum;

(b) a first coating of the core comprising at least one layer of a polymer coating; and

(c) a second coating comprising an enteric coating.

151. A stabilized pharmaceutical unit dosage form according to claim 150 wherein the compound of formula I is 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole.

152. The stabilized pharmaceutical unit dosage form according to claim 150 wherein the compound of formula II is sodium 2-(6-methoxy-2-naphthyl)propionic acid.

153. A stabilized pharmaceutical unit dosage form according to claim 150 wherein the core comprises pharmaceutically acceptable excipients.

154. A stabilized pharmaceutical unit dosage form according to claim 150 wherein excipients comprise a filler, a binder or a lubricant.

155. A stabilized pharmaceutical unit dosage form according to claim 154, wherein the filler is a hydroxyalkylcellulose.

156. A stabilized pharmaceutical unit dosage form according to claim 155, wherein the hydroxyalkylcellulose is hydroxypropylcellulose.

157. A stabilized pharmaceutical unit dosage form according to claim 154, wherein the filler is a polyvinylpyrrolidone.

158. A stabilized pharmaceutical unit dosage form according to claim 154, wherein the lubricants are talc or magnesium stearate.

159. A stabilized pharmaceutical unit dosage form according to claim 150, wherein the polymer coating comprises a hydroxyalkylcellulose, polyethylene glycol and a pigment.

160. A stabilized pharmaceutical unit dosage form according to claim 159, wherein the hydroxyalkylcellulose is hydroxypropylmethylcellulose.

161. A stabilized pharmaceutical unit dosage form according to claim 150, wherein the enteric coating is a methacrylic acid copolymer.

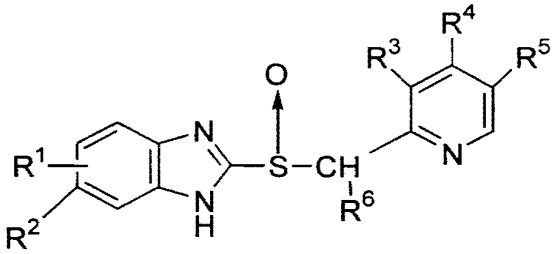
162. A stabilized pharmaceutical unit dosage form according to claim 161, wherein the methacrylic acid copolymer is a copolymer of methacrylic acid and ethyl acrylate.

163. A stabilized pharmaceutical unit dosage form according to claim 150, wherein the dosage form is a tablet.

164. A stabilized pharmaceutical unit dosage form according to claim 150, comprising 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxybenzimidazole, sodium 2-(6-methoxy-2-naphthyl)propionic acid, hydroxypropylcellulose, polyvinylpyrrolidone, talc and magnesium stearate first coated with hydroxypropylmethylcellulose, polyethylent glycol, pigment and enteric coated with methacrylic acid ethyl acrylate copolymer.

165. A process for the preparation of a stabilized pharmaceutical unit dosage form comprising the steps of:

(a) granulating a mixture of a compound of formula I



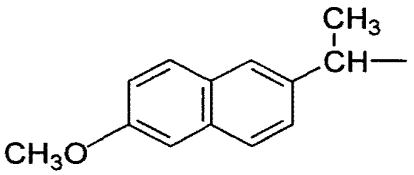
I

wherein R^1 hydrogen; R^2 is methoxy; R^6 is hydrogen; R^3 and R^5 are methyl; and R^4 is methoxy or a pharmaceutically acceptable acid addition salt thereof, and

a compound of formula II

R^7CO_2M II

wherein R^7 is an organic radical selected from the group consisting of



and M is a cation selected from the group consisting of sodium potassium, magnesium, calcium, barium and aluminum;

(b) drying the granulate of step (a)

(c) coating the dried granulate of step (b) with a first coating;

(d) drying the first coated granulation of step (c);

(e) coating the dried granulate of step (d) with an enteric coating.

166. The process for the preparation of a stabilized pharmaceutical unit dosage form according to claim 165 comprising the steps of:

(a) granulating a mixture of 2-[2-(3,5-dimethyl-4-methoxy)pyridinylmethylsulfinyl]-(5-methoxy)benzimidazole, sodium 2-(6-methoxy-2-naphthyl)propionic acid, hydroxypropylycellulose, polyvinylpyrrolidone, talc and magnesium stearate;

(b) drying the granulate in step (a);

(c) coating the dried granulate of step (b) with a first coating comprising hydroxypropylmethylcellulose, polyethylene glycol and a pigment;

(d) drying the coated granulate from step (c); and

(e) coating the dried granulate from step (d) with an enteric coating comprising a methacrylic acid ethyl acrylate copolymer.

INTERNATIONAL SEARCH REPORT

Inter.. .onal Application No
PCT/US 99/11389

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/44 A61P1/04

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)
IPC 7 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 00380 A (ASTRA) 7 January 1999 (1999-01-07) claims 1,11 --- -/--	1-4, 9-11, 19-23, 28,29, 37-40, 45-47, 55-58, 63-65, 73-76, 81-83, 100,101

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

[X] Patent family members are listed in 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
3 March 2000	10/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Peeters, J

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter...onal Application No
PCT/US 99/11389

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 12817 A (WARNER-LAMBERT) 8 July 1993 (1993-07-08) claims 1,2,5,7-9	1-4, 9-11, 19-23, 28,29, 37-40, 45-47, 55-58, 63-65, 73-76, 81-83, 100,101
X	EP 0 426 479 A (MCNEIL-PPC) 8 May 1991 (1991-05-08) claims 1-4 column 6, line 13 column 6, line 36-38 column 7, line 1-16	1-4, 9-13, 15-23, 28,29, 37-40, 45-47, 55-58, 63-65, 73-76, 81-83, 100-103
X	WO 98 22117 A (PROCTER & GAMBLE) 28 May 1998 (1998-05-28) claims 1-3,5,8,11 page 4, line 31 -page 5, line 6	1-4, 9-13, 19-23, 28,29, 37-40, 45-47, 55-58, 63-65, 73-76, 81-83, 100-103

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ..onal Application No
PCT/US 99/11389

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9900380	A	07-01-1999	SE	510643 C	14-06-1999
			AU	8135398 A	19-01-1999
			SE	9702483 A	28-12-1998
WO 9312817	A	08-07-1993	AU	3247593 A	28-07-1993
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			US	5417980 A	23-05-1995
			US	5204118 A	20-04-1993
			ZA	9008775 A	29-07-1992
WO 9822117	A	28-05-1998	EP	0941101 A	15-09-1999
			NO	992469 A	22-07-1999

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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7 December 2000 (07.12.2000)

PCT

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(21) International Application Number: PCT/SE00/01071

(22) International Filing Date: 25 May 2000 (25.05.2000)

(25) Filing Language: English

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(30) Priority Data:

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9904704-5	21 December 1999 (21.12.1999)	SE

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(72) Inventors; and

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(74) Agent: **ASTRAZENECA AB**; Global Intellectual Property, Patents, S-151 85 Södertälje (SE).

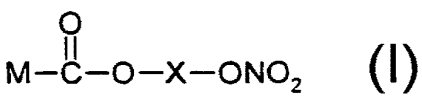
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW USE OF COMPOUNDS AS ANTIBACTERIAL AGENTS



(I)

(57) Abstract: The present invention discloses a new use of NO-releasing NSAIDs, especially NO-releasing NSAIDs of formula (I), or a pharmaceutically acceptable salt or enantiomer thereof, for the manufacture of a medicament for the treatment of bacterial infections, especially caused or mediated by *Helicobacter pylori*. Disclosed is also the new use of a NO-releasing NSAID in combination with an acid susceptible proton pump inhibitor for the treatment of bacterial infections.

WO 00/72838 A1

NEW USE OF COMPOUNDS AS ANTIBACTERIAL AGENTS

Field of the invention

The present invention is directed to a new use of nitric oxide-releasing Non Steriodal Antiinflammatory Drugs (NO-releasing NSAIDs). More particularly the invention is directed to the use of NO-releasing NSAIDs for the manufacture of a medicament for the treatment of bacterial infections, paticularly caused or mediated by *Helicobacter pylori* as well as a combination with acid susceptible proton pump inhibitors for the treatment of bacterial infections.

Background of the invention and prior art

NSAIDs, are among the most commonly prescribed and used drugs world WIDE. Despite the therapeutic benefits of NSAIDs, their use is limited. The use of NSAIDs may lead to gastric mucosal damage due to inhibited production of prostaglandins which increases the risk of gastrointestinal side-effects.

A recent proposal for reducing the side-effects associated with NSAIDs treatment is to use nitric oxide-releasing NSAID derivatives (NO-releasing NSAIDs) (*del Soldato P et al., NO-releasing NSAID:s , A novel class of safer and effective antiinflammatory agents; Inflammopharmacology, 1996; 4; 181-188*). NO-releasing NSAIDs reduce the gastrointestinal side-effects but still have the pharmacological activity characteristic of the frequently used NSAIDs.

NO-releasing NSAIDs and pharmaceutically acceptable salts thereof are for instance described in WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641.

Helicobacter pylori is a gram-negative spirilliform bacteria which colonises in the gastric mucosa. The relationship between gastrointestinal disorders and infections with

Helicobacter pylori proposed in 1983 by Warren (*Warren JR Lancet 1983;1.1273*) is well established today.

A number of different therapies have been proposed for the treatment of *Helicobacter pylori* infections. Combination therapies are commonly used. The most commonly used comprise a proton pump inhibitor in combination with one or more antibacterial compounds such as claritromycin and amoxicillin. For instance WO93/00327 discloses the combination of a substance with inhibiting effect on the gastric acid secretion which increases the intragastric pH, and an acid degradable antibacterial compound. Some of these therapies also comprise a bismuth compound, se for instance WO 98/03219 and WO98/22117, which latter application discloses a composition containing bismuth, an antimicrobial agent and a non-steriodal antiinflammatory agent for the treatment of gastrointestinal disorders caused or mediated by *Helicobacter pylori*.

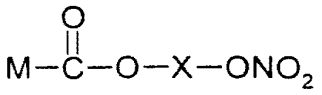
In view of the vast number of the population suffering from gastrointestinal disorders caused or mediated by bacterial infections, such as *Helicobacter pylori* infections, and also in view of the fact that many bacterial strains develop a resistance to commonly used antibiotics, a continuing need exists for a safe and effective medicament having an antibacterial effect, especially for the treatment of *Helicobacter pylori* infections.

Outline of the invention

It has now surprisingly been found that NO-releasing NSAIDs have an antibacterial effect, which makes them useful for the treatment of bacterial infections.

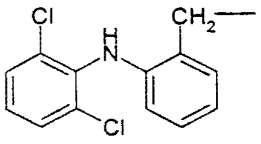
The present invention is related to the use of a NO-releasing NSAID as well as pharmaceutically acceptable salts or enantiomers thereof, for the manufacture of a medicament for the treatment of bacterial infections.

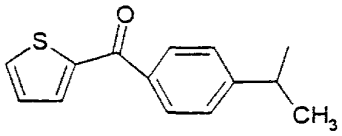
Preferably the NO-releasing NSAID is defined by the formula I

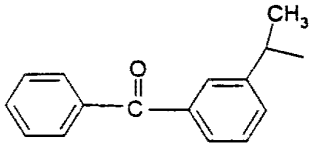


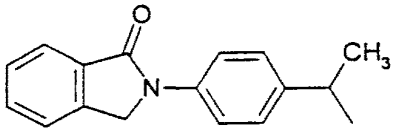
I

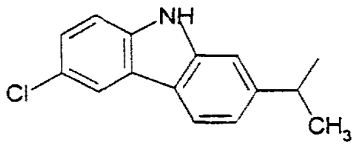
wherein M is selected from anyone of

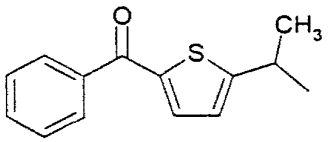


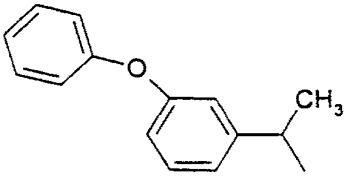


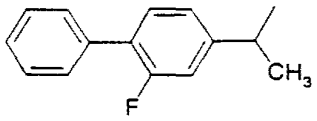


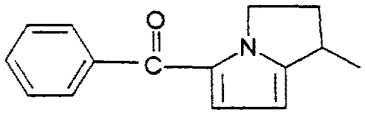


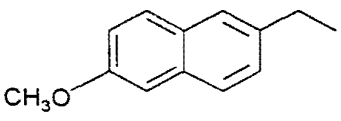


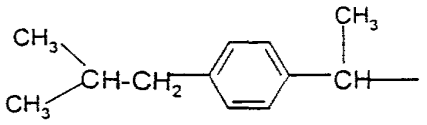


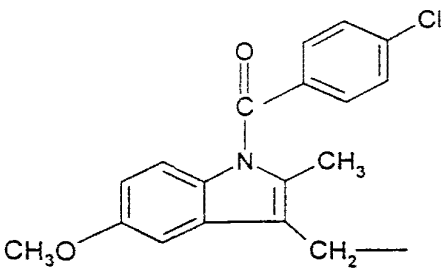


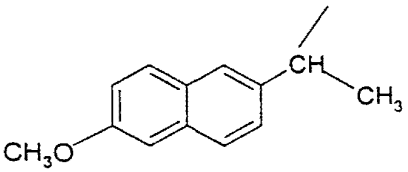


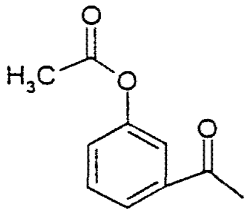










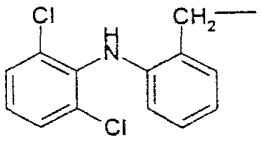
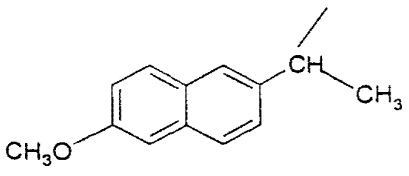
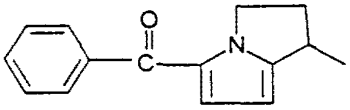
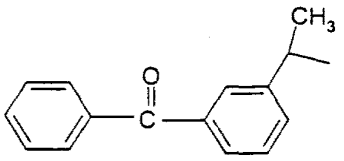


and X is a spacer, i.e. a compound forming a bridge between the nitrogen oxide donating group and the NSAID moiety, or a pharmaceutically acceptable salt or enantiomer thereof;

X is preferably selected from linear, branched or cyclic $-(CH_2)-_n$ wherein n is an integer of from 2 to 10; $-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$.

M is not limited by the above definition but may be any other compound giving the corresponding NSAID by hydrolysis of the compound according to formula I.

In a preferred embodiment of the invention M is selected from

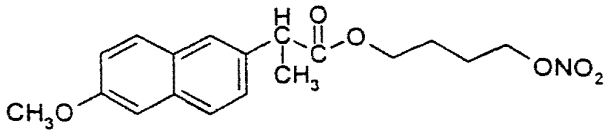





and X is selected from

linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6;

$-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

In an even more preferred embodiment of the invention the NO-releasing NSAID is a compound according to any one of the formulas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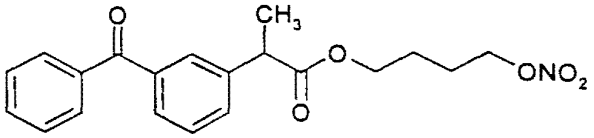
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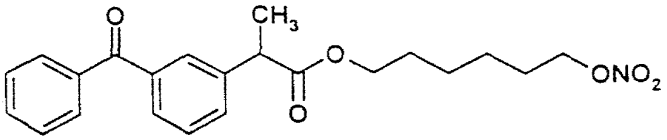
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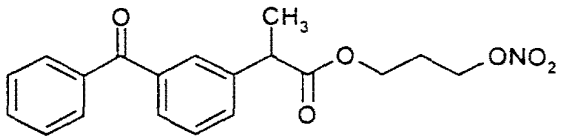
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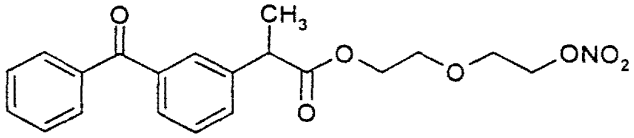
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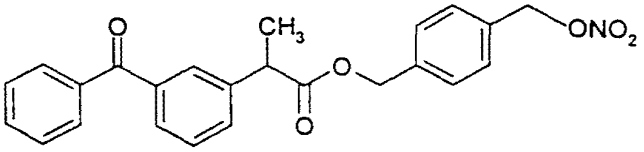
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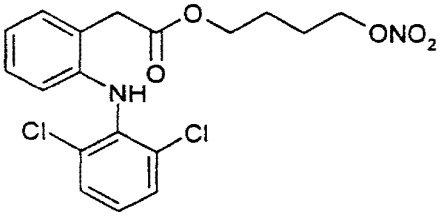
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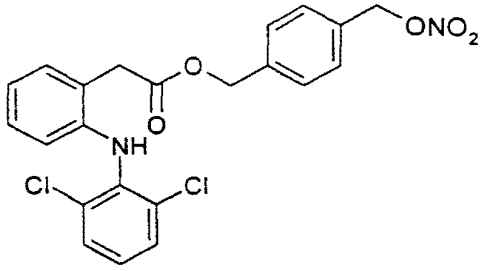
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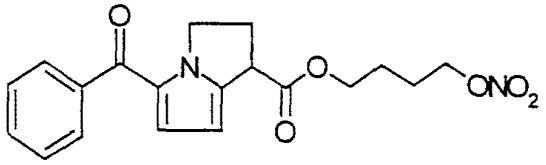
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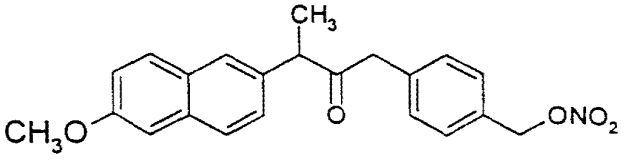
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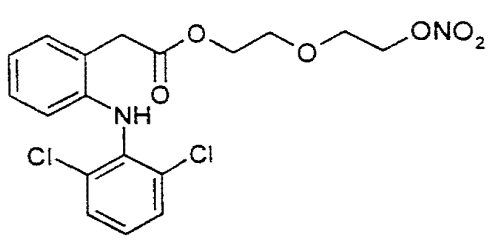

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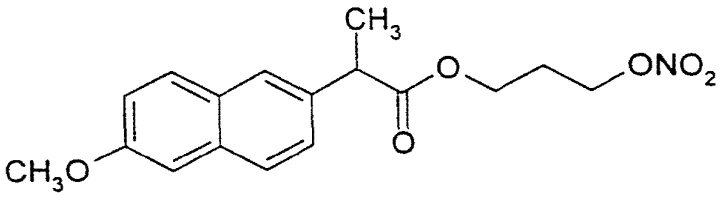

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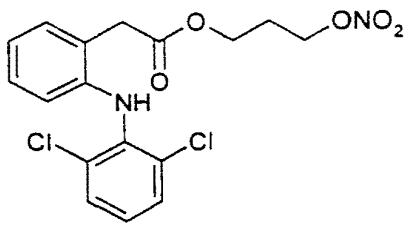

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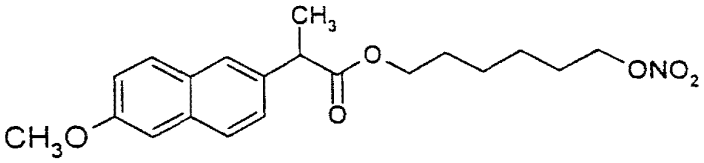

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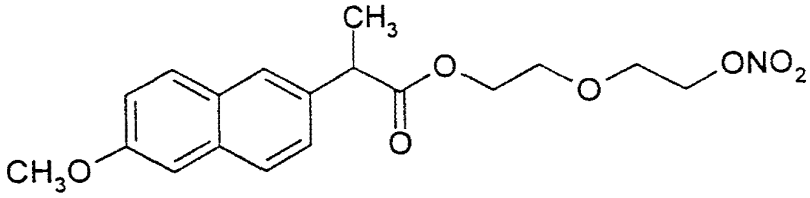

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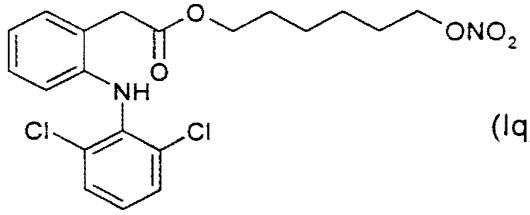


(Iq)

In a particularly preferred embodiment of the invention the NO-releasing NSAID is a compound according to formula Ia.

A further aspect of the invention is the use of a NO-releasing NSAID, preferably a compound of the formula I above, in the manufacture of a medicament for use in the treatment of *Helicobacter pylori* infections, especially in the treatment of gastrointestinal disorders caused or mediated by *Helicobacter pylori*.

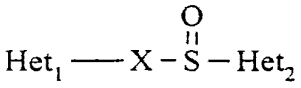
Still a further aspect of the invention is a method for the treatment of bacterial infections, in particular *Helicobacter pylori* infections, whereby an effective amount of a medicament comprising a NO-releasing NSAID, preferably a compound of the formula I, as active agent is administered to a subject suffering from said bacterial infection.

Also a pharmaceutical formulation suitable for use in the treatment of bacterial infections, which formulation comprising a NO-releasing NSAID, preferably a compound of the formula I, is within the scope of the invention.

Furthermore, the invention is related to the use of a NO-releasing NSAID, preferably a compound of the formula I, in combination with an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer in the manufacture of pharmaceutical formulations intended for simultanous, separate or sequential administration in the treatment of bacterial infections, especially *Helicobacter pylori* infections.

The invention may be applied in combination with other agents generally associated with treatment of bacterial infections, such as for instance antibacterial agents.

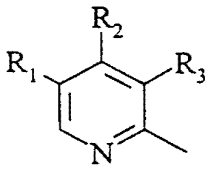
An acid susceptible proton pump inhibitor is, for instance, a compound of the general formula II



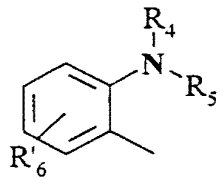
II

wherein

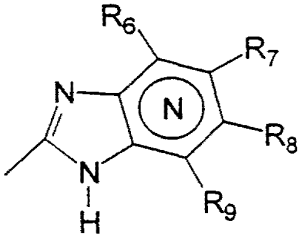
Het_1 is



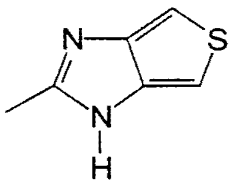
or



Het_2 is



or



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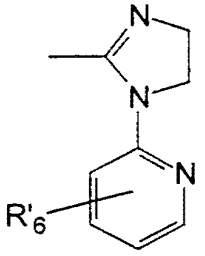
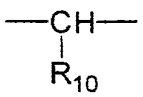
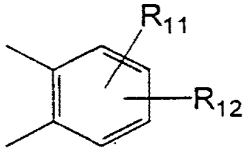


X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

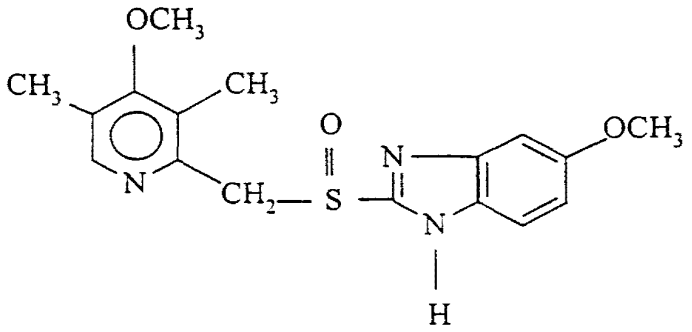
R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

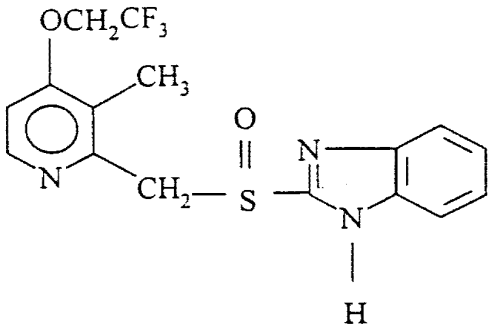
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof . The substituents may be branched or straight C_1 - C_9 -chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

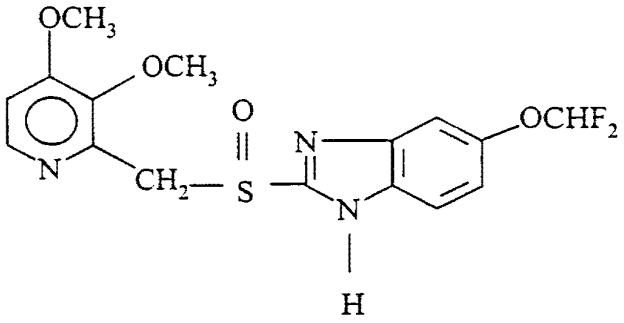
Examples of proton pump inhibitors according to formula II are



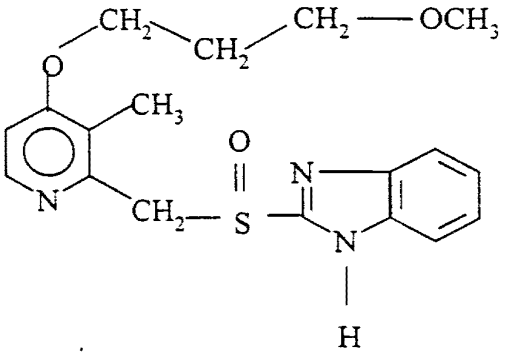
Omeprazole



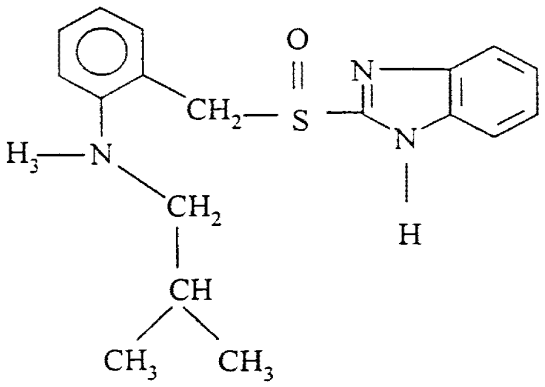
Lansoprazole



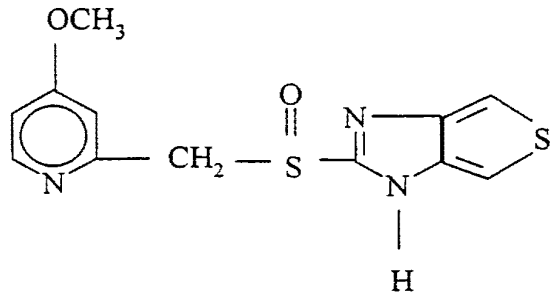
Pantoprazole

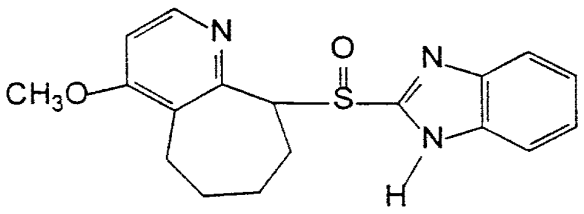


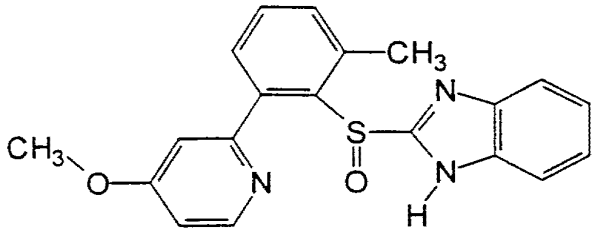
Pariprazole

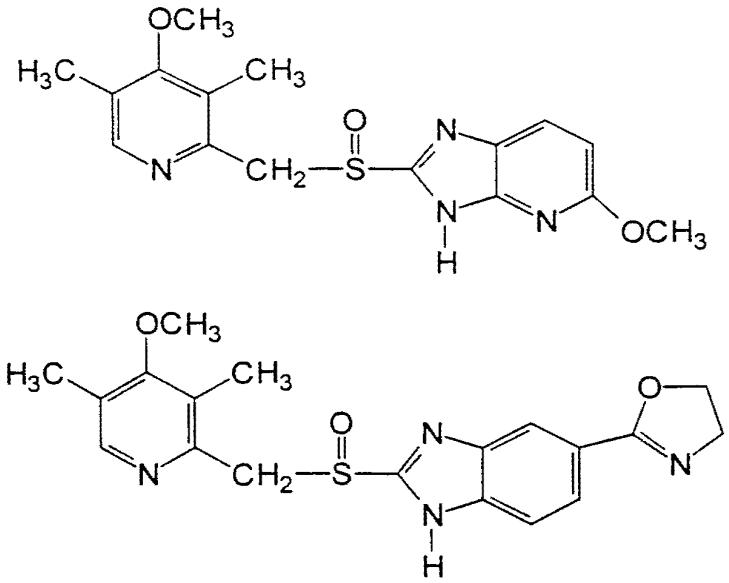


Leminoprazole









The proton pump inhibitor may also be used in the form of a pharmaceutical acceptable salt or a single enantiomer in the claimed combination.

Preferably the proton pump inhibitor omeprazole, or an alkaline salt of omeprazole, such as the magnesium salt, or (*S*)-omeprazole or an alkaline salt of (*S*)-omeprazole, such as the magnesium salt is used in the claimed combination.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO90/06925, and further the especially suitable compounds are described in WO95/01977 and WO94/27988.

According to the invention there is further provided a method for treating bacterial infections, particularly *Helicobacter Pylori* infections, which method comprises simultaneous, separate or sequential administration to a subject suffering from a bacterial infection one or more pharmaceutical formulations comprising a NO-releasing NSAID, preferably a compound according to the formula I, and an acid susceptible proton pump

inhibitor. Also pharmaceutical formulations for simultaneous, separate or sequential administration to be used in the treatment of bacterial infections, which formulations comprise an NO-releasing NSAID, preferably a compound of the formula I and an acid susceptible proton pump inhibitor are within the scope of the invention.

The NO-releasing NSAID alone or in combination with an acid susceptible compound may be in a dosage form administered orally, rectally, epidurally, intravenously, intramuscularly, subcutanously, by infusion, nasally or any other way suitable for administration. Preferably the active compound(-s) is administered orally.

The active compound(-s) are administered one to several times a day, preferably once or twice daily. The typical daily dose of the active compound(-s) varies and will depend on various factors such as the individual requirements of the patients, the mode of administration and disease. In general each dosage form will comprise 0.5 – 5000 mg, preferably 5 – 1000 mg, of the NO-releasing NSAID. If a combination with a proton pump inhibitor is used 0.5 – 5000 mg of the NO-releasing NSAID, and 0.1 – 200 mg of the proton pump inhibitor will be comprised in each dosage form, or in two separate dosage forms. Preferably, the amount of the NO-releasing NSAID in each dosage form is 5 – 1000 mg, and the amount of the proton pump inhibitor 10 - 80 mg.

Detailed description of the invention

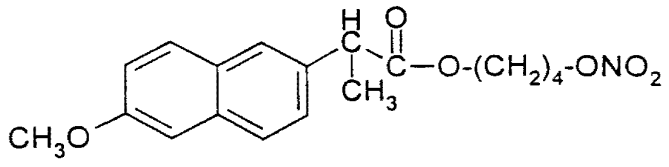
The invention is described in more detail by the following non-limiting examples.

The examples below support that NO-releasing NSAIDs are active against *Helicobacter pylori*, and that the antibacterial activity is concentration dependent.

Example 1.

Strain: *Helicobacter pylori* reference strain NCTC 11 637 (National Type Culture Collection, from Smittskyddsinstitutet in Solna, Sweden), an antibiotic sensitive reference strain

Substance:



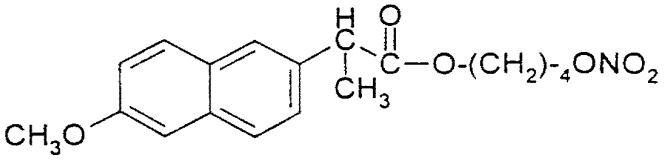
Ia

Helicobacter pylori was grown on blood agar plates, having a diameter of 90 mm, for three days under microaerophilic conditions at 37°C. The bacteria were suspended in PBS (phosphate buffer saline) to approximately 10^8 cfu/ml. Approximately 2 ml of the suspension was added to one agar plate and spread even on the surface of the agar. Overflow was removed with a syringe. Wells, like small holes, 3 mm in diameter, were made in the agarplate by removing agar. Three wells per plate were made.
A stock solution of a compound of the formula Ia having the concentration 100 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.
Result: The inhibition zone around each well was large, i.e. it was not possible to measure the diameter of the zone.

Example 2.

Strain: *Helicobacter pylori* reference strain NCTC 11 637 (see Example 1), an antibiotic sensitive reference strain

Substance:



Ia

The plates with the wells were prepared according to Example 1.

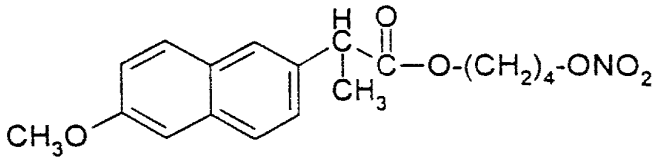
A stock solution of a compound of the formula Ia having the concentration 10 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around each well was large, i.e. it was not possible to measure the diameter of the zone.

Example 3.

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance:



Ia

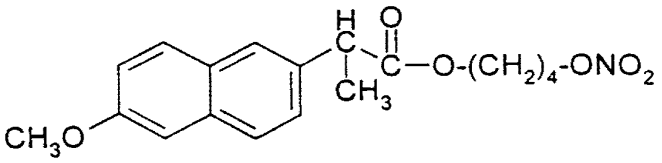
The plates with the wells were prepared according to Example 1.
A stock solution of a compound of the formula Ia having the concentration 1 000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around each well was 13 mm.

Example 4.

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance:



Ia

The plates with the wells were prepared according to Example 1.

A stock solution of a compound of the formula Ia having the concentration 100 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around each well was 10.4 mm.

Comparative tests

Example A

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

The plates with the wells were prepared according to Example 1.

A stock solution of Naproxen having the concentration 10 000 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: The inhibition zone around the each well was 16.6 mm.

Example B

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

The plates with the wells were prepared according to Example 1.

A stock solution of Naproxen having the concentration 1000 µg/ml was prepared. 30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: No inhibition zones around the wells were formed.

Example C

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Naproxen

The plates with the wells were prepared according to Example 1.

A stock solution of Naproxen having the concentration 100 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: No inhibition zones around the wells were formed.

Example D

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: S-nitroso-N-acetyl-penicillamin (SNAP)

The plates with the wells were prepared according to Example 1.

A stock solution of SNAP with the concentration 10 000 µg/ml was prepared.
30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

Result: No inhibition zones around the wells were formed.

Example E

Strain: *Helicobacter pylori* reference strain NCTC 11 637, an antibiotic sensitive reference strain (see Example 1)

Substance: Di-methyl-sulphate-oxide (DMSO)

The plates with the wells were prepared according to Example 1.

A solution of DMSO alone with the concentration 20 µg/ml was prepared.

30 µl of the solution was added to the wells. The plates were incubated for four days before they were checked for inhibition zones around the wells.

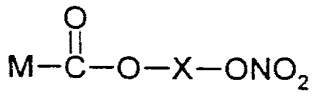
Result: No inhibition zones around the wells were formed.

Claims

1. Use of a NO-releasing NSAID as well as a pharmaceutically acceptable salt or an enantiomer thereof, for the manufacture of a medicament for the treatment of bacterial infections.

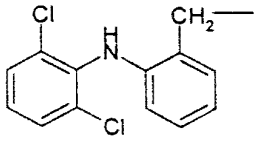
2. Use of a NO-releasing NSAID and an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer in the manufacture of pharmaceutical formulations intended for simultaneous, separate, or sequential administration in the treatment of bacterial infections.

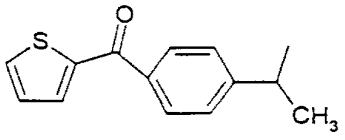
3 Use according to claim 1 or 2 wherein the NO-releasing NSAID is a compound of the formula I

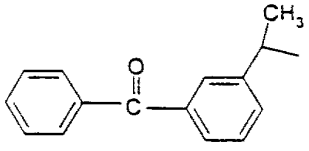


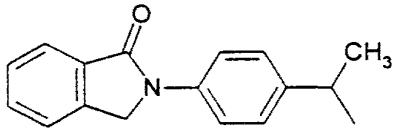
I

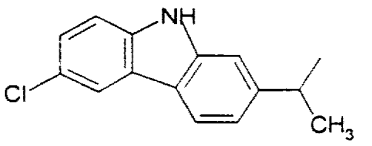
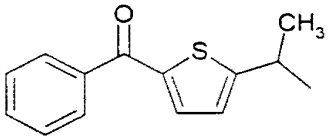
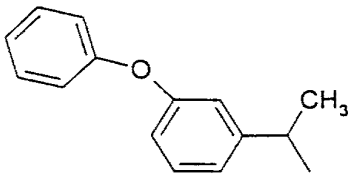
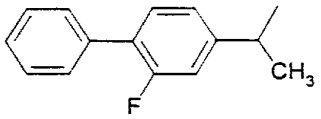
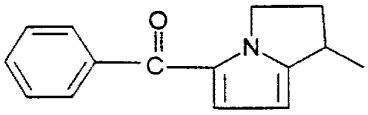
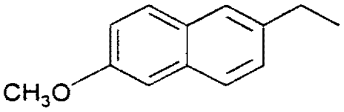
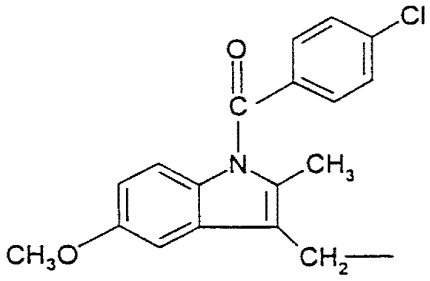
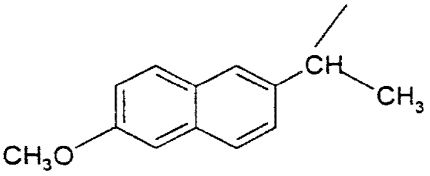
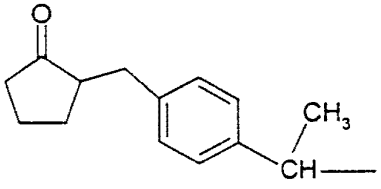
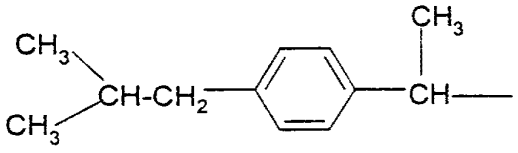
wherein M is selected from anyone of









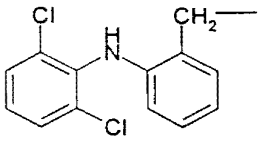
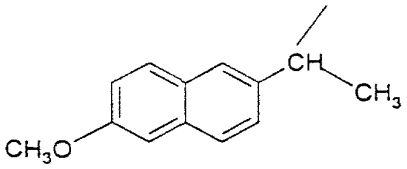
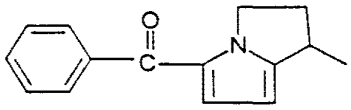
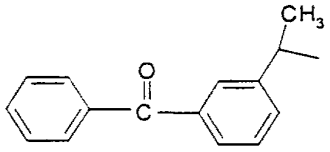
and X is selected from

linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to 10;

$-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to10; and $-CH_2-pC_6H_4-CH_2-$,

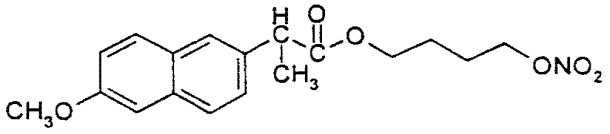
or a pharmaceutically acceptable salt or enantiomer thereof.

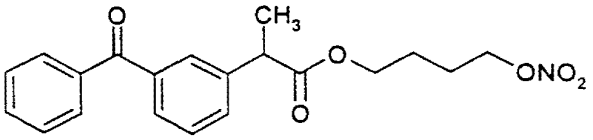
4. Use according to claim 3 wherein M in formula I is selected from

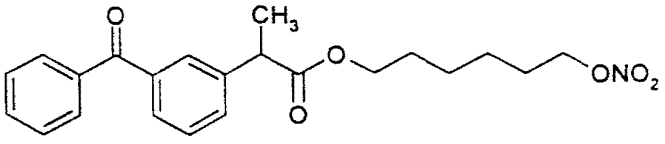





5. Use according to claim 3 or 4 wherein X in formula I is selected from linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6, $-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

6. Use according to any one of claims 1 - 3 wherein the NO-releasing NSAID is a compound according to any one of the formulas Ia - Iq


(Ia) ;


(Ib) ;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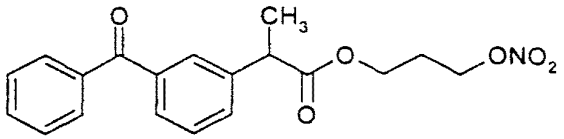
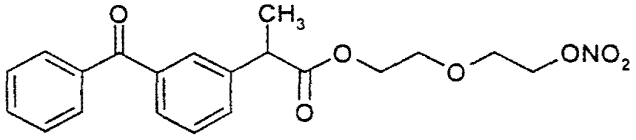
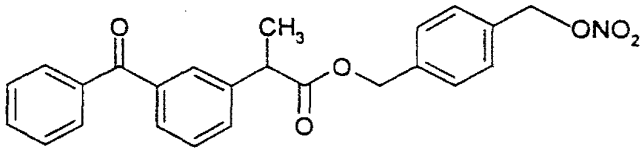


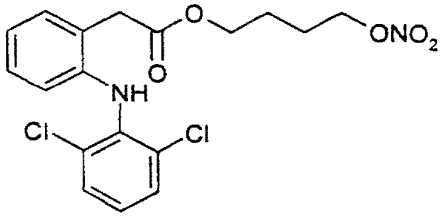
(Ic) ;



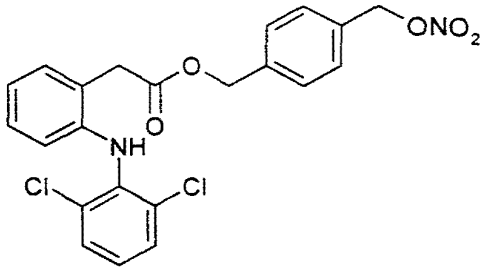
(Ie) ;



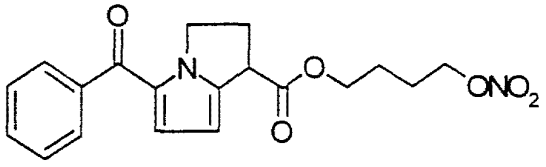
(If) ;



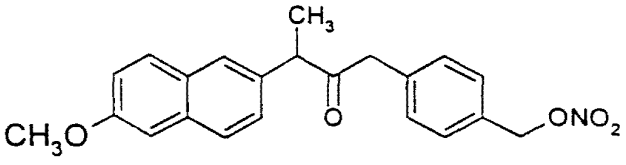
(Ig) ;



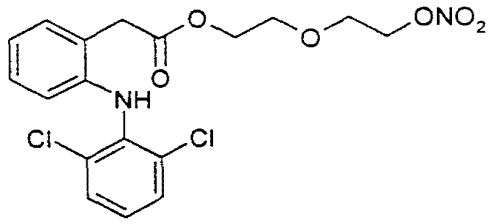
(Ii) ;



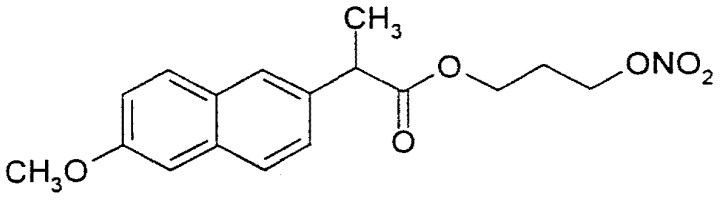
(Ij) ;



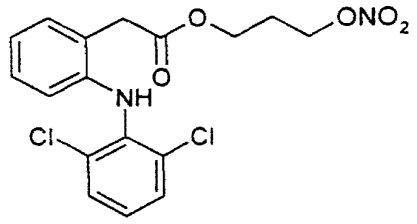
(Ik) ;



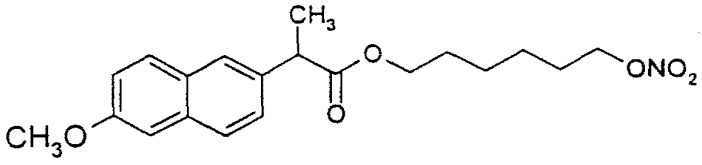
(IL) ;



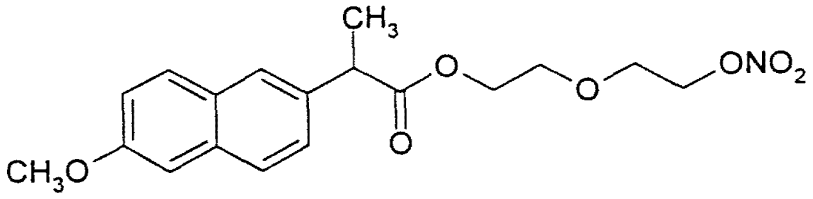
(Im) ;



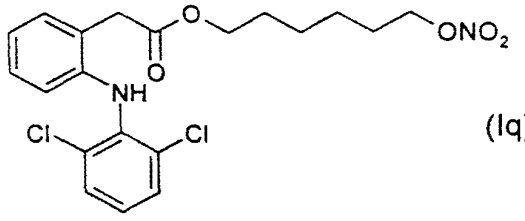
(In) ;



(Io) ;

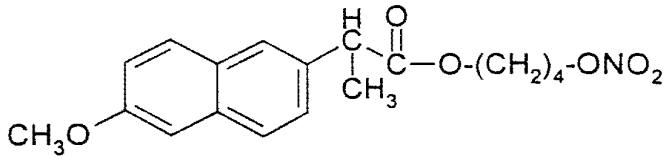


(Ip) ; and



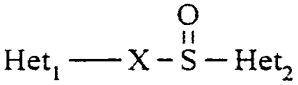
(Iq)

7. Use according to claim 6, wherein the NO-releasing NSAID is a compound of formula Ia



(Ia)

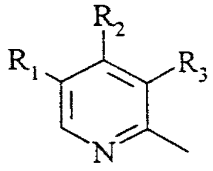
8. Use according to claim 2 wherein the acid susceptible proton pump inhibitor is a compound of the formula II



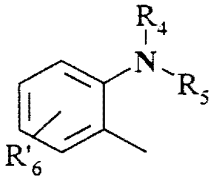
II

wherein

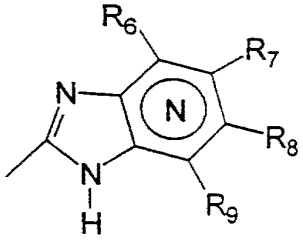
Het_1 is



or



Het_2 is



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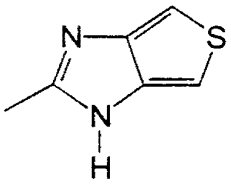

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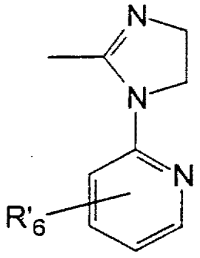
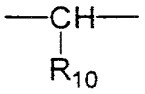


X =



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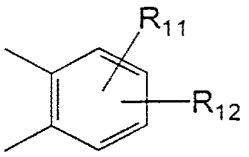


wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof, they may be branched or straight C_1 - C_9 - chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

9. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is selected from omeprazole, an alkaline salt thereof, (*S*)-omeprazole and an alkaline salt thereof.

10. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is lansoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

11. Use according to claim 8 wherein the acid susceptible proton pump inhibitor is pantoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

12. Use according to any one of the preceeding claims 1 to 11, wherein the bacterial infection is caused or mediated by *Helicobacter pylori*.

13. Use according to claim 1, wherein the amount of NO-releasing NSAID in each dosage form is 0.5 – 5000 mg.

14. Use according to claim 13, wherein the amount of NO-releasing NSAID is 5 – 1000 mg.

15. Use according to claim 2, wherein the amount of NO-releasing NSAID is 0.5 – 5000 mg and the amount of proton pump inhibitor is 0.1 – 200 mg together in one dosage form or in two separate dosage forms.

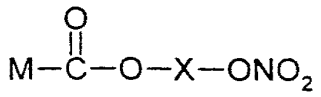
16. Use according to claim 15, wherein the amount of NO-releasing NSAID is 5 – 1000 mg and the amount of proton pump inhibitor is 10 – 80 mg.

17. A method for the treatment of a bacterial infection, comprising administering to a patient suffering from said bacterial infection, an effective amount of a NO-releasing NSAID or a pharmaceutically acceptable salt or an enantiomer thereof.

18. A method for the treatment of a bacterial infection, comprising simultaneously, separately or sequentially administration to a patient suffering from said bacterial infection,

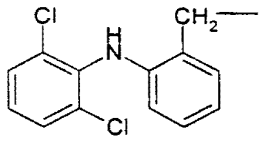
an effective amount of a NO-releasing NSAID and an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer.

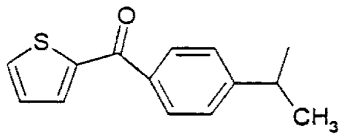
19. A method according to claim 17 or 18 wherein the NO-releasing NSAID is a compound of the formula I

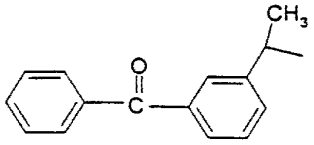


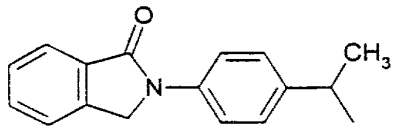
I

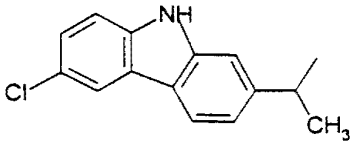
wherein M is selected from

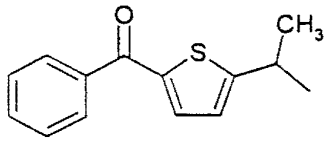


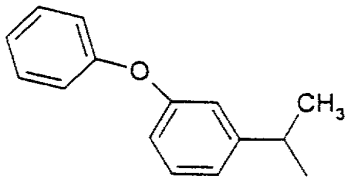


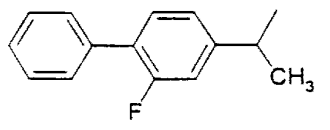


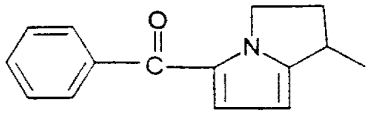
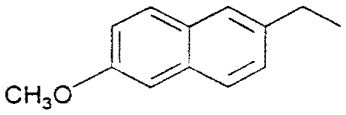
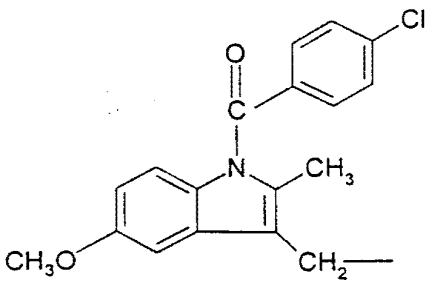
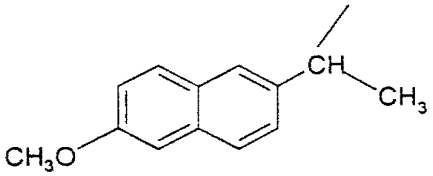


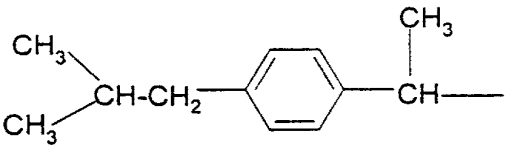










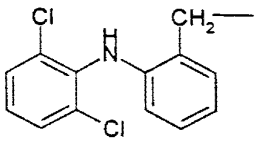
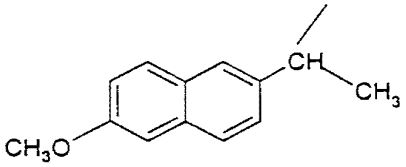
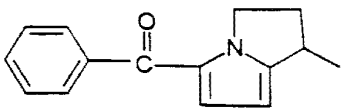
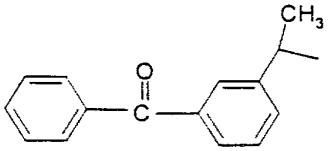
and X is selected from

linear, branched or cyclic $-(CH_2)_n-$ wherein n is an integer of from 2 to 10;

$-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$,

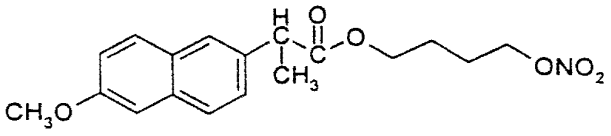
or a pharmaceutically acceptable salt or enantiomer thereof.

20. A method according to claim 19 wherein M in formula I is selected from

21. A method according to claim 19 or 20 wherein X in formula I is selected from linear $-(CH_2)_n-$ wherein n is an integer of from 2 to 6, $-(CH_2)_2-O-(CH_2)_2-$ and $-CH_2-pC_6H_4-CH_2-$.

22. A method according to any one of claim 17 – 19, wherein the NO-releasing NSAID is a compound according to any one of the formulas Ia - Iq



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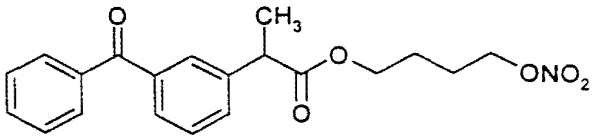
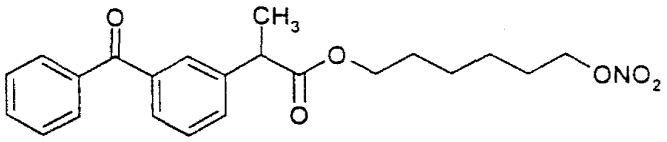
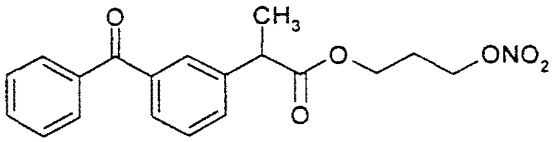


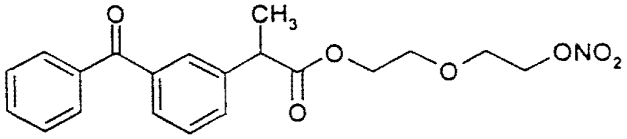
(Ib) ;



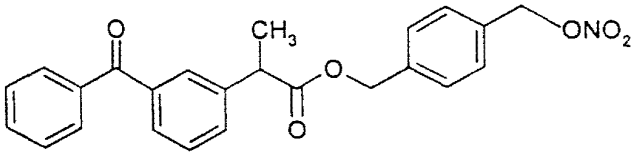
(Id) ;



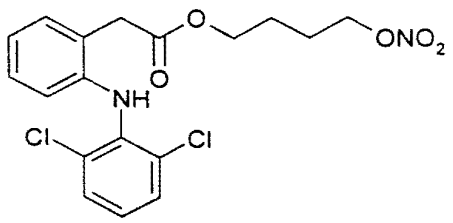
(Ic) ;



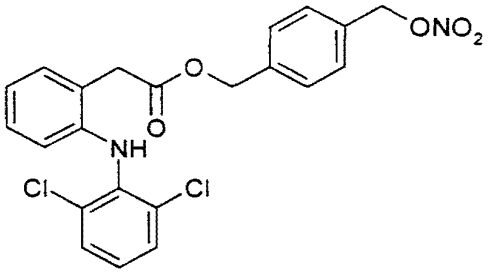
(Ie) ;



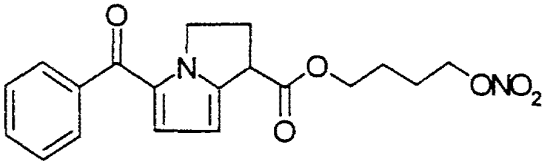
(If) ;



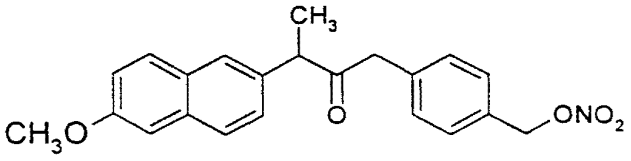
(Ig) ;



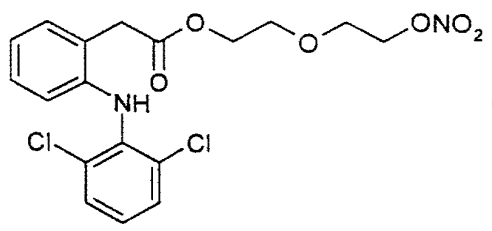
(Ii) ;



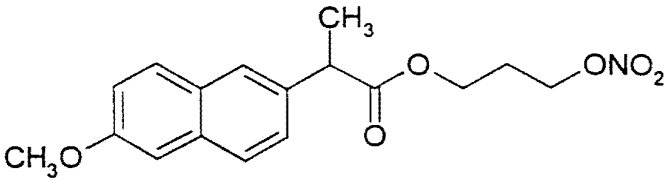
(Ij) ;



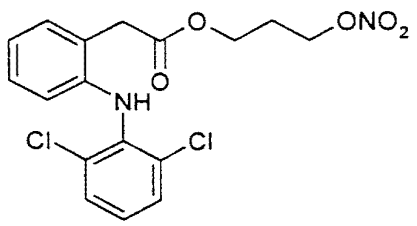
(Ik) ;



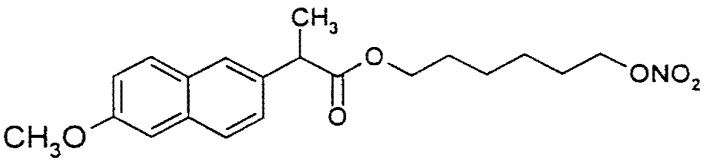
(IL) ;



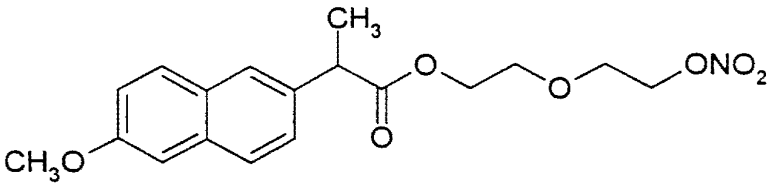
(Im) ;



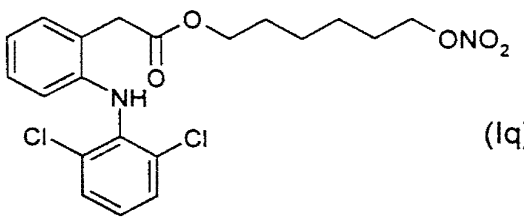
(In) ;



(Io) ;

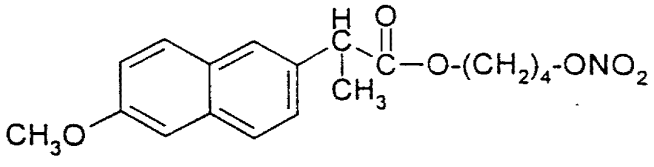


(Ip) ; and



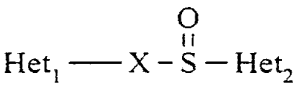
(Iq)

23. A method according to claim 22, wherein the NO-releasing NSAID is a compound of formula Ia



(Ia)

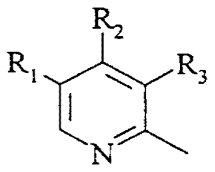
24. A method according to claim 18 wherein the acid susceptible proton pump inhibitor is a compound of the formula II



II

wherein

Het_1 is



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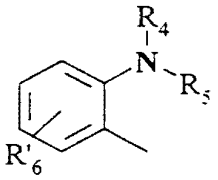
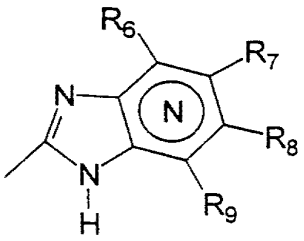
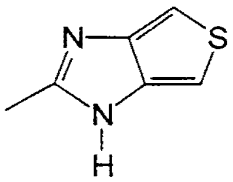


Het_2 is



or



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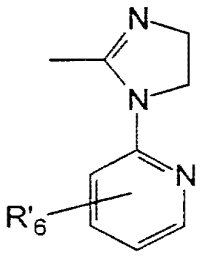
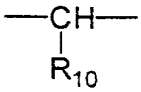
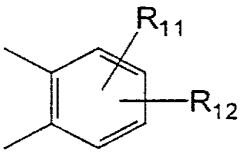


X =



or



wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl, alkyl groups, alkoxy groups and moities thereof , they may be branched or straight C_1 - C_9 - chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

25. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is selected from omeprazole, an alkaline salt thereof, (*S*)-omeprazole and an alkaline salt thereof .

26. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is lansoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

27. A method according to claim 24 wherein the acid susceptible proton pump inhibitor is pantoprazole or a pharmaceutically acceptable salt thereof or an enantiomer or a salt of the enantiomer.

28. A method according to any one of the preceeding claims 17 to 27, wherein the bacterial infection is caused or mediated by *Helicobacter pylori*.

29. A method according to claim 17, wherein the amount of NO-releasing NSAID in each dosage form is 0.5 – 5000 mg.

30. A method according to claim 29, wherein the amount of NO-releasing NSAID is 5 – 1000 mg.

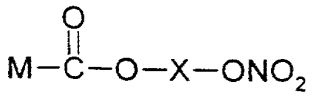
31. A method according to claim 18, wherein the amount of NO-releasing NSAID is 0.5 – 5000 mg and the amount of proton pump inhibitor is 0.1 – 200 mg together in one dosage form or in two separate dosage forms.

32. A method according to claim 31, wherein the amount of NO-releasing NSAID is 5 – 1000 mg and the amount of proton pump inhibitor is 10 – 80 mg.

33. A pharmaceutical formulation suitable for use in the treatment of bacterial infections, comprising a NO-releasing NSAID or a pharmaceutically acceptable salt or an enantiomer thereof as active agent.

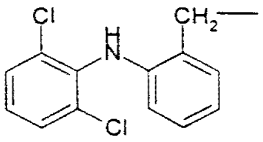
34. A pharmaceutical formulation suitable for use in the treatment of bacterial infections, comprising a NO-releasing NSAID and an acid susceptible proton pump inhibitor or a salt thereof or an enantiomer or a salt of the enantiomer as active agents.

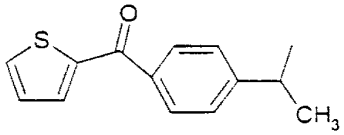
35. A pharmaceutical formulation according to claim 25 or 26 wherein the NO-releasing NSAID is a compound of the formula I

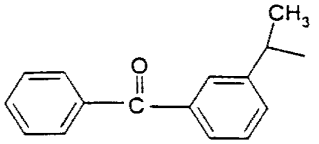


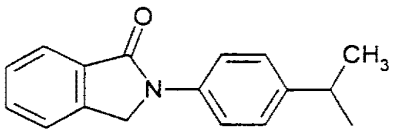
I

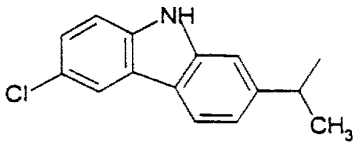
wherein M is selected from

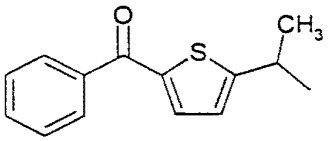


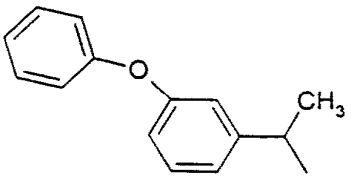


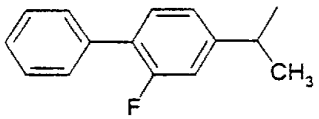


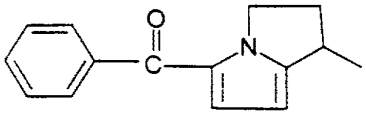


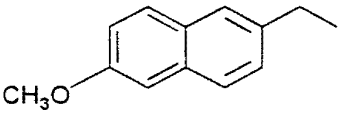


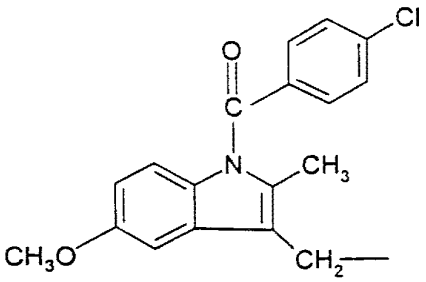


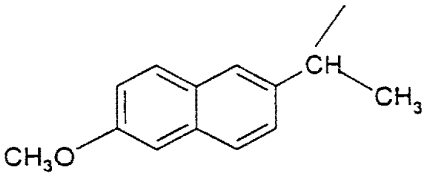


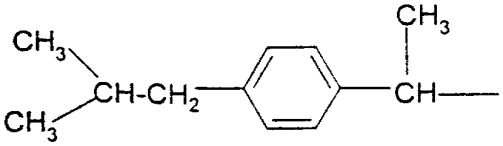












and X is selected from

linear, branched or cyclic -$(CH_2)_n$- wherein n is an integer of from 2 to10;

-$(CH_2)_m$-O-$(CH_2)_p$- wherein m and p are integers of from 2 to 10; and -CH_2-pC_6H_4-CH_2-;

or a pharmaceutically acceptable salt or enantiomer thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01071

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/04, A61K 31/196, A61K 31/33, A61P 1/04, A61P 31/00
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)

IPC7: A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1999:500417, Document no. 131:255524, Yanaka, Akinori: "Role of nitric oxide in the pathogenesis of gastrointestinal deseases"; & Ensho (1999), 19 (3), 129-135 --	1-32
X	Pharmacol Ther, Volume 11, 1997, N.M. DAVIES et al, "NO-naproxen vs. naproxen: ulcerogenic, analgesic and anti-inflammatory effects" page 69 - page 79 --	1-32
X	WO 9967210 A1 (DUKE UNIVERSITY MEDICAL CENTER), 29 December 1999 (29.12.99), see part. page 3, line 18-19, page 15, line 17-20 --	1-32

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"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
18 Sept 2000	20 -09- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/GH Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01071

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9509612 A1 (ENTREMED, INC. ET AL), 13 April 1995 (13.04.95), see part. page 8, line 26, page 9, line 3 and 7	1-32
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X	WO 9404484 A1 (CORLAY S.L. ET AL), 3 March 1994 (03.03.94)	33-35
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X	WO 9509831 A1 (NICOX LIMITED), 13 April 1995 (13.04.95)	33-35
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X	WO 9412463 A1 (HCT-HEALTH CARE TRADING LTD.), 9 June 1994 (09.06.94)	33-35
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X	WO 9530641 A1 (NICOX LIMITED), 16 November 1995 (16.11.95)	33-35
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01/08/00

International application No.
PCT/SE 00/01071

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International application No.
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INTERNATIONAL SEARCH REPORT

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01/08/00

International application No.
PCT/SE 00/01071

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		NO 992469 A	22/07/99

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(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LUNDBERG, Per, Johan** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). **SJÖBLOM, Brita** [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE).

(74) Agent: **ASTRAZENECA AB**; Global Intellectual Property, Patents, S-151 85 Södertälje (SE).

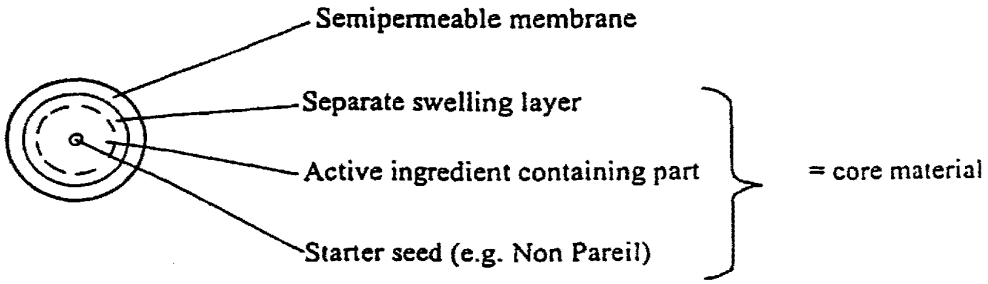
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW FORMULATION



(57) Abstract: An oral dosage form comprising a core material coated with a semipermeable membrane wherein the core material comprises an active ingredient selected from the group of omeprazole, an alkaline salt thereof, *S*-omeprazole and an alkaline salt thereof, in admixture with one or more alkaline additives, one or more swelling agents, and optionally pharmaceutically acceptable excipients, and the dosage form is not enteric coated.

WO 00/78293 A1

NEW FORMULATION

Field of the invention

The present invention relates to new oral pharmaceutical dosage forms comprising as active ingredient omeprazole, an alkaline salt of omeprazole, *S*-omeprazole or an alkaline salt of *S*-omeprazole. The dosage form comprises a core material of the active ingredient, one or more alkaline additives, and one or more swelling agents, wherein the core material is covered with a semipermeable membrane and without an enteric coating. Furthermore, the invention refers to the manufacture of such dosage forms and their use in medicine.

Background of the invention and prior art.

The acid labile H^+, K^+-ATPase inhibitor known under the generic name omeprazole is disclosed in EP-0005129. Certain salts of omeprazole are described in EP-124495, a magnesium salt of omeprazole is described in WO 95/01977, and the single enantiomers of omeprazole and certain salts thereof are described in WO 94/27988.

Omeprazole is useful for inhibiting gastric acid secretion in mammals including man by controlling gastric acid secretion at the final step of the acid secretory pathway and thus reduce basal and stimulated gastric acid secretion irrespective of stimulus. In a more general sense, omeprazole may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcer, duodenal ulcer and Zollinger-Ellison syndrome. Furthermore, it may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with Non Ulcer Dyspepsia, and in patients with symptomatic gastro-oesophageal reflux disease (GORD). Omeprazole may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and post-operatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, it may be useful in the treatment of psoriasis

as well as in the treatment of *Helicobacter* infections and diseases related to these where therapeutic control of gastric acid secretion is fundamental in the treatment.

Omeprazole is, however, susceptible to degradation or transformation in acidic and neutral media. The stability of omeprazole is also affected by moisture, heat, organic solvents and to some degree by light. With respect to the stability properties of omeprazole, it is established that an oral solid dosage form must be protected from contact with the acidic gastric juice and that omeprazole must be transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption can occur.

A pharmaceutical dosage form of omeprazole is best protected from contact with acidic gastric juice by an enteric coating layer. For instance, US 4,786,505 describes such enteric coated formulations. These formulations have a core comprising an alkaline salt of the drug or a core comprising the drug together with an alkaline reacting compound, the core is coated with a water soluble or in water rapidly disintegrating separating layer and further with an enteric coating layer. There are numerous published patent applications from different companies describing enteric coated formulations comprising omeprazole or other proton pump inhibitor compounds.

WO 96/01623 describes tableted dosage forms of omeprazole, wherein enteric coating layered pellets are compressed into a multiple unit tableted dosage form. It is essential in these tableted formulations that the enteric coating layer can withstand the compression forces.

There are different technologies and pharmaceutical formulations described in the prior art which provide a delayed release of an administered drug. Such formulations are for instance based on osmotic differences, slow-eroding/dissolving layers, diffusion through a membrane, time controlled explosion systems or any combinations thereof. In the following some of these principles are exemplified. For instance, US 4 871 549 describes a time controlled explosion system. Conte et al (Drug Development and Industrial

Pharmacy, 1989, vol. 15, pp. 2583 –96) describes a three-layer tablet giving a double pulsed system suitable for ibuprofen. US 5 567 441 describes a dosage form for diltiazem comprising a mixture of one fraction of slow release pellets and another fraction of delayed pulse release membrane coated pellets. WO97/02020 describes a dosage form of pantoprazole in combination with antibacterial substances wherein one part of the pantoprazole dose is in slow release form with a continuously release during time. US 5 178 867 describes a dosage form with an exit port or hole that connects the interior of the dosage form with the exterior.

Summary of the invention

The present invention provides - in contrast to earlier presented oral dosage forms for proton pump inhibitor compounds - a dosage form without an enteric coating layer.

The dosage form according to the present invention comprises a core material coated with a semipermeable membrane. The core material contains an active ingredient selected from omeprazole, an alkaline salt thereof, *S*-omeprazole or an alkaline salt thereof, one or more alkaline additives, and one or more swelling agents. The semipermeable membrane is able to disrupt or may change its permeability after a pre-determinated time. One or more swelling agents are placed in the core material to effectuate a disruption or an increased permeability of the semipermeable membrane after such a suitable time. Optionally pharmaceutically acceptable excipients such as an osmotic agent may also be included in the core material.

Surprisingly, the formulation according to the present invention is prepared without an enteric coating, which previously have been almost an axiom for dosage forms containing omeprazole or any other proton pump inhibitor compounds. The present invention also provides the possibility to avoid the separating layer needed under an enteric coating layer to separate omeprazole from the enteric coating polymer. Omeprazole should preferably not be in contact with the enteric coating due to discoloration and degradation of

omeprazole. Thus, the present invention provides a simplified process than previous manufacture processes requesting double coating layers on the core material. See for instance, EP 247 983.

According to a further aspect of the present invention, the dosage form may preferably be in the form of a multiple unit pellet system. The prepared core material, in the form of small pellets coated with a semipermeable membrane and without an enteric coating may be filled into a capsule or compressed into a multiple unit tablet.

The core material comprises an alkalizing agent, that is sufficiently alkaline and is present in a sufficiently high amount. The core material also comprises a swelling agent that upon contact with moisture starts to swell. When the coated pellets pass the stomach small amounts of gastric fluid will be absorbed through the semipermeable membrane. The alkalizing agent in the core material will neutralize the absorbed acidic fluid and protect the active ingredient against degradation. At the same time the swelling agent, will be exposed to the penetrating fluid or moisture, and it will start to expand. After a pre-determined time interval this expansion leads to disruption of the superimposed semipermeable membrane by the built-up pressure or to a swelling that will increase the permeability of the membrane. The time interval is to be determined so that the pellets have had time to pass the stomach at that very moment, and have reached the small intestines. The entire dose of the active ingredient will then start to be released into the small intestine where absorption can occur.

Detailed description of the drawings

Figures 1 – 4 illustrate principles for construction of dosage forms according to the present invention. The invention comprises a core material layered with a semipermeable membrane. The core material can be prepared according to at least four different principles as shown in the Figures. The drawings are not intended to illustrate the size or relative sizes of the dosage form or its different parts.

Detailed description of the invention

The present invention provides a core material in the form of pellets or small tablets coated with a semipermeable membrane. The composition of the core material protect the active ingredient against the gastric fluid, that permeates through the semi permeable coating during the pellet's passage through the stomach. Such pellet formulations are generally emptied from the stomach within 2-4 hours. When the pellets have left the stomach, the semipermeable membrane covering the individual pellets disrupts and/or starts to release the active ingredient in the small intestine.

The pellets coated with the semipermeable membrane may be filled into capsules prepared from gelatine or hydroxypropyl methylcellulose (HPMC), be filled into sachets or be mixed with tablet excipients and compressed to a fast disintegrating tablet or to an effervescent tablet.

Core material

The core material may be produced with starter seeds, for instance sugar spheres like Non-pareils™, by layering the active ingredient on the seeds by conventional technique or by the use of a centrifugal granulator/ roto granulator. Alternatively, the core material has a homogenous distribution of the active agent and excipients, and is prepared e.g. by extrusion and spheronization, or by compression. Other conventional techniques known in the art are also suitable in preparing the core material.

The core material is in the form of pellets, spheroids or small tablets. The size of the formulated core materials is approximately between 0.1 and 4 mm, and preferably the core material has a diameter of 0.2 to 2.5 mm.

The core material comprises the active ingredient, an alkalizing agent, a swelling agent and optionally binders, osmotic agents and other pharmaceutically acceptable excipients.

The active ingredient is selected from the group consisting of omeprazole, an alkaline salt thereof, *S*-omeprazole or an alkaline salt thereof. Suitable alkaline salts are for instance the Mg^{2+}, Ca^{2+}, Na^{+}, K^{+} salts, preferably the Mg^{2+} salts in a highly crystalline form. A preferred magnesium salt of omeprazole having a crystallinity of more than 70% determined by X-ray powder diffration is described in WO95/01977, hereby incorporated by references.

Before the seeds are layered, the active ingredient may be mixed with further components to obtain preferred handling and processing properties and a suitable concentration of the active ingredient in the final mixture.

Such further components can be binders, surfactants, fillers or other pharmaceutically acceptable ingredients, alone or in mixtures. The binders are for example cellulose derivatives such as hydroxypropyl methylcellulose, methylcellulose, hydroxypropyl cellulose and carboxymethyl-cellulose sodium, and others such as polyvinyl pyrrolidone, gelatine, sugars, starches or other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic surfactants, such as polysorbate 80, or ionic surfactants such as for instance sodium lauryl sulphate.

An alkalizing agent is incorporated in the core material together with the active ingredient and/or the swelling agent, preferably together with the active ingredient. The alkalizing agent is present in an amount of approximately 5 to 35 % w/w in the core material, preferably 10 to 35 % w/w, or most preferably 15 to 35 % by weight calculated on the weight of the core material excluding the weight of the optional starter seed.

The alkalizing agent is selected from compounds like disodium hydrogen phosphate, trisodium phosphate, arginine or talc etc, provided that they give a pH of not less than 8.5 when measured in a 2% w/w water solution/dispersion with a pH-measuring electrode. At least one alkalizing agent has to be incorporated in the core material, but also any combinations of alkalizing agents can be used.

The swelling agent is selected among pharmaceutically acceptable disintegrants, preferably among crosslinked polyvinyl pyrrolidone, crosslinked sodium carboxymethylcellulose, sodium starch glycolate or low-substituted hydroxypropyl cellulose (L-HPC), alone or in any combinations. The amount of swelling agent is pre-determined to effectuate the start of dissolution of the core material at a proper time. Preferably, the core material comprises approximately 20 to 60 % by weight of the swelling agent calculated on the weight of the core material excluding any optional starting seed. More preferably a concentration of 25 to 55 % by weight, or especially 30 to 50 % by weight of the swelling agent calculated in the same manner.

Alternatively, the swelling agent or a portion of the swelling agent may optionally be prepared and incorporated in a separate layer. Such a separate layer will cover the core material and also comprise binders and optionally an alkalizing agent and/or pharmacetically acceptable excipients.

Optionally, an osmotic agent is incorporated in the core material. Such an osmotic agent is watersoluble and will provide an osmotic pressure in the tablet. Examples of osmotic agents are magnesium sulphate, sodium chloride, lithium chloride, potassium chloride, potassium sulphate, sodium carbonate, lithium sulphate, calcium bicarbonate, sodium sulphate, calcium lactate, urea, magnesium succinate, sucrose or mixtures thereof.

Alternatively, the active ingredient, optionally mixed with any of the components defined above, can be formulated into a core material. Said core material may be produced by extrusion/spheronization, balling or compression utilizing different process equipments.

For extrusion/spheronization processes incorporation of a microcrystalline cellulose and a low-substituted hydroxypropylcellulose in the core material is preferred.

Semipermeable membrane.

The membrane comprises a water insoluble polymer and a modifying additive and optionally pharmaceutically acceptable excipients like fillers, colorants etc. The excipients should be insoluble or hardly soluble in acidic solutions, or present in such amounts that they do not influence the solubility properties of the membrane.

Preferably, water insoluble polymer may be selected among semipermeable water insoluble polymers like ethylcellulose, cellulose acetate, polyvinyl acetate, and ammonio methacrylate copolymer type A and type B (Eudragit RL, Eudragit RS) etc.

The modifying agent in the semipermeable membrane may be a talc or fumed silica (e.g. Aerosil or Cab-O-Sil.). Preferably an alkaline reacting modifying agent such as talc is used.

Preferred composition of the semipermeable membrane comprises an amount of modifying agent to water insoluble polymer on a weight to weight ratio of from 90:10 up to 50:50. Preferably the amount of modifying agent to water insoluble polymer on a weight to weight ratio is from 80:20 up to 60:40 in the membrane.

The core material will be layered with a sufficient amount of the semipermeable membrane composition to cover the core material. Preferably, the amount of semipermeable membrane applied is approximately 3-30% by weight of the weight of the core material. The amount of semipermeable membrane for a desired dosage form is adjusted to obtain a desired lagtime and an adequate dissolution.

Final dosage form

The prepared core material coated with the semipermeable membrane is filled into a capsule (gelatine or HPMC capsule), or optionally mixed with tablet excipients and compressed into a multiple unit tableted dosage form. In the expression "tablet excipients" is also effervescent tablet excipients included when referring to multiple unit tablets. Prepared tablets are optionally covered with filmforming agent(s) to obtain a smooth surface of the tablet and/or to further enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

The claimed dosage forms are suitable for oral administration. The dose will depend on the nature and severity of the disease to be treated. The dose may also vary according to the age, body weight, and response of the individual patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. In the treatment of severe conditions higher doses than average may be used.

Preferably, a dosage form comprising for instance 1 - 100 mg of omeprazole or S-omeprazole will be administered once a day. Suitable doses comprise preferably 10 - 80 mg. The dosage form may be administered together with other suitable drugs, such as antibacterial compound(s), NSAID(s), motility stimulating agents, and/or antacids.

Examples

The following examples describe the invention more in detail without restricting the scope of the invention.

Example 1

Core materials in the form of pellets made by extrusion and spheronization.

The following compositions were used to prepare core materials;

	Pellets A		Pellets B		Pellets C	
Compound	Amount (g)	% of dry pellets	Amount (g)	% of dry pellets	Amount (g)	% of dry pellets
Omeprazole	40.0		40.0		40.0	
Low-substituted Hydroxypropyl cellulose	82.0	20.6	-	-	84.0	21.0
Polyvinyl pyrrolidone crosslinked micronized	-	-	84.0	21.0	-	-
Microcrystalline cellulose PH 101	58.0		60.2		78.4	
Mannitol powder	136.0		115.0		136.5	
Sodium chloride (<0.20 mm)	60.0		20.0		40.3	
Trisodium phosphate*	20.0	4.8	-	-	-	-
Disodium hydrogen phosphate*	-	-	-	-	20.0	5.0
Arginine	-	-	80.0	20.0	-	-
Sodium lauryl sulphate	2.0		0.8		0.8	
Water purified	170	-	151	-	199	-
Total weight of dry subst.	418		400		400	

* In this example the amounts for all phosphates are indicated as free of crystal water.

The powders were mixed and then wetted with the granulating solution. When needed extra water was added afterwards, until total amount added water corresponded to the value given in the table above. The wet mass was subjected for extrusion through a screen having 1.0 mm in diameter apertures. The strings obtained were shaped to pellets in a

spheronizer operated at 350 rpm. The pellets were dried in a fluid bed apparatus with inlet air temperature set to 50 degrees Celsius.

Granulating liquid used for composition A was 2.72 g of the trisodium phosphate and all the sodium lauryl sulphate dissolved in 50 grams of the water.

Granulating liquid used for composition B was 10.0 g of the arginine and all the sodium lauryl sulphate dissolved in 100 grams of the water.

Granulating liquid used for composition C was 8.06 g of the disodium hydrogen phosphate and all the sodium lauryl sulphate dissolved in 100 grams of the water.

Remark: Only parts of composition B were possible to get through the extruder, however material for further experimentation was obtained.

Example 2

Core material in the form of pellets prepared by layering technique.

A drug containing suspension was made according to the composition below;

Compound	Amount
Omeprazole	219 g
HPMC, 6 cps	39.8 g
Disodiumhydrogen phosphate	42.9 g
Polysorbate 80	4.8 g
Purified water	919 g

First the polysorbate 80 was dissolved in the water. Then the phosphate was dissolved during stirring. Then the HPMC was dissolved whereafter the drug was suspended in the obtained solution. The suspension was sprayed onto 150 g of sugar spheres (Non-pareil) in

a fluidized bed. The weight of the obtained product was 355 g and the omeprazole content was 456 mg/g.

A suspension containing swellable substance was prepared according to the following composition;

		%
Cross-linked polyvinyl pyrrolidone micronized (Kollidon CL-M)	187.8 g	41*
Hydroxypropylcellulose L (HPC-L from Nisso)	46.9 g	
Talc	140.8 g	
EtOH (99.5%)	1500 g	

* % w/w of core material not including starter seed.

HPC-L was dissolved in ethanol during stirring, then the talc and swelling agent Kollidon CL-M was added. The suspension was sprayed onto 130 g of the drug-layered spheres as prepared above in a Wurster equipped fluidized bed until the omeprazole content of the obtained core material was 130 mg/g. The weight of the obtained product was 455 g.

Example 3

Membrane coated pellets.

The core material from Example 2 was coated in a fluid bed apparatus with an ethyl cellulose solution having talc suspended therein. The composition of the suspension used was:

Substance	Amount	% of dry membrane
Ethyl cellulose N-10	13.5 parts	30%
Ethanol (99.5%)	1455 parts	-
Talc	31.5 parts	70%
Total	1500 parts	100%

80 grams of core material from example 2 was coated with this suspension until the omeprazole content was 107 mg/g.

Example 4

Test of the prepared membrane coated pellets.

The prepared membrane coated core material was tested for gastric acid resistance and dissolution as described below.

Test for gastric acid resistance

The pellets were tested for gastric acid resistance by immersing them in 0.1 M HCl for 2 hrs and the determining the remaining drug fraction. The fluid phase (the HCl) had an addition of 0.1 g/liter of sodium lauryl sulphate as wetting agent. The remaining drug fraction was 96%.

Test for dissolution

Dissolution of active substance was tested accordingly, first pellets were immersed in the test-fluid described above for 2 hrs, then buffer components (phosphate salts) were added to change the pH to 6.8.

Samples of the dissolution medium were withdrawn and analyzed with HPLC at the given time intervals. Results;

Time , Hrs (after 2hrs of pre-exposure in acid medium)	% Dissolved
0.5	3
1	18
2	60
3	73

Claims

1. An oral dosage form comprising a core material coated with a semipermeable membrane wherein the core material comprises an active ingredient selected from the group of omeprazole, an alkaline salt thereof, *S*-omeprazole and an alkaline salt thereof, in admixture with one or more alkaline additives, one or more swelling agents, and optionally pharmaceutically acceptable excipients, and the dosage form is not enteric coated

2. A dosage form according to claim 1 wherein the semipermeable membrane is able to disrupt.

3. A dosage form according to claim 1 wherein the active ingredient is omeprazole.

4. A dosage form according to claim 1 wherein the active ingredient is a magnesium salt of omeprazole having a crystallinity of more than 70% determined by X-ray powder diffration.

5. A dosage form according to claim 1 wherein the active ingredient is magnesium salt of *S*-omeprazole.

6. A dosage form according to claim 1 wherein the core material comprises a sugar sphere layered with a suspension or solution of the active ingredient, one or more alkaline additives, one or more swelling agents and optionally pharmaceutically acceptable excipients.

7. A dosage form according to claim 1 wherein the dosage form comprises individual pellets of the core material coated with the semipermeable membrane.

8. A dosage form according to claim 1 wherein the core material comprises a further component in the form of an osmotic agent.

9. A dosage form according to claim 1 wherein the alkaline additive is an agent selected from the group of compounds that give a pH of not less than 8.5 when measured in a 2% w/w water solution/dispersion with a pH-measuring electrode.

10. A dosage form according to claim 9 wherein the alkaline additive is an agent selected from the group of disodium hydrogen phoshate, trisodium phosphate, arginine and talc.

11. A dosage form according to claim 1 wherein the alkaline additive is present in an amount of approximately 5 to 35 % by weight of the core material excluding the weight of an optional sugar sphere.

12. A dosage form according to claim 1 wherein the alkaline additive is present in an amount of 15 to 35 % by weight of the core material excluding the weight of an optional sugar sphere.

13. A dosage form according to claim 1 wherein the swelling agent is selected from the group of crossliked polyvinyl pyrrolidone, crosslinked sodium carboxymethylcellulose, sodium starch glycolate and low-substituted hydroxypropyl cellulose (L-HPC).

14. A dosage form according to claim 1 wherein the swelling agent is present in an amount of approximately 20 to 60 % by weight of the core material excluding the weight of an optional sugar sphere.

15. A dosage form according to claim 1 wherein the swelling agent is present in an amount of 30 to 50 % by weight of the core material excluding the weight of an optional sugar sphere.

16. A dosage form according to claim 1 wherein the semipermeable membrane comprises a water insoluble polymer and a modifying agent such as talc or fumed silica.

17. A dosage form according to claim 1 wherein the water insoluble polymer is selected from the group of ethylcellulose, cellulose acetate, polyvinyl acetate, and ammonio methacrylate copolymer type A and type B.

18. A dosage form according to claim 1 wherein the water insoluble polymer is present in an amount of approximately 3-30% by weight of the core material.

19. A dosage form according to claim 1 wherein the semipermeable membrane comprises a modifying agent and a water insoluble polymer in a ratio of between 90:10 and 50:50.

20. A process for the manufacture of a dosage form as defined in claim 1, wherein a core material is formed comprises an active ingredient selected from the group of omeprazole, an alkaline salt thereof, *S*-omeprazole and an alkaline salt thereof, in admixture with one or more alkaline additives, one or more swelling agents, and optionally pharmaceutically acceptable excipients, the core material is coated with a semipermeable membrane and has no enteric coating.

21. Use of an oral pharmaceutical dosage form as defined in any of claims 1 - 19 in the manufacture of a medicament with improved inhibition of gastric acid secretion.

22. Use of an oral pharmaceutical dosage form as defined in any of claims 1 - 19 in the manufacture of a medicament with improved therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion.

23. A method for improving inhibition of gastric acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical dosage form as defined in any of claims 1 - 19.

24. A method for improving the therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical dosage form as defined in any of claims 1 - 19.

Fig. 1

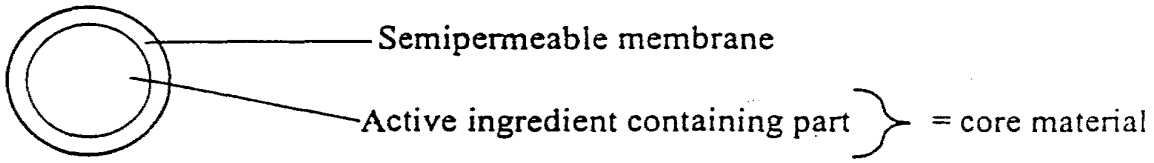


Fig. 2

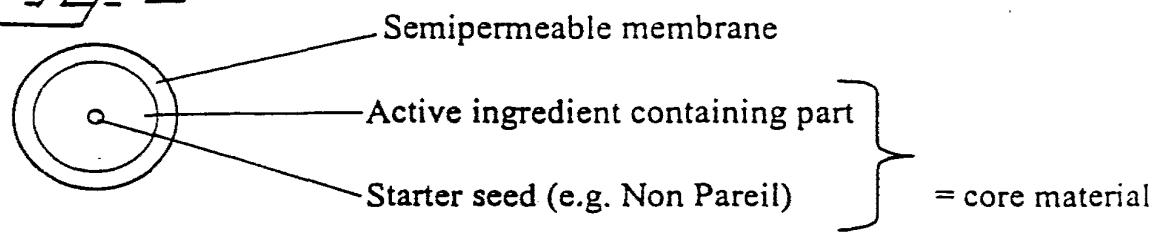


Fig. 3

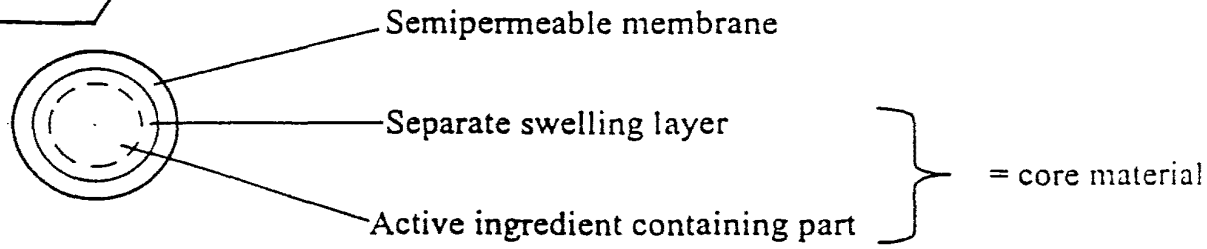
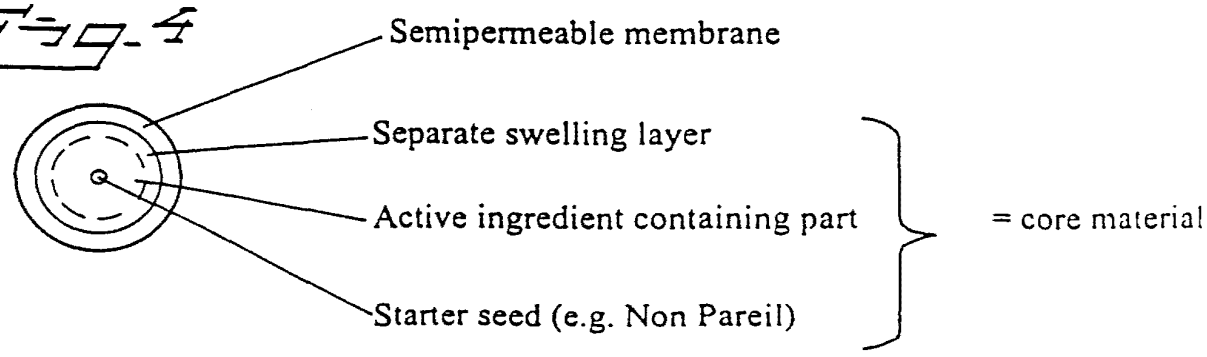


Fig. 4



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01310

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/36, A61P 1/04
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)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 0009092 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 24 February 2000 (24.02.00)	1-24
X	EP 0237200 A2 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 16 Sept 1987 (16.09.87), page 8, line 1 - page 9, line 8	1-24
Y	WO 9725979 A1 (PERIO PRIDUCTS LTD.), 24 July 1997 (24.07.97), page 10 - page 11	1-24
Y	WO 9819668 A1 (SHARMATED, INC.), 14 May 1998 (14.05.98), page 5, line 9 - page 6, line 25	1-24

[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" erlier 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
13 October 2000	18 -10- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Hampus Rystedt/GH Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01310

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9501783 A1 (ASTRA AKTIEBOLAG), 19 January 1995 (19.01.95)	1-24

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INTERNATIONAL SEARCH REPORT

Int ional application No.
PCT/SE00/01310

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 23,24
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 23 and 24 relate to methods for treatment of the human body, a search has been carried out. The search has been based on the alleged effects of the claimed composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 00/01310

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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EP 0237200 A2	16/09/87	SE 0237200 T3	
		BG 61202 B	28/02/97
		CA 1327010 A	15/02/94
		CA 1338377 A	11/06/96
		CA 1338399 A	18/06/96
		DE 3750431 D,T	22/12/94
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		DE 3780045 A,T	06/08/92
		EP 0423748 A,B	24/04/91
		SE 0423748 T3	
		EP 0446961 A,B	18/09/91
		SE 0446961 T3	
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		HK 1002021 A	00/00/00
		JP 1893359 C	26/12/94
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		EP 0941074 A	15/09/99
		NO 992186 A	05/05/99
		ZA 9709937 A	18/05/99

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 00/01310

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9501783 A1	19/01/95	AU 681686 B	04/09/97
		AU 7198294 A	06/02/95
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		SK 2196 A	09/04/97
		US 5690960 A	25/11/97
		ZA 9404934 A	20/02/95

Electronic Acknowledgement Receipt

EFS ID:	13603656
Application Number:	12822612
International Application Number:	
Confirmation Number:	6136
Title of Invention:	Method for Treating a Patient at Risk for Developing an NSAID-associated Ulcer
First Named Inventor/Applicant Name:	Brian Ault
Customer Number:	22466
Filer:	David Michael Gryte/Elizabeth Ashton
Filer Authorized By:	David Michael Gryte
Attorney Docket Number:	103786-1 US/NS
Receipt Date:	28-AUG-2012
Filing Date:	24-JUN-2010
Time Stamp:	12:38:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	103786US_SB08A.pdf	620650 1bcc50a22bc5573a22a5f364e492bcb949647047	no	20

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	103786US_SB08A_2.pdf	618386 bf29960ef0438c34ad077cd3acc2fcbdb0bc5c04	no	14
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(Not for submission under 37 CFR 1.99)

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

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	1	Panara et al., "Effects of the novel anti-inflammatory compounds, N-[2-(cyclohexyloxy)-4-nitrophenyl] methanesulphonamide (NS-398) and 5-methanesulphonamido-6-(2,4-difluorothio-phenyl)-1-inda none (L-745,337), on the cyclo-oxygenase activity of human blood prostaglandin endoperoxide synthases," British Journal of Pharmacology, 116, pp. 2429-2434 (1995)	☐
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	12	Roth, et al., "Cimetidine Therapy in Nonsteroidal Anti-inflammatory Drug Gastropathy: Double-blind Long-term Evaluation," Arch. Intern. Med., 147, pp. 1798-1801 (1987)	☐
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	23	Sharma et al., "Comparison of 24-hour intragastric pH using four liquid formulations of lansoprazole and omeprazole," Am. J. Health-Syst. Pharm., 56, Supp. 4, pp. S18-S21 (1999)	☐
	24	Silverman, The Organic Chemistry of Drug Design and Drug Action, 2nd Edition, Academic Press, pp. 102 & 527 (2004)	☐
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	34	Wagner et al., "Effects of nonsteroidal anti-inflammatory drugs on ulcerogenesis and gastric secretion in pylorus-ligated rat," Digestive Diseases and Sciences, Vol. 40, pgs. 134-140 (1995)	☐
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	38	Weil et al., "Prophylactic aspirin and risk of peptic ulcer bleeding," Br. Med. J., 310, pp. 827-830 (1995)	☐
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	3	200056339	WO		2000-09-28	Pharma-Science Inc.		☐
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	11	2003017980	WO		2003-03-06	Takeda Chemical Industries, Ltd.		☐
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(54) Title: NOVEL PHARMACEUTICAL COMPOSITIONS

(57) Abstract: Novel pharmaceutical compositions are provided, in particular oral formulations for once a day administration of a drug/medicament and to novel solid dose units for incorporation therein are provided. The solid dose units provide a phased release of drug to target or prolong the pharmaceutical effect. The compositions are particularly useful for multiphase delivery of proton pump inhibitors such as lansoprazole, pantoprazole, omeprazole, perprazole, etc.

NOVEL PHARMACEUTICAL COMPOSITIONS

The present invention relates to novel pharmaceutical compositions such as oral formulations for once a day administration of a drug/medicament and to novel solid dose units for incorporation therein. The solid dose units provide a phased release of drug to target or prolong the pharmaceutical effect. The compositions are particularly useful for multiphase delivery of proton pump inhibitors such as lansoprazole, pantoprazole, omeprazole, perprazole, etc.

The treatment of certain medical conditions requires an effect to be achieved over a 24 hour period, e.g. in conditions such as duodenal ulcers, peptic ulcers and reflux oesophagitis there is a need to control gastric pH. Similarly in the treatment of rheumatoid arthritis there is a need to control pain and ease mobility difficulties and in the treatment of patients with high blood pressure there is a need to control blood pressure. Immediate release dosing regimes often result in periods during the day where the desired effect is not achieved and so such conditions are often treated with multiple doses of drug each day, but this is inconvenient and can lead to reduced patient compliance. These conditions are often treated with sustained release formulations but if there is not a constant requirement for the drug during the 24 hour period this can lead to the use of more drug than necessary. Frequently there is not a constant requirement for the drug, i.e. when an initial dose of the drug is capable of achieving the desired effect and it is only as this effect begins to diminish that further drug is required. Another example is when symptoms may only occur intermittently, perhaps at particular times of the day, e.g. during the night or early in the morning.

In the treatment of conditions such as duodenal ulcers, peptic ulcers and reflux oesophagitis with proton pump inhibitors there are benefits in increasing the time that the intragastric pH is maintained above 3.0, preferably above 4.0, in particular there are benefits in maintaining the pH above 3.0, preferably above 4.0, over a 24 hour period. Current immediate release dosing regimes often result in periods during the day where this is not achieved and this may become particularly acute at night where "breakthrough pH" occurs. There is not a constant requirement for the inhibitor because it is postulated that the initial dose inhibits the receptors and it is only when the receptors begin to regenerate that further inhibitor is required. The use of sustained release formulations therefore involves the use of more inhibitor than necessary. It is desirable to

provide pulsed release formulations capable of releasing a second dose of inhibitor when the effects of the first dose begin to diminish.

There is a need for pharmaceutical formulations capable of delivering drug at timed periods during 24 hours when a condition and/or symptom occurs or reoccurs, in particular formulations capable of providing pulsed release of a drug, where the drug is released in at least two pulses, the second pulse releases drug when the effect of the first release is at least partially diminished and, if applicable, any further pulses also release drug when the effects of the previous pulse are at least partially diminished. There is also a need for pharmaceutical formulations capable of providing a single daily dose of a drug affecting gastric pH such as a proton pump inhibitor, in particular formulations capable of maintaining the gastric pH above about above 3.0, preferably above 4.0, for a period of about 24 hours after a single daily dose, e.g. formulations capable of delivering drug at timed periods during 24 hours when an increase in pH is expected.

In the treatment of conditions where symptoms occur at a known period of the day, e.g. during the night, as the patient wakes or as the patient gets out of bed, it is desirable to treat the symptoms in advance so that they can be avoided or at least minimised. Again sustained release formulations can be used, e.g. before the patient goes to bed, but they often result in the use of more drug than required. There is therefore a need for delayed release formulations capable of releasing drug in anticipation of symptoms. A formulation which could be taken at night and which would release the drug the following morning so that its effects are achieved before the patient wakes would be particularly advantageous. The formulation could suitably include multiple doses such that it can be taken to provide immediate relief followed by further relief after a predetermined period of time. One condition which could be treated with such a formulation is rheumatoid arthritis. Patients suffering from rheumatoid arthritis experience difficulty in moving when they wake and so it would be advantageous to provide a formulation which could be taken at night and which would release the drug the following morning so that its effects are achieved before the patient wakes. The formulation could suitably include multiple doses such that it can be taken during the day to provide immediate relief in addition to relief the following morning.

There is a need for delayed release formulations capable of releasing drug after a predetermined delay, preferably being such that the delayed release of the drug coincides with and/or anticipates the occurrence or reoccurrence of the symptom or condition to be treated.

The present invention addresses one or more of the problems discussed above. It has been found that the inclusion of a disintegrant in the core of a solid dose unit, surrounded by an outer semi-permeable membrane comprising a permeable water insoluble polymer and at least 50 % by weight glidant surprisingly provides the desired delay and subsequent release profile. The novel formulation is capable of delaying the release in a largely pH independent manner. After the period of delay, drug release is immediately initiated.

The delay and the subsequent release profile can be manipulated by the selection of the composition and/or thickness of the semi-permeable membrane and/or the composition and/or amount of disintegrant included in the core. The arrangement of the disintegrant in the core can also be adapted to influence the delay and subsequent release profile, e.g. it can be included as a separate outer layer of the core.

A first aspect of the invention provides a solid dose unit for the delayed release of a drug comprising:

a) a core comprising the drug and at least one disintegrant

and b) an outer semi-permeable membrane surrounding the core which comprises a permeable water insoluble polymer and at least 50 % by weight glidant.

The solid dose units may suitably be pellets, mini-tablets, granules, tablets etc. which are well known in the art. The drug may be included in the units by any suitable conventional means, e.g. it may be incorporated in the core material or it may be applied to a seed core as a coat, with or without other constituents which make up the unit. The drug and the disintegrant may be included as separate layers of the core or they may be mixed together in the core.

The units are preferably such that when they are subjected to in-vitro exposure to simulated intestinal fluid minimal drug is released until after at least four

hours exposure and substantially all of the drug is released after 24 hours exposure. Preferred embodiments are those wherein minimal drug is released until after at least six hours in-vitro exposure to simulated intestinal fluid. Further embodiments of the invention are those which provide minimal drug release until after at least 8, 9, 10, 11 and 12 hours in-vitro exposure to simulated intestinal fluid respectively. For each of these embodiments substantially all of the drug is released after 24 hours in-vitro exposure to simulated intestinal fluid, more preferably substantially all of the drug is released after 22 hours in-vitro exposure to simulated intestinal fluid.

The in-vitro dissolution profile may be determined by techniques known in the art, for example using USP apparatus IV at 16 ml/min in 0.5M phosphate buffer pH 6.5, temperature 37°C. The results should vary only a little depending on the method of measurement.

Theoretically one should be able to measure 100% release of the drug after in vitro exposure to simulated intestinal fluid. However, in practice this if often not attainable and no more than, e.g. 85 % of the drug can be measured after even a very long period of time. This is due in part to limitations inherent in the detection equipment, but also to the fact that certain drugs may break down to other chemicals and hence go undetected or a small proportion may take a very long time to release. The point at which "substantially all the drug has been released" is therefore taken to be the point at which no further increase in the amount of drug released is seen, i.e. when minimal further release is seen. All other measurements, i.e. percentages are measured against the total drug included in the formulation.

In another embodiment of the invention less than 10% of the drug is released after four hours in-vitro exposure to simulated intestinal fluid, at least 30% is released after ten hours exposure and at least 70% is released after 24 hours exposure, preferably at least 70% is released after 20 hours exposure. These measurements are cumulative, i.e. the term "is released after" indicates the total amount of released drug that is measured at the stated time, i.e. after 4, 10 or 20 hours in-vitro exposure to simulated intestinal fluid.

In a further embodiment less than 5% of the drug is released after four hours in-vitro exposure to simulated intestinal fluid, at least 35% is released after ten hours exposure and at least 75% is released after is released after 24 hours

exposure, preferably at least 75% is released after 20 hours exposure. In a further embodiment less than 5% of the drug is released after four hours in-vitro exposure to simulated intestinal fluid, at least 40% is released after ten hours exposure and at least 80% is released after 20 hours exposure.

In another embodiment of the invention less than 10% of the drug is released after six hours in-vitro exposure, at least 30% is released after ten hours and at least 70% is released after 24 hours, preferably at least 70% is released after 20 hours. In a further embodiment less than 5% of the drug is released after six hours in-vitro exposure, at least 35% is released after ten hours and at least 75% is released after 20 hours. In a further embodiment less than 5% of the drug is released after six hours in-vitro exposure, at least 40% is released after ten hours and at least 80% is released after 20 hours.

In yet another embodiment of the invention less than 10% of the drug is released after 8 hours in-vitro exposure, at least 30% is released after 12 hours and at least 70% is released after 24 hours, preferably at least 70% is released after 20 hours. In a further embodiment less than 5% of the drug is released after 8 hours in-vitro exposure, at least 35% is released after 12 hours and at least 75% is released after 20 hours. In a further embodiment less than 5% of the drug is released after 8 hours in-vitro exposure, at least 40% is released after ten hours and at least 80% is released after 20 hours.

In yet another embodiment of the invention less than 10% of the drug is released after 10 hours in-vitro exposure, at least 30% is released after 14 hours and at least 70% is released after 24 hours exposure, preferably at least 70% is released after 22 hours. In a further embodiment less than 5% of the drug is released after 10 hours in-vitro exposure, at least 35% is released after 14 hours and at least 75% is released after 22 hours. In a further embodiment less than 5% of the drug is released after 10 hours in-vitro exposure, at least 40% is released after 14 hours and at least 80% is released after 22 hours.

In yet another embodiment of the invention less than 10% of the drug is released after 12 hours in-vitro exposure, at least 30% is released after 16 hours and at least 70% is released after 24 hours. In a further embodiment less than 5% of the drug is released after 12 hours in-vitro exposure, at least 35% is released after 16 hours and at least 75% is released after 24 hours. In a further embodiment less

than 5% of the drug is released after 12 hours in-vitro exposure, at least 40% is released after 16 hours and at least 80% is released after 24 hours.

Suitable disintegrants include croscarmellose sodium, crospovidone, sodium starch glycolate etc. These materials result in swelling and disintegration of the dosage unit.

The semi-permeable membrane comprises a permeable water insoluble polymer and at least 50 % by weight glidant. The weight of the glidant accounts for at least 50% of the total weight of the membrane. The semi-permeable membrane may optionally comprise further components, but preferred embodiments are those wherein the membrane comprises the permeable water insoluble polymer and the glidant only.

The semi-permeable membrane preferably comprises at least 55% glidant, more preferably at least 60% glidant and most preferably at least 65% glidant. Particular embodiments of the invention include a semi-permeable membrane which comprises at least 66 % glidant.

Suitable glidants include talc, silicon dioxide, kaolin, glycerol monostearate, metal stearates such as magnesium stearate, titanium dioxide and starch. preferred glidants are talc, silicon dioxide and kaolin. The most preferred glidant is talc. Pharmaceutical compositions usually comprise less than 30% glidants such as talc, however the function of the glidant in the present invention is completely different from the conventional function, the high level of glidant included in the semi-permeable membrane affects the mechanical and physical properties of the membrane. Suitable polymers include methacrylic acid polymers such as Eudragits, addition polymers such as PVAP, PVP and PVA, cellulose derivatives such as cellulose acetate, ethylcellulose, cellulose acetate succinate, cellulose acetate phthalate, hydroxypropylmethylcellulose and suitable resins such as shellac. Preferred polymers are methacrylic acid derivatives, ethylcellulose and cellulose acetate. The most preferred polymers are methacrylic acid polymers such as Eudragits, particularly Eudragit RS. The membrane preferably lacks a plasticiser.

The semi-permeable membrane is surprisingly capable of resisting pressure from the swelling of the disintegrant material until a critical point at which it ruptures and drug release immediately commences.

The units preferably release the drug in a non-osmotic, largely pH independent manner. The units preferably lack protection from the environment of the stomach, e.g. they lack an enteric coat. The units preferably lack osmotic modifiers.

The units are particularly suitable for the controlled release of proton pump inhibitors, preferably lansoprazole, pantoprazole, omeprazole, perprazole, etc. They may be included in formulations suitable for the treatment of duodenal ulcers, peptic ulcers and reflux oesophagitis. The units are also suitable for the controlled delivery of other drugs, e.g. drugs that are conventionally administered in multiple doses or when timing is important for the reasons discussed above. Drugs which may be included in the units include, e.g. proton pump inhibitors, anti-inflammatories, antihypertensives, antibiotics, hormonal drugs and drugs which are active on the endocrine system. The term proton pump inhibitor when used herein refers not only to the active compounds but also to appropriate prodrugs and derivatives. The term also covers appropriate salts of the compounds, prodrugs and derivatives.

The cores may suitably comprise one or more of the following: a stabiliser such as magnesium carbonate; a binder such as hydroxypropylcellulose LF grade or EXF grade; a disintegrant such as hydroxypropylcellulose (low substituted) 1-hpc 31; a binder or diluent such as sucrose, maize starch; and/or a lubricant such as magnesium stearate.

A second aspect of the invention provides a plurality of solid dose units as described above which collectively exhibit the following in-vitro dissolution profile when subjected to in-vitro exposure to simulated intestinal fluid:

i) after four hours exposure less than 10% of the drug is released

ii) after ten hours exposure at least 30% drug is released

and iii) after 24 hours exposure at least 70% drug is released.

After four hours in-vitro exposure to simulated intestinal fluid less than 10% of the drug is released, preferably less than 7% is released, more preferably less than 5% is released and most preferably less than 2% is released. Preferred embodiments are those wherein after six hours in-vitro exposure to simulated

intestinal fluid less than 10% of the drug is released, preferably less than 7% is released, more preferably less than 5% is released and most preferably less than 2% is released. Further embodiments of the invention are those wherein after at least 8, 9, 10, 11 and 12 hours in-vitro exposure to simulated intestinal fluid respectively less than 10% of the drug is released, preferably less than 7% is released, more preferably less than 5% is released and most preferably less than 2% is released. For each of these embodiments after ten hours in-vitro exposure to simulated intestinal fluid at least 50% of the drug is released, preferably at least 55% is released, more preferably at least 60% is released and most preferably at least 65% is released. For each of these embodiments after 24 hours in-vitro exposure to a simulated intestinal fluid at least 70% of the drug is released, preferably at least 75% is released, more preferably at least 80% is released.

In one embodiment of the invention less than 10% of the drug is released after four hours in-vitro exposure, at least 30% is released after ten hours and at least 70% is released after 20 hours. In a further embodiment less than 5% of the drug is released after four hours in-vitro exposure, at least 35% is released after ten hours and at least 75% is released after 20 hours. In a further embodiment less than 5% of the drug is released after four hours in-vitro exposure, at least 40% is released after ten hours and at least 80% is released after 20 hours.

In another embodiment of the invention less than 10% of the drug is released after six hours in-vitro exposure, at least 30% is released after ten hours and at least 70% is released after 20 hours. In a further embodiment less than 5% of the drug is released after six hours in-vitro exposure, at least 35% is released after ten hours and at least 75% is released after 20 hours. In a further embodiment less than 5% of the drug is released after six hours in-vitro exposure, at least 40% is released after ten hours and at least 80% is released after 20 hours.

In yet another embodiment of the invention less than 10% of the drug is released after 8 hours in-vitro exposure, at least 30% is released after 12 hours and at least 70% is released after 20 hours. In a further embodiment less than 5% of the drug is released after 8 hours in-vitro exposure, at least 35% is released after 12 hours and at least 75% is released after 20 hours. In a further embodiment less than 5% of the drug is released after 8 hours in-vitro exposure, at least 40% is released after ten hours and at least 80% is released after 20 hours.

In yet another embodiment of the invention less than 10% of the drug is released after 10 hours in-vitro exposure, at least 30% is released after 14 hours and at least 70% is released after 22 hours. In a further embodiment less than 5% of the drug is released after 10 hours in-vitro exposure, at least 35% is released after 14 hours and at least 75% is released after 22 hours. In a further embodiment less than 5% of the drug is released after 10 hours in-vitro exposure, at least 40% is released after 14 hours and at least 80% is released after 22 hours.

In yet another embodiment of the invention less than 10% of the drug is released after 12 hours in-vitro exposure, at least 30% is released after 16 hours and at least 70% is released after 24 hours. In a further embodiment less than 5% of the drug is released after 12 hours in-vitro exposure, at least 35% is released after 16 hours and at least 75% is released after 24 hours. In a further embodiment less than 5% of the drug is released after 12 hours in-vitro exposure, at least 40% is released after 16 hours and at least 80% is released after 24 hours.

A third aspect of the invention provides an oral formulation for the controlled release of a drug which comprises solid dose units as described above. These include oral formulations for the controlled release of a drug which comprises a first population of solid dose units comprising the drug and a second population of solid dose units comprising the drug wherein the first population comprises units which exhibit the following in-vitro dissolution profile when subjected to in-vitro exposure to simulated intestinal fluid:

i) after two hours exposure at least 60% of the total drug included in the first population is released

and ii) after three hours exposure at least 80% of the total drug included in the first population is released

and the second population comprises units as described above.

The units of the first population are preferably such that after two hours in-vitro exposure to simulated intestinal fluid at least 65% of the total drug included in the first population is released, more preferably at least 70% is released, most preferably at least 75% is released. The units of the first population are preferably such that after three hours in-vitro exposure to simulated intestinal fluid at least 80% of the total proton pump drug included in the first population

is released, more preferably at least 85% is released, most preferably at least 90% is released.

The units of the invention may be included in any suitable oral formulation, e.g. tablets, capsules and microcapsules. Other examples will be apparent to a person of skill in the art, as will suitable excipients and for inclusion in the formulations.

The units of the first population preferably release the drug when the formulation or the units pass from the stomach into the intestine as a result of the change in pH. This may be achieved by known means, e.g. by coating the units with an enteric coat. The change in pH when the environment of the duodenum is reached causes the enteric coat to dissolve and release the drug. Suitable materials from which enteric coats may be prepared are well known in the art, e.g. cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, Preferred materials are Eudragit S100, Eudragit L 100, Eudragit L 100.55 and Eudragit L30D-55, most preferably Eudragit L30D-55.

The formulations are suitable for the multiphase delivery of proton pump inhibitors, preferably lansoprazole, pantoprazole, omeprazole or perprazole. These formulations are suitable for the treatment of duodenal ulcers, peptic ulcers and reflux oesophagitis. The formulations are also suitable for the phased delivery of other drugs, e.g. drugs that are conventionally administered in multiple doses or at as sustained release formulations for the reasons discussed above. Drugs which may be included in the formulations include, e.g. proton pump inhibitors, anti-inflammatories, antihypertensives, antibiotics, hormonal drugs and drugs which are active on the endocrine system. The drug included in the first and second populations of units may be different or identical. Preferred formulations are those in which the drug included in the first and second populations of units are identical. The amount of drug included in the first and second populations of units may be different or identical.

The units may suitably be incorporated in a delivery system which provides multiphased delivery of a drug, i.e. which provides at least two phases of delivery from a single dosage formulation. Further phases of delivery can be provided by including further populations of solid dose units adapted to deliver drug after a different period of delay. The time interval between phases can be manipulated by the selection of the composition of the units, i.e. the selection of

the composition and/or thickness of the semi-permeable membrane and/or the composition and/or amount of disintegrant included in the core and/or the arrangement of the disintegrant in the core of each population.

The formulations are preferably suitable for once daily administration. They are preferably suitable for controlling gastric pH over a 24 hour period. Particularly preferred formulations are those capable of controlling gastric pH over a 24 hour period so as to prevent the pH falling below 4.0 over this period.

The present invention also provides a composition comprising a permeable water insoluble polymer and at least 50 % by weight of glidant which is suitable in the preparation of the solid dose units described above. The composition more preferably comprises at least 55% by weight glidant, even more preferably at least 60% glidant and most preferably at least 65% by weight glidant. Particular embodiments of the invention include at least 66 % by weight glidant. Preferred glidant materials include talc, silicon dioxide, kaolin, glycerol monostearate, magnesium stearate and other metal stearates, the most preferred glidant is talc. The polymer may suitably be a methacrylic acid polymers, e.g. a Eudragit.

The present invention still further provides a method for the preparation of the solid dose units described above which comprises coating a core comprising a drug and a disintegrant with a composition comprising a permeable water insoluble polymer and at least 50 % by weight glidant. The present invention also provides a method for the preparation of the oral formulations described above which comprises bringing solid dose units as described above into association with suitable components to provide a pellet, mini-tablet, granule or tablet.

The present invention will now be exemplified with reference to the following Examples, by way of illustration only.

FIGURES

Figure 1. is a graph showing the in-vitro release profile of the type A lansoprazole pellets of Example 1 in pH 6.5 phosphate buffer.

Figure 2. is a graph showing the in-vitro release profile of the type B lansoprazole pellets of Example 1 in pH 6.5 phosphate buffer.

Figure 3. is a graph showing the in-vitro release profile of lansoprazole formulations A and B of Example 2 in pH 6.5 phosphate buffer.

Figure 4. is a graph showing the in-vivo release profile of lansoprazole formulations A and B of Example 2.

Figure 5. is a graph showing the in-vitro release profile of a single lansoprazole minitablet of Example 3 in pH 6.5 phosphate buffer.

Example 1: Preparation of pellets containing lansoprazole

Sugar spheres were loaded onto a Glatt granulator and were sprayed with a binder solution of hydroxypropylcellulose in isopropylalcohol. At the same time a powder blend of hydroxypropylcellulose (low sub), magnesium carbonate, lansoprazole, sucrose and corn starch was added to provide drug containing cores having the following composition:

	w/w
Sugar spheres	30.6 %
HPC	1.8 %
Lansoprazole	17.7 %
Magnesium carbonate	13.2 %
Hydroxypropyl cellulose (low sub)	8.3 %
Sucrose	17.7 %
Corn Starch	10.6 %

The resulting drug containing cores were sieved and returned to the rotor. A suspension of hydroxypropylcellulose in isopropylalcohol and croscarmellose sodium and was sprayed onto the cores to provide disintegrant layered cores having the following composition:

	w/w
Croscarmellose sodium	22.9 %
Hydroxypropyl cellulose	5.7 %
Drug containing core	71.4 %

The disintegrant coated cores were sieved and placed in a fluidisation chamber operating in a Würster mode. A polymer coat consisting of Eudragit RS and suspended talc was sprayed onto the cores continuously to provide pellets having the following compositions:

Type A	w/w
Eudragit RS	14.0 %
Talc	28.1 %
Disintegrant layered core	57.9 %

Type B	w/w
Eudragit RS	17.1 %
Talc	34.1 %
Disintegrant layered core	48.8 %

The in-vitro dissolution profile of the two types of pellets was determined using USP apparatus IV at 16 ml/min in 0.5M phosphate buffer pH 6.5, temperature 37°C. The results are presented in Table 1.

Table 1: Dissolution profiles for delayed release pellets

	% Release:	
Time (min)	Type A Pellet	Type B Pellet
0	0	0
60	0	0
120	0.2	0
180	0.3	0
240	1.0	0
300	4.9	0
360	18.6	0.2
390	29.6	2.6
420	39.4	6
450	49.1	11.5
480	56.5	18.7
510	62.4	28
540	67.1	38.3
570	70.4	47
600	73.7	54.5
630	76.6	61.1
660	79.4	66.7
690	81.8	71.1
720	83.9	74.3
750	85.7	76.7
780	87.5	78.8
810	89.1	80.6
840	90.5	82.3
870	91.8	83.9
900	93.0	85.8
930	94.2	87.3
960	95.4	88.6

These results are presented in Figures 1 and 2.

Example 2: Preparation of a mixture of: pellets according to Example 1 and immediate release pellets

The method described above was repeated to provide drug containing cores having the following composition:

	w/w
Sugar spheres	36.7 %
HPC	0.5 %
Lansoprazole	10.0 %
Magnesium carbonate	7.5 %
Hydroxypropyl cellulose (low sub)	13.3 %
Sucrose	19.9 %
Corn Starch	12.1 %

An enteric coat was added to the drug containing core in the following proportions:

	w/w
Drug containing core	81.2 %
Eudragit L30D-55	12.1 %
Talc	3.8 %
Polyethylene glycol 6000	1.2 %
Titanium dioxide	1.2 %
Polysorbate 80	0.5 %

The in-vitro dissolution profile of the resulting immediate release pellets was determined using USP apparatus IV at 16 ml/min in 0.5M phosphate buffer pH 6.5, temperature 37°C. The immediate release pellets were then mixed with the pellets prepared according to Example 1 and incorporated into capsules to provide two formulations:

Formulation A: Type A pellets and Immediate release pellets
Formulation B: Type B pellets and Immediate release pellets

The in-vitro dissolution profile of the two formulations was determined using USP apparatus IV at 16 ml/min in 0.5M phosphate buffer pH 6.5, temperature 37°C. The results are presented in Table 2.

Table 2: Dissolution profiles for formulations comprising immediate release pellets and delayed release pellets

Time (Mins)	Mean Drug Release (%)	
	Formulation A	Formulation B
60	27	33
120	39	44
180	44	46
240	47	48
300	53	49
360	64	51
420	74	54
480	81	62
540	85	71
600	89	80
660	92	87
720	95	93
780	98	98

These results are presented in Figure 3.

In-vivo mean concentrations of lansoprazole concentrations were measured in healthy male adults aged 18 to 45 and within 10% of desirable weight. A five way open, randomised, placebo controlled, cross over study was performed and the results obtained from the subjects treated with capsules comprising approximately two hundred pellets, equivalent to a total dose of 30 mg. The results are presented in Figure 4. In addition to the results for formulations A and B the graph includes data for Zoton ™ (a lansoprazole formulation having a conventional enteric coat) and formulation C (formulation A pellets coated with an enteric coat). These additional formulations were tested for comparative purposes.

Example 3: Preparation of delayed release minitablets containing lansoprazole

A dry granulation was prepared from lansoprazole, lactose, microcrystalline cellulose and magnesium stearate by mixing and dry granulation. A second granulation containing magnesium carbonate, crospovidone and hydroxyporpylcellulose was prepared by wet granulation . The wet granulation product was dried and milled to an appropriate size before mixing with the product of the dry granulation. The resultant blend was compressed into minitablets of 4 mm diameter using standard tooling on a Kilian LX tablet press.

	mg	w/w
Magnesium carbonate	2.24	7.47 %
Croscarmellose sodium (AcDisol)	1.2	4.00 %
Hydroxypropyl cellulose	0.9	3.00 %
Lansoprazole	3.0	10.0 %
Lactose Fast Flo	11.225	37.42 %
Microcrystalline Cellulose (Avicel PH101)	11.225	37.42 %
Magnesium stearate	0.21	0.70 %

The uncoated minitablets were coated, as described in Example 1, with Eudragit and talc:

	w/w
Eudragit RS	7.5%
Talc	15.2 %
Uncoated minitablets	77.3%

The in-vitro dissolution profile of a single minitablet was determined using USP apparatus IV at 16 ml/min in 0.5M phosphate buffer pH 6.5, temperature 37°C. The results are presented in Table 3.

Table 3: Dissolution profile for a single minitablet

Time (Mins)	Mean Drug Release (%)
240	0
270	0
300	0
330	0
360	0
390	0
420	4.7
450	29.9
480	30.6
510	48.7
540	54.4
570	58.1
600	60.7
630	63.1
660	65.5
690	67.2
720	69.9
750	72.2
780	73.7
840	79.0
900	81.7
960	85.1

These results are presented in Figure 5.

CLAIMS

1. A solid dose unit for the delayed release of a drug characterised in that it comprises:

a) a core comprising the drug and at least one disintegrant

and b) an outer semi-permeable membrane surrounding the core which comprises a permeable water insoluble polymer and at least 50 % by weight glidant.

2. A solid dose unit as claimed in Claim 1 characterised in that when the unit is subjected to in-vitro exposure to simulated intestinal fluid minimal drug is released until after at least four hours exposure and substantially all of the drug is released after 24 hours exposure.

3. A solid dose unit as claimed in Claim 2 characterised in that minimal drug is released until after at least six hours exposure.

4. A solid dose unit as claimed in Claim 2 or Claim 3 wherein the glidant is talc.

5. A solid dose unit as claimed in any one of Claims 1 to 4 which lacks an enteric coat.

6. A solid dose unit as claimed in any one of Claims 1 to 5 which comprises a proton pump inhibitor.

7. A solid dose unit as claimed in any one of Claims 1 to 6 which is a pellet, granule, minitablet or tablet.

8. A plurality of solid dose units as claimed in any one of Claims 1 to 7 which collectively exhibit the following in-vitro dissolution profile when subjected to in-vitro exposure to simulated intestinal fluid:

i) after four hours exposure less than 10% of the drug is released

ii) after ten hours exposure at least 30% drug is released

and iii) after 24 hours exposure at least 70% drug is released.

9. A plurality of solid dose units as claimed in Claim 8 wherein after six hours exposure less than 10% of the drug is released.

10. A plurality of solid dose units as claimed in Claim 8 or Claim 9 wherein after 20 hours exposure at least 70% of the drug is released.

11. A plurality of solid dose units as claimed in Claim 8 wherein after 8 hours exposure less than 10% of the drug is released, after 12 hours exposure at least 30% is released and after 20 hours exposure at least 70% is released.

12. A plurality of solid dose units as claimed in any one of Claims 1 to 7 which collectively exhibit the following in-vitro dissolution profile when subjected to in-vitro exposure to simulated intestinal fluid: after 10 hours exposure less than 10% of the drug is released, after 14 hours exposure at least 30% is released and after 22 hours exposure at least 70% is released.

13. A plurality of solid dose units as claimed in any one of Claims 1 to 7 which collectively exhibit the following in-vitro dissolution profile when subjected to in-vitro exposure to simulated intestinal fluid: after 12 hours exposure less than 10% of the drug is released, after 16 hours exposure at least 30% is released and after 24 hours exposure at least 70% is released.

14. A plurality of solid dose units as claimed in Claim 8 wherein after four hours exposure less than 5% of the drug is released, after ten hours exposure at least 35% is released and after 20 hours exposure at least 75% is released

15. A plurality of solid dose units as claimed in Claim 8 wherein after six hours exposure less than 5% of the drug is released, after ten hours exposure at least 35% is released and after 20 hours exposure at least 75% is released.

16. An oral formulation for the controlled release of a drug which comprises solid dose units as claimed in any one of Claims 1 to 15.

17. An oral formulation for the controlled release of a drug which comprises a first population of solid dose units comprising the drug and a second population of solid dose units comprising the drug wherein the first population

comprises units which exhibit the following in-vitro dissolution profile when subjected to in-vitro exposure to simulated intestinal fluid:

i) after two hours exposure at least 60% of the total drug included in the first population is released

and ii) after three hours exposure at least 80% of the total drug included in the first population is released

and the second population comprises units as claimed in any one of Claims 1 to 15.

18. An oral formulation as claimed in Claim 16 or Claim 17 which is a tablet or capsule.

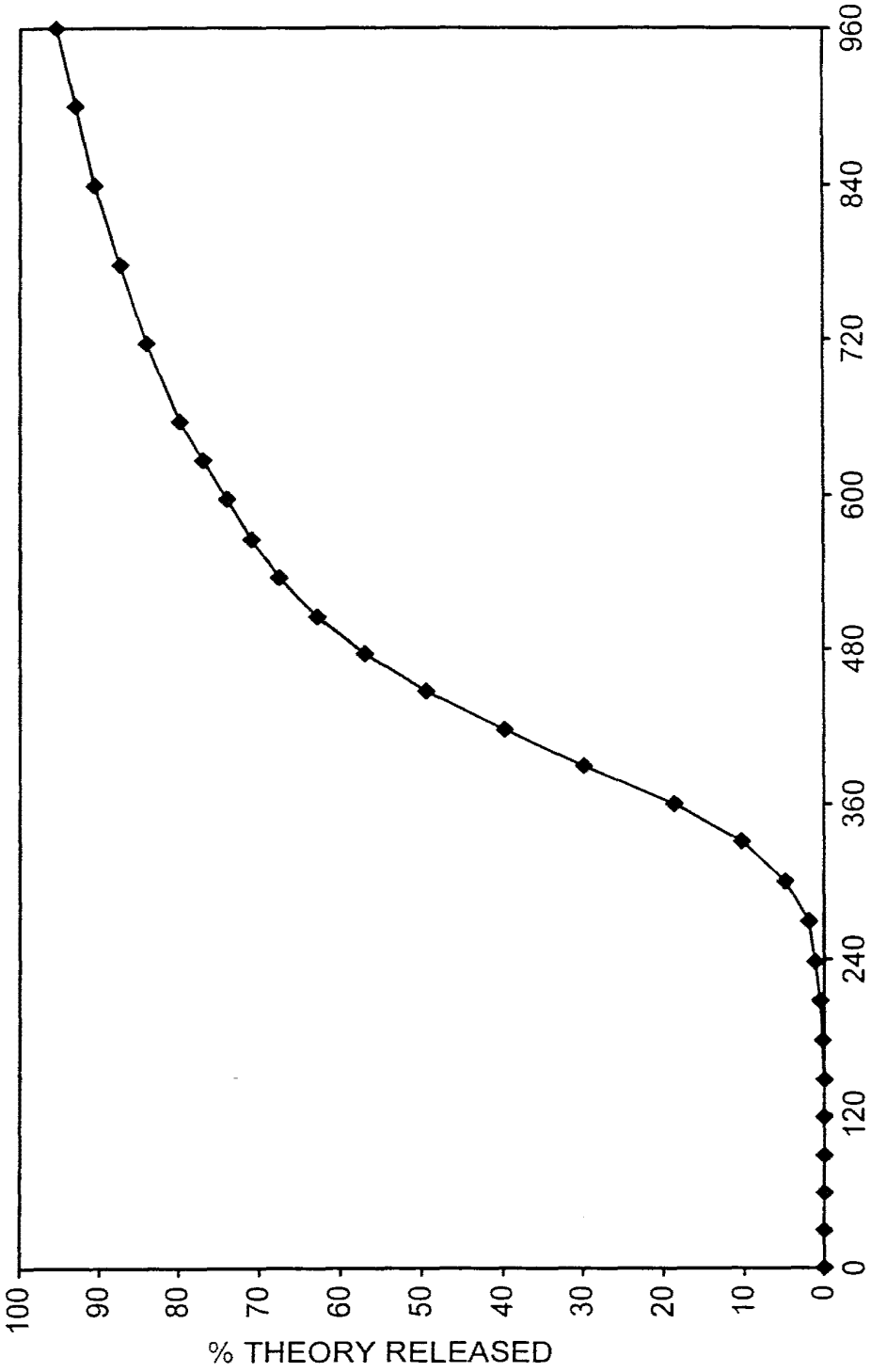
19. An oral formulation as claimed in any one of Claims 16 to 18 suitable for once daily administration.

20. An oral formulation as claimed in any one of Claims 16 to 19 suitable for controlling gastric pH over a 24 hour period.

21. An oral formulation as claimed in any one of Claims 16 to 20 capable of controlling gastric pH over a 24 hour period so as to prevent the pH falling below 4.0 over this period.

22. A composition comprising a permeable water insoluble polymer and at least 50 % by weight glidant suitable in the preparation of a solid dose unit as claimed in any one of Claims 1 to 15.

23. A process for the preparation of solid dose units as claimed in any one of Claims 1 to 16 which comprises coating a core comprising a drug and a disintegrant with a composition comprising a permeable water insoluble polymer and at least 50 % by weight glidant.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90
80
70
60
50
40
30
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% THEORY RELEASED
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240
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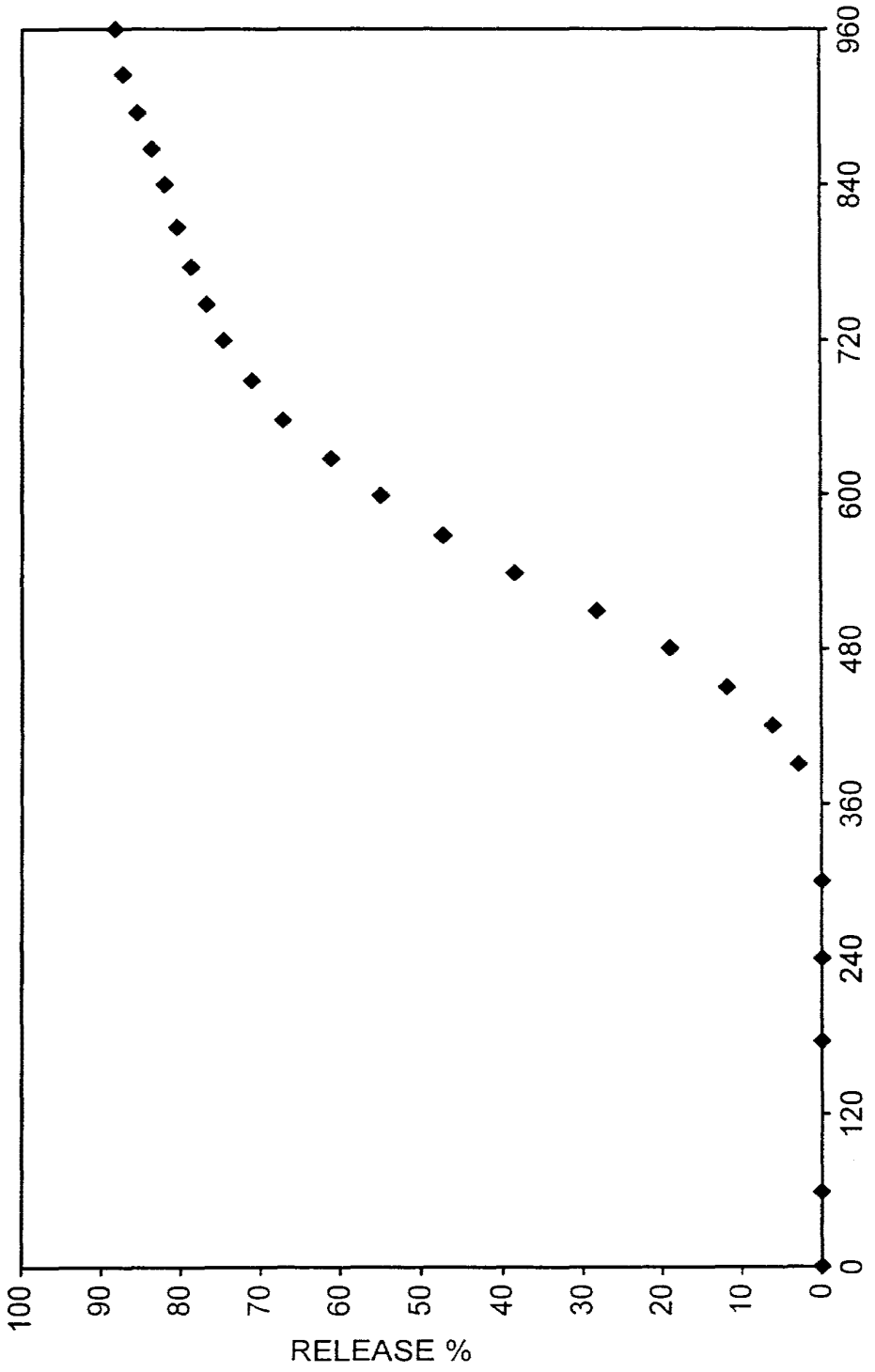
720
840
960
TIME IN MINS

FIG. 1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90
80
70
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TIME (MIN)
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120
240
360
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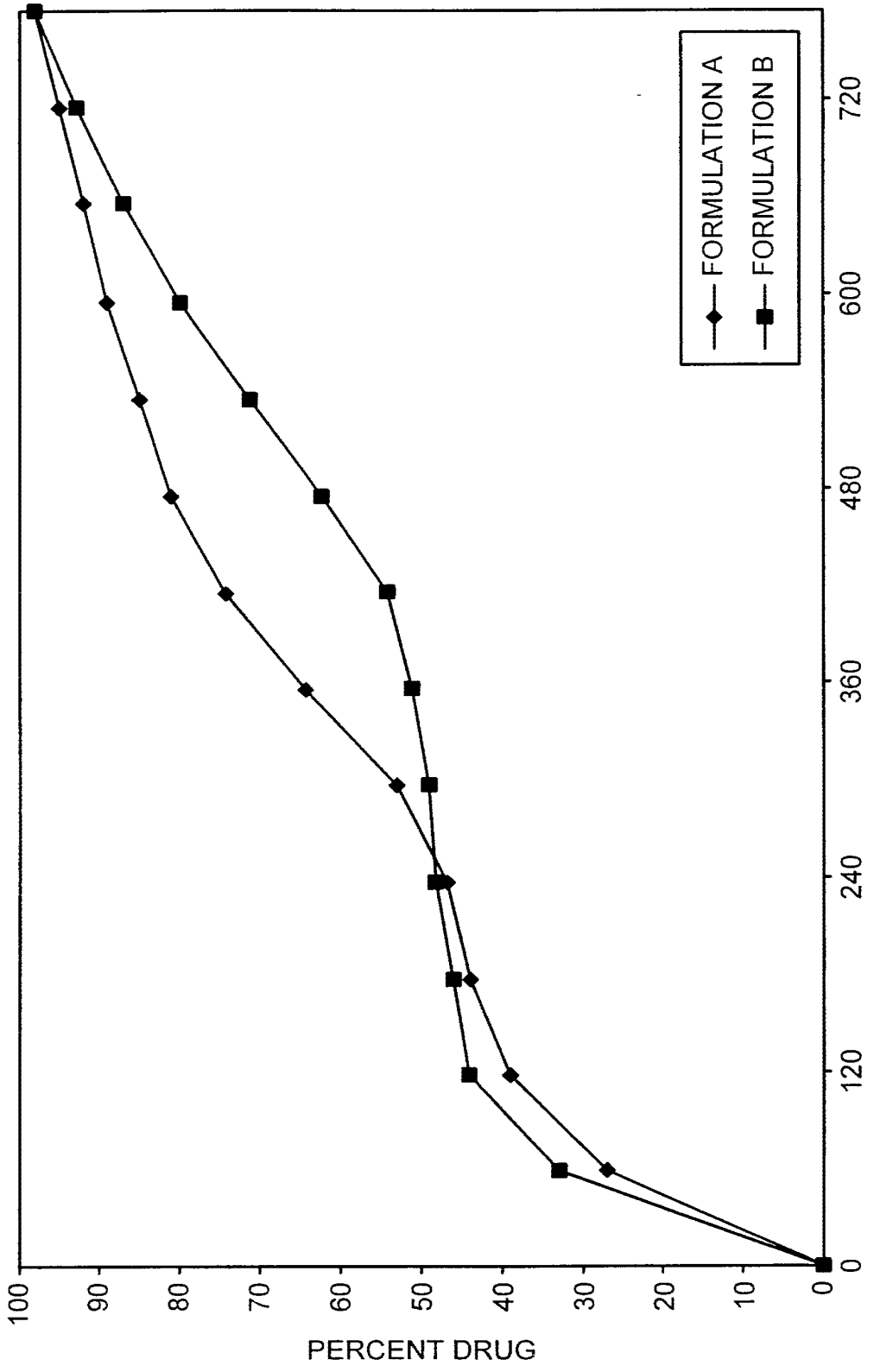
600
720
840
960

FIG. 2


FORMULATION A
FORMULATION B
PERCENT DRUG
TIME (MIN)
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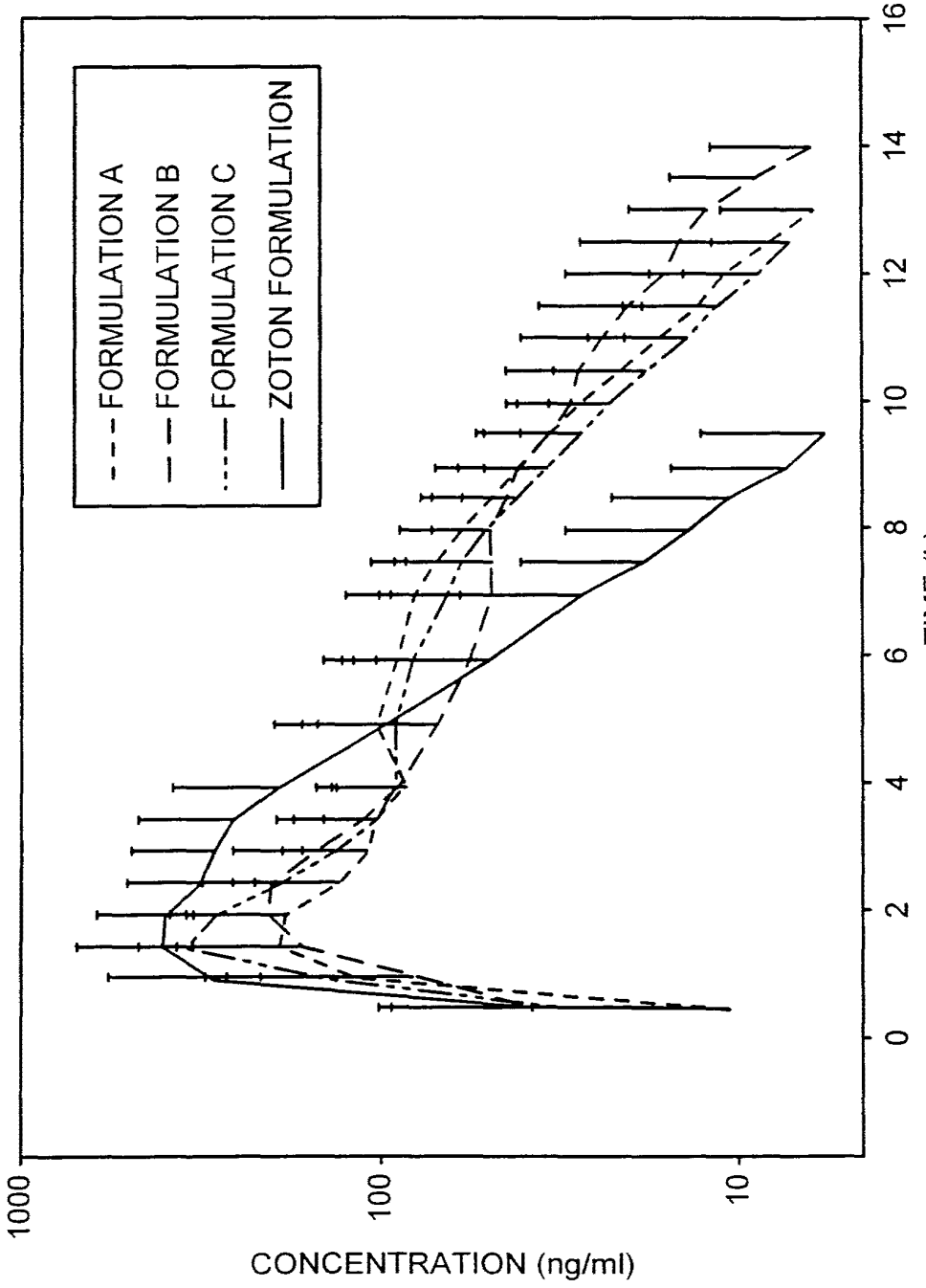
30
40
50
60
70
80
90
100
0
120
240
360
480
600
720

FIG. 3


FORMULATION A
FORMULATION B
FORMULATION C
ZOTON FORMULATION
1000
100
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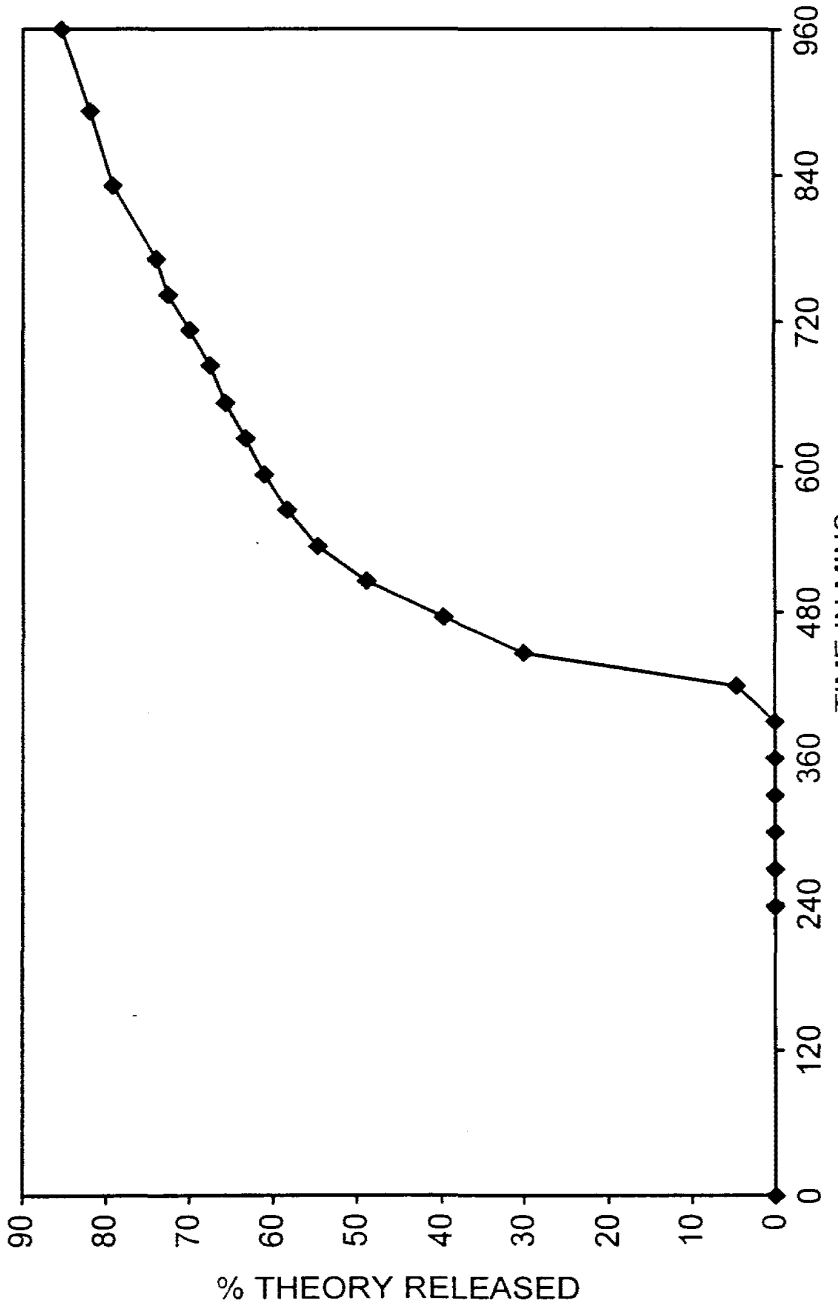
CONCENTRATION (ng/ml)
0
2
4
6
8
10
12
14
16
TIME (h)

FIG. 4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% THEORY RELEASED
0
120
240
360
480
600
720
840
960
TIME IN MINS

FIG. 5

INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/EP 00/09576

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K9/28 A61K9/20

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)
IPC 7 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)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99 32093 A (ASTRA) 1 July 1999 (1999-07-01) claims 1,4,7,12,16 figures 1-5 example 1 page 15, line 4 - line 15	1-23
A	WO 94 02140 A (YOSHITOMI) 3 February 1994 (1994-02-03) the whole document	1-23
A	WO 93 25204 A (ETHYPHARM) 23 December 1993 (1993-12-23) the whole document	1-23

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2001	26/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ventura Amat, A

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ational Application No
PCT/EP 00/09576

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(21) International Application Number: PCT/EP00/09576

(22) International Filing Date:
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(25) Filing Language: English

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(30) Priority Data:
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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
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2 August 2001

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/24777 A1

(54) Title: COATED SOLID DOSAGE FORMS

(57) Abstract: Novel pharmaceutical compositions are provided, in particular oral formulations for once a day administration of a drug/medicament and to novel solid dose units for incorporation therein are provided. The solid dose units provide a phased release of drug to target or prolong the pharmaceutical effect. The compositions are particularly useful for multiphase delivery of proton pump inhibitors such as lansoprazole, pantoprazole, omeprazole, perprazole, etc.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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13 September 2001 (13.09.2001)

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(25) Filing Language: English

(26) Publication Language: English

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0000773-2 8 March 2000 (08.03.2000) SE

(71) Applicant *(for all designated States except US)*: **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

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(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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WO 01/66088 A1

(54) Title: NEW SELF EMULSIFYING DRUG DELIVERY SYSTEM

(57) Abstract: The present invention claims and discloses a pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprising: (i) one or more NO-releasing NSAID(s); (ii) one or more surfactants; (iii) optionally an additional oil or semi-solid fat; said composition forming an *in-situ* oil-in-water emulsion upon contact with gastrointestinal fluids. The composition may optionally also comprise one or more short-chain alcohols. Also within the scope of the invention is a combination with a proton pump inhibitor. The pharmaceutical composition is useful in the treatment of pain and inflammation. Further within the scope of the invention is kit comprising a pharmaceutical composition according to the invention in a unit dosage form, in combination with a proton pump inhibitor, and said proton pump inhibitor is enteric coated.

NEW SELF EMULSIFYING DRUG DELIVERY SYSTEM

Field of the invention

The present invention is directed to a new pharmaceutical composition in form of an emulsion pre-concentrate, a unit dosage form comprising said composition, its use in therapy as well as a process for the preparation thereof.

Background and prior art

Non-steroidal anti-inflammatory drugs, commonly abbreviated NSAIDs, are well-known drugs for the treatment of pain and inflammation. One of the major drawbacks with NSAIDs is that they have severe gastro-intestinal side-effects. Patients undergoing treatment with NSAIDs for a longer period of time, such as naproxen, often experience problems with stomach gastrointestinal side-effects.

Nitrogen oxide releasing NSAID compounds (in the following NO-releasing NSAIDs), have recently been found to have an improved side-effect profile, see e.g. WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641.

NO-releasing NSAIDs are lipophilic compounds with poor aqueous solubility. They can be classified into class 2 according to the Biopharmaceutical Classification System proposed by Amidon et al. *(Pharm. Res. 12 (1995) pp. 413-420)*. Drugs of this class are characterised by low aqueous solubility but reasonably well permeability. A biopharmaceutical problem with these compounds is that their absorption from the gastro-intestinal tract (GIT) may be dissolution rate limited, resulting in poor bioavailibility upon oral administration.

WO 95/08983 discloses a self-emulsifying composition for oral administration that forms a microemulsion *in situ* when in contact with biological fluids. This composition can be characterised as a self-microemulsifying drug delivery system (SMEDDS), and comprises at least

- an active compound,
- a lipophilic phase consisting of a mixture of glycerides and fatty acid esters,
- a surface-active agent,
- a cosurfactant, and
- a hydrophilic phase which is achieved after ingestion by the physiological liquid of the digestive medium.

The present invention distinguishes in several aspects from WO 95/08983 and other SMEDDS. Whereas the compositions disclosed in WO 95/08983 form a microemulsion *in situ*, the compositions of the present invention form an emulsion. The SMEDDS of WO 95/08983 require the presence of a lipophilic phase to solubilise the active compound. Such a lipophilic solubiliser phase is not needed for the present invention since the active compound, the NO-releasing NSAID, is able to solely constitute the oil phase of the *in situ* emulsion. Compositions of WO 95/08983 comprise *inter alia* a cosurfactant in addition to a surface-active agent. The presence of a cosurfactant is not necessary for compositions of the present invention reducing toxicological concern to a minimum.

EP 274 870 discloses a pharmaceutical composition comprising a non-steroidal anti-inflammatory drug (NSAID) and a surfactant, the composition being capable of forming micelles containing the NSAID upon oral administration. These micelles have been found to present a particularly appropriate form to administer NSAIDs orally, alleviating their adverse effects on the gastrointestinal tract (GIT). Micelles are aggregates in which the surfactant molecules are generally arranged in a spheroidal structure with the hydrophobic region at the core shielded, in an aqueous solution, from the water by a mantle of outer hydrophilic regions. The drug is usually solubilised in the surfactant. Micelles are to be contrasted in terms of their structure with emulsions which are formed by compositions of the present invention. Whereas micelles are thermodynamically stable one-phase-systems (according to the Gibbs phase law) in which the aggregates usually have a diameter of approximately two lengths of the surfactant molecule forming it, i.e. in the order of some

ten to hundred Ångström (Å). emulsions are much larger aggregates, in the order of nanometers to micrometers in diameter, consisting of an oily core which is surrounded by one or several layers of surfactants. Emulsions are generally two-phase-systems, and they are thermodynamically unstable (but may be kinetically stable). Another major difference between the compositions of EP 274 870 and the present invention is the nature of the active compound. Whereas NSAIDs are crystalline powders by nature, the NO-releasing NSAIDs or mixtures of NO-releasing NSAIDs used in the present invention are in oil form or a thermosoftening semisolid. Moreover, micelles usually require a much higher drug:surfactant ratio compared to the oil:surfactant ratio required to form an emulsion.

One of the unique features with NO-releasing NSAIDs is that many of these compounds are oils or thermosoftening semisolids which are practically insoluble in water. With high-dose NO-releasing NSAIDs, e.g. when the dose is above about 350 mg, it is difficult to formulate a tablet of reasonable size of the large amount of oil or semisolid. The lipophilic NO-releasing NSAIDs can, however, be formulated as oil-in-water emulsions where the compound constitutes, or is part of, the oil phase emulsified in water by one or more surfactants.

In pharmacokinetic animal studies it has been surprisingly found that such oil-in-water emulsions of NO-releasing NSAIDs display a much better bioavailability compared to the unemulsified substance. A problem with emulsions is, however, that they are thermodynamically unstable and have a poor long-term storage stability since they often tend to coalescence, creaming/sedimentation or phase separation. Moreover, they do not represent a convenient dosage form for oral administration since often large volumes are needed to incorporate one dose, and unpleasant bitter or soapy taste may be a major problem. It is *inter alia* not possible to fill oil-in-water emulsions into gelatine capsules since the high water content of the emulsion is incompatible with the capsule shell and would dissolve it.

Outline of the invention

The problems mentioned above have now been solved by providing a novel Self Emulsifying Drug Delivery System, commonly known as SEDDS, suitable for oral administration. More particularly, the present invention is directed to a pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprising

(i) one or more NO-releasing NSAID(s);
(ii) one or more surfactants;
(iii) optionally an oil or semi-solid fat;

said composition forming an *in-situ* oil-in-water emulsion upon contact with aqueous media such as gastrointestinal fluids.

The composition according to the present invention may optionally further comprise one or more short-chain alcohols.

The composition will form an *in situ* oil-in-water emulsion of small droplets of nanometer to micron size upon contact with gastrointestinal fluids, the droplets being constituted of one or more NO-releasing NSAIDs forming the core of the droplet which is covered by one or several layers of surfactant. The *in situ* formed oil-in-water emulsion will provide a good bioavailability of the NO-releasing NSAID upon oral administration. Storage stability of the emulsion is not a concern since the emulsion is not formed until the pre-concentrate has been taken by the patient, i.e. first at the moment of administration. The possibly unpleasant taste of the pre-concentrate is not a problem when filled into capsules.

The pharmaceutical composition according to the present invention is an emulsion

pre-concentrate at the time of administration to a patient. The emulsion pre-concentrate can be filled into single unit dosage forms such as capsules, drinking ampoules and dose cushions, or may alternatively be formed as other suitable dosage forms such as chewable soft pills and chewy-base lozenges.

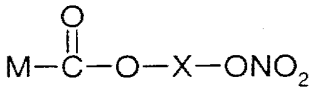
Upon contact with aqueous media such as gastrointestinal fluids, the emulsion pre-concentrate transforms into an oil-in-water emulsion. Thus, the composition will form an *in-situ* oil-in-water emulsion in the gastrointestinal tract (GI tract). The drug release rate of the composition is determined by the droplet size of the *in situ* emulsion and the polarity of the emulsion droplets, the latter being governed by the hydrophilic-lipophilic balance (HLB) of the drug/surfactant mixture, and the concentration of the surfactant. Generally, small droplet size and high polarity gives rise to a high drug release rate *(N.H. Shah et al., Int. J. Pharm. 106 (1994), pp. 15-23)*

The wording "NSAID" is defined as a non-steroidal anti-inflammatory drug, i.e. any drug having an anti-inflammatory effect, but which compound does not belong to the compound class "steroids". A person skilled in the art will know whether a compound falls under the definition NSAID. Examples of specific NSAIDs are naproxen, diclofenac, aceclofenac, indomethacine, ketorolac, sulindac, meloxicam, piroxicam, tenoxicam, ibuprofen, ketoprofen, naproxen, azapropazon, nabumeton, carprofen, tiaprofenic acid, suprofen, indoprofen, etodolac, fenoprofen, fenbufen, flurbiprofen, bermoprofen, pirazolac, zaltoprofen, nabumetone, bromfenac, ampiroxicam, and lornoxicam. This list should however not be considered as exhaustive in any way. The wording "NO-releasing NSAID" is contemplated to include any non-steroidal anti-inflammatory drug (NSAID), a salt or an enantiomer thereof, which has the capability to release nitrogen oxide.

NO-releasing NSAIDs are lipophilic compounds with poor aqueous solubility. They can be classified into class 2 according to the Biopharmaceutical Classification System proposed by *Amidon et al. (Pharm. Res. 12 (1995) 413-420)*. Drugs of this class are characterised by low aqueous solubility but reasonably well permeability. A biopharmaceutical problem

with these compounds is that their absorption from the gastro-intestinal tract (GIT) may be dissolution rate limited resulting in poor bioavailibility upon oral administration.

Preferred NO-releasing NSAIDs in accordance with the present invention, are compounds of the formula I

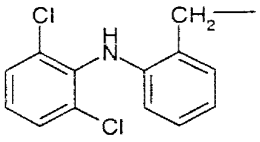


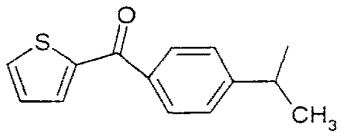
I

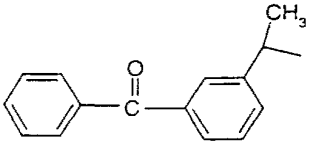
wherein

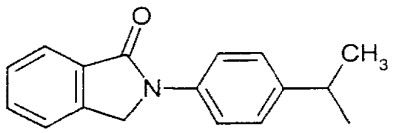
X is a spacer, i.e. a compound forming a bridge between the nitrogen oxide donating group and the NSAID; and

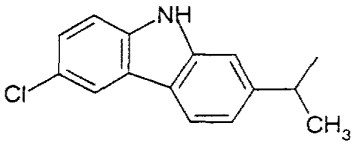
M is selected from anyone of

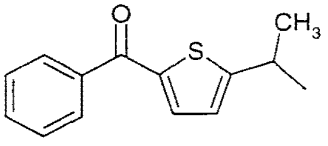


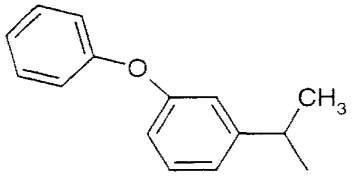


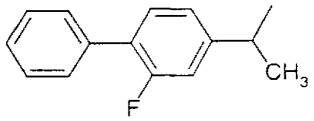


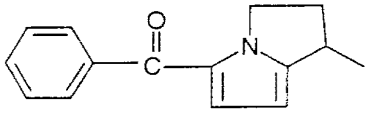


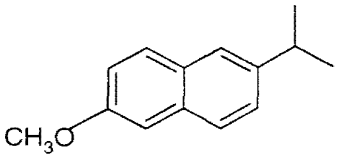


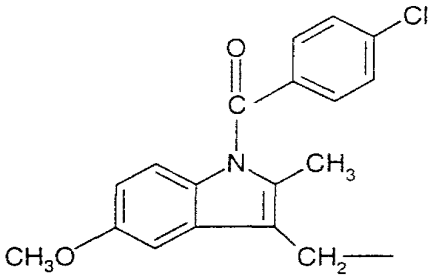


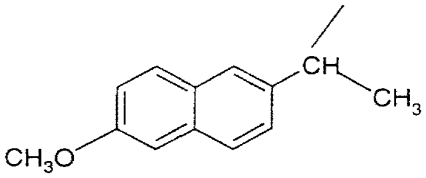


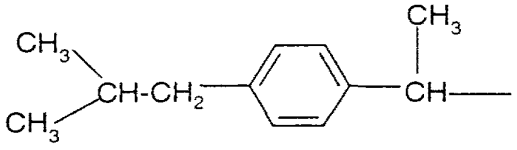












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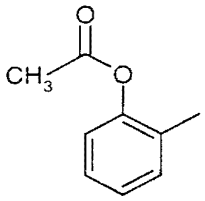
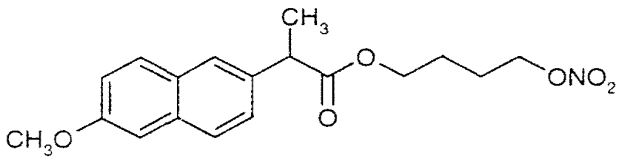


In a preferred embodiment of the invention, the spacer X is selected from a linear, branched or cyclic alkylene group $-(CH_2)-_n$ wherein n is an integer of from 2 to 10; and $-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$.

In one embodiment of the invention, NO releasing NSAIDs contemplated as active compound(s) in the SEDDS formulation according to the present invention, are compounds disclosed and claimed in WO 94/04484, WO 94/12463, WO 95/09831 and WO 95/30641, which are hereby incorporated by reference.

Specific NO-releasing substances useful in accordance with the present invention are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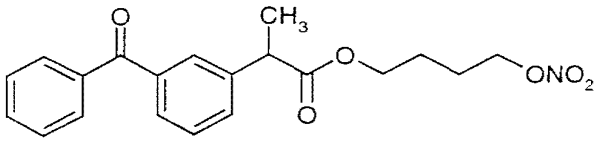
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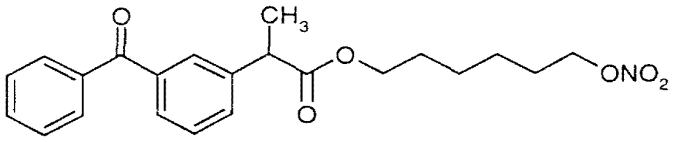
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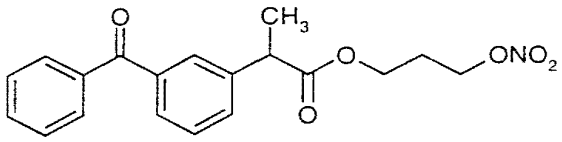
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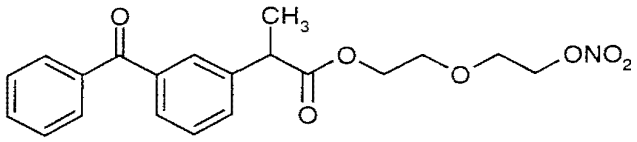
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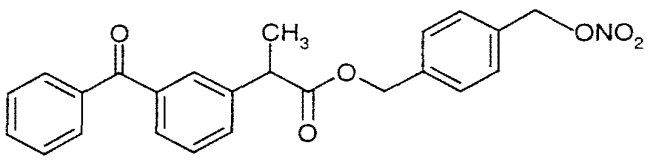
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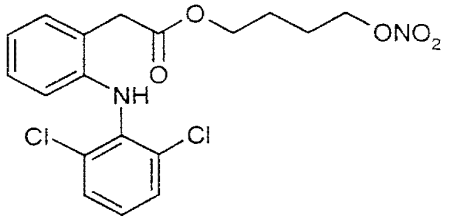

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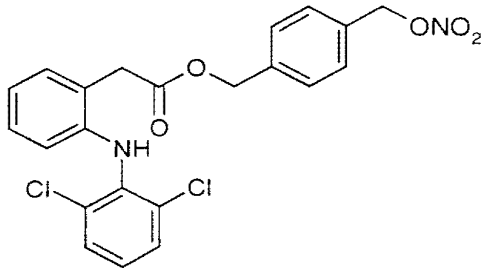

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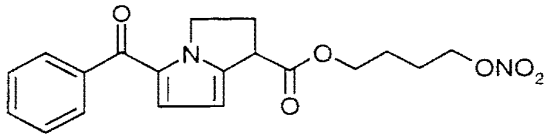

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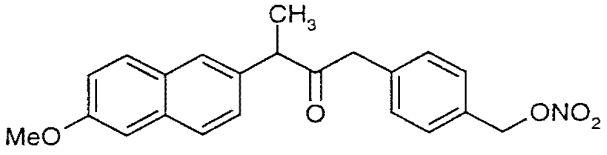

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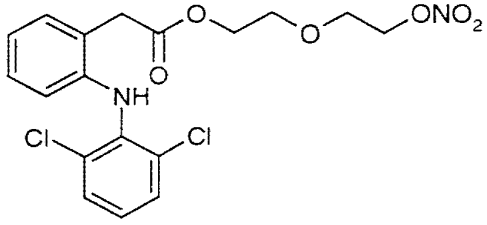

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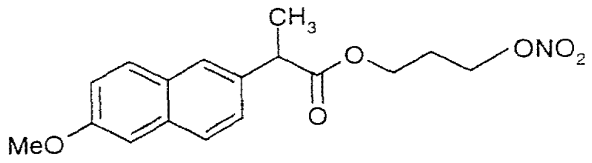

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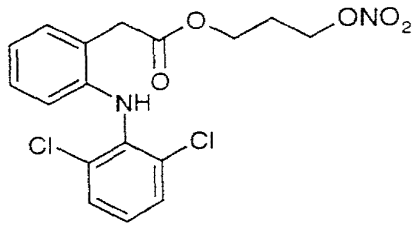

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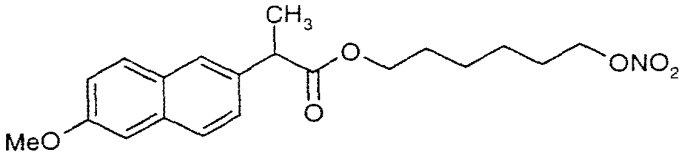

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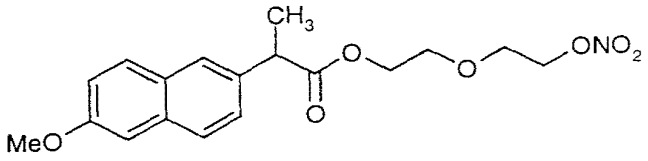

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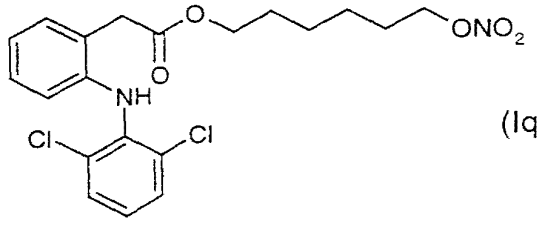


(Iq)

NSAIDs are by nature in form of a powder, whereas NO-releasing NSAIDs predominantly provide a compound in semi-solid or oil form as such, due to the spacer. This unique feature provides the advantage that no external lipophilic oil or semisolid matrix needs to be added to the emulsion pre-concentrate, since this is an inherent feature of the drug. Additionally, a pharmacologically inert oil or semisolid fat may be added to the pharmaceutical composition by means of a filler or as a viscosity regulator. A filling agent may be required to increase dosing accuracy for low dose compounds. A viscosity regulator may be required in order to adjust optimal viscosity for filling of the composition into e.g. capsules. In particular high speed liquid filling of capsules requires careful adjustment of viscosity within a range that prevents splashing on the low viscosity end and thread-formation on the high viscosity end. Moreover, the viscosity range must be chosen so as to give a pumpable formulation. The viscosity range typically required for liquid filling of capsules is from 0.1 to 25 Pa s.

The total amount of NO-releasing NSAID(s) used in the composition of the invention is preferably in the range 50-1500 mg per unit dose. In still a further preferred embodiment, the amount of NO-releasing NSAID(s) used in the composition is 125-500 mg per unit dose.

The wording "unit dose" is defined as the amount of active compound administered in one single capsule, or dissolved in one glass of water.

The wording "surfactant" is defined as surface-active amphiphilic compounds such as block co-polymers. Preferred surfactants in accordance with the present invention are non-ionic surfactants, for example those containing polyethylene glycol (PEG) chains, particularly block co-polymers such as poloxamers.

Examples of suitable poloxamers are Poloxamer 407 (Pluronic F127®); Poloxamer 401 (Pluronic L121®); Poloxamer 237 (Pluronic F87 ®); Poloxamer 338 (Pluronic F138®); Poloxamer 331 (Pluronic L101®); Poloxamer 231 (Pluronic L81®); tetrafunctional polyoxyethylene polyoxypropylene block copolymer of ethylene diamine, known as Poloxamine 908 (Tetronic 908®); Poloxamine 1307 (Tetronic 1307®); Poloxamine 1107 polyoxyethylene polyoxybutylene block copolymer, known as Polyglycol BM45® . This list is only intended to serve as exemplification of surfactants that may be used in accordance with the present invention, and should not in any way be considered as exhaustive or as limiting the invention.

All surfactants described above are commercially available from e.g. BASF, Dow Chemicals, and Gattefossé.

The total amount of surfactant(s) in accordance with the invention may be within the range of from 12.5-6000 mg, preferably of from 100-500 mg.

The ratio NO-releasing NSAID:surfactant may vary from 1:0.1 to 1:10, preferably from 1:0.3 to 1:3.

If an additional oil is added to the pharmaceutical composition this may be any oil as long as it is inert and compatible with the capsule material, as well as being acceptable for use in pharmaceuticals. A person skilled in the art will appreciate which oil to select for the intended purpose. Examples of suitable oils that may be used in accordance with the present invention are vegetable oils such as coconut oil, corn oil, soybean oil, rape seed oil, safflower oil and castor oil. Also animalic oils such as fish oil and triglycerides are suitable for the purposes of the present invention.

If a semi-solid fat is used as a filler for the pharmaceutical composition, this may preferably be selected from mono-, di- and triglycerides, and fatty acid alcohol such as stearyl alcohol, Gelucires 33/01®, 39/01®, 43/01®, glyceryl palmitostearate such as Precirol ATO5®. Gelucire is a mixture obtained by mixing mono-, di-, and tri-esters of glycerol, mono- and di-esters of PEG, or free PEG.

In one aspect of the present invention, an oily (lipophilic) or semi-solid NO-releasing NSAID is used as the active ingredient.

If an additional oil or semi-solid fat is used in the pharmaceutical composition according to the invention, this may serve as a filler or as a viscosity regulator.

The wording "short-chain alcohols" used in accordance with the present invention is herein defined as linear or branched mono-, di- or tri-alcohols having 1-6 carbon atoms. Examples of such short-chain alcohols useful in accordance with the invention are ethanol, propylene glycol and glycerol.

If a short-chain alcohol is added to the pharmaceutical composition according to the invention, the solubility is enhanced and a smaller amount of surfactant is required.

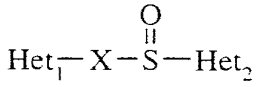
In another aspect of the invention, two or more NO-releasing NSAIDs are used as active ingredients, where anyone of said drugs may be present as an oil or as a semi-solid, or where at least one of said drugs is present as an oil or as a semi-solid and the other one(s) may be present as a solid which is dissolved or suspended in the oily or semi-solid compound. Combinations of two or more NO-releasing NSAIDs may be advantageous in case the high NO-load of a high-dose low potent NO-releasing NSAID is desired to be supplemented with a low dose of high potent NO-releasing NSAID.

A further aspect of the invention is a combination of one or more NO-releasing NSAIDs and an acid susceptible proton pump inhibitor (PPI) compound. The NO-NSAIDs should be formulated such that it is emulsified in the stomach, i.e. as a SEDDS formulation as described above, while the acid susceptible proton pump inhibitor (PPI) must be protected from contact with the acidic gastric juice by for instance an enteric coating. The enteric coating layered PPI remain unaffected until it reaches the intestine, where the PPI is released. Individually prepared enteric coating layered units of the proton pump inhibitor (PPI) may be mixed into the SEDDS melt. Alternatively the PPI´s may be filled into a capsule filled with solidified SEDDS, where a layer of protective paraffin may be needed between SEDDS and the prepared PPI pellets. In still an alternative embodiment the prepared PPI pellets may be mixed into a liquid SEDDS formulation.

The combination may thus either be a fix combination, i.e. as a formulation where the NO-releasing NSAID(s) and the acid susceptible proton pump inhibitor are mixed and thereafter filled into a suitable dosage unit. In an alternative embodiment of the invention the acid susceptible proton pump inhibitor may be filled into a capsule with an already solidified SEDDS formulation of one or more NO-releasing NSAID(s) – in this case a layer of protective paraffin or other inert material may be required between the SEDDS formulation and the acid susceptible proton pump inhibitor. In still an alternative embodiment the acid susceptible proton pump inhibitor is mixed into a liquid SEDDS formulation of the NO-releasing NSAID(s).

In an alternative embodiment of the invention, the NO-releasing NSAID(s) and the PPI may be provided in form of a kit, where the NO-releasing NSAID and the PPI are administered sequentially, i.e. one after the other. The order of administration is not crucial, meaning that either of the NO-releasing NSAID or the PPI may be administered before the other. Thus, one embodiment of the invention comprises a combination treatment where one or more NO-releasing NSAIDs are administered to a patient in need of treatment, whereafter a PPI is administered, or vice versa.

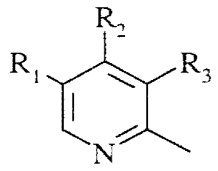
Examples of proton pump inhibitors suitable in a combination with a NO-releasing NSAID in accordance with the present invention as stated above, is a compound of the general formula I or a pharmaceutically acceptable alkaline salt thereof, or one of its single enantiomer or an alkaline salt of the single enantiomer:



I

wherein

Het_1 is



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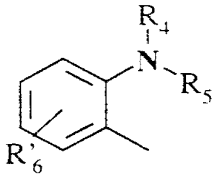

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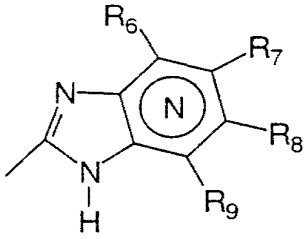

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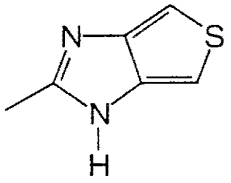

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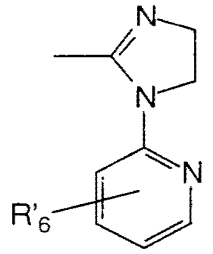

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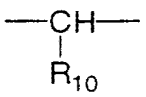

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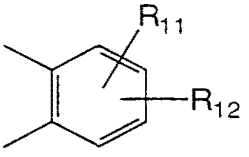


wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

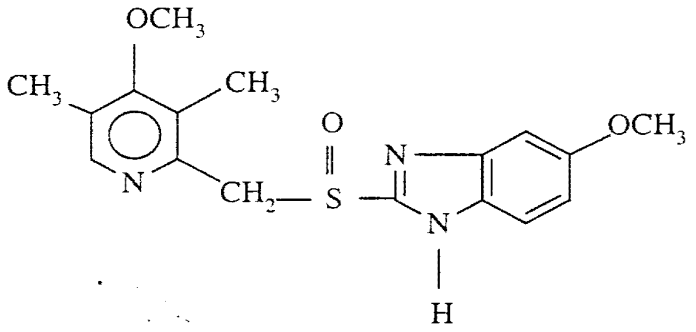
R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

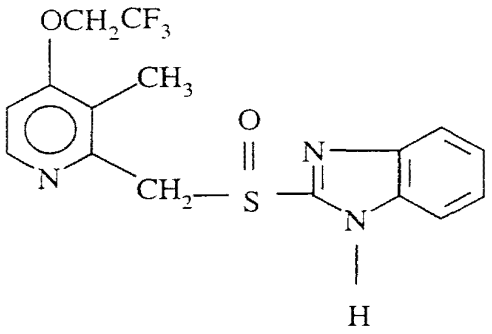
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl;
alkyl groups, alkoxy groups and moities thereof , they may be branched or straight C_1 - C_9 -chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

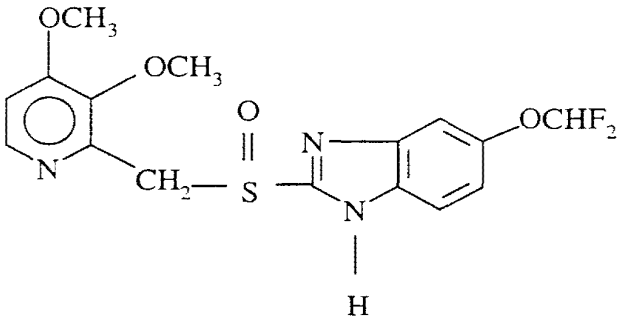
Examples of specific proton pump inhibitors suitable in accordance with the present invention are



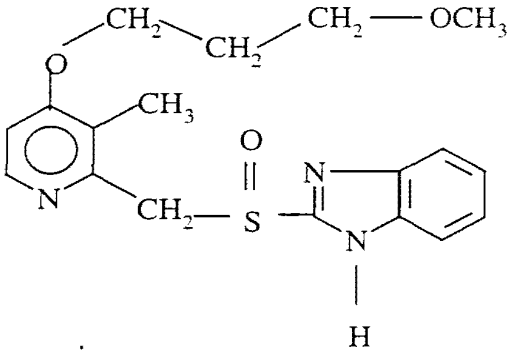
Omeprazole



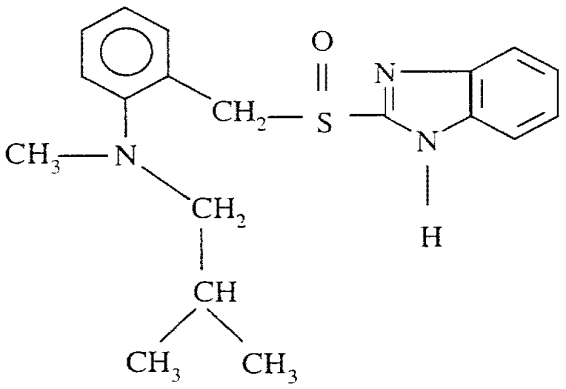
Lansoprazole



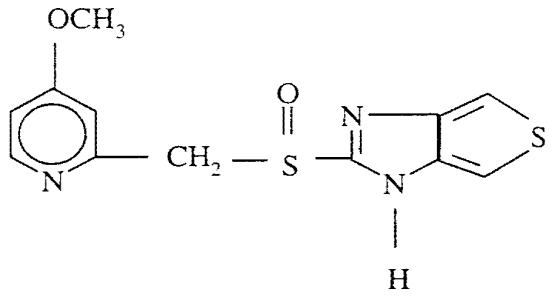
Pantoprazole

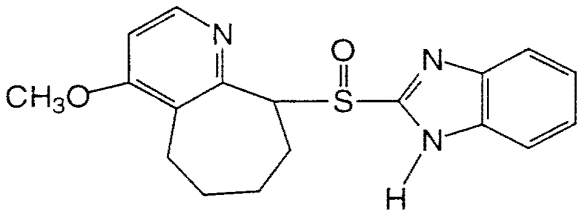


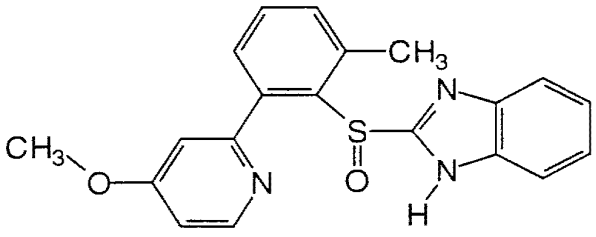
Pariprazole

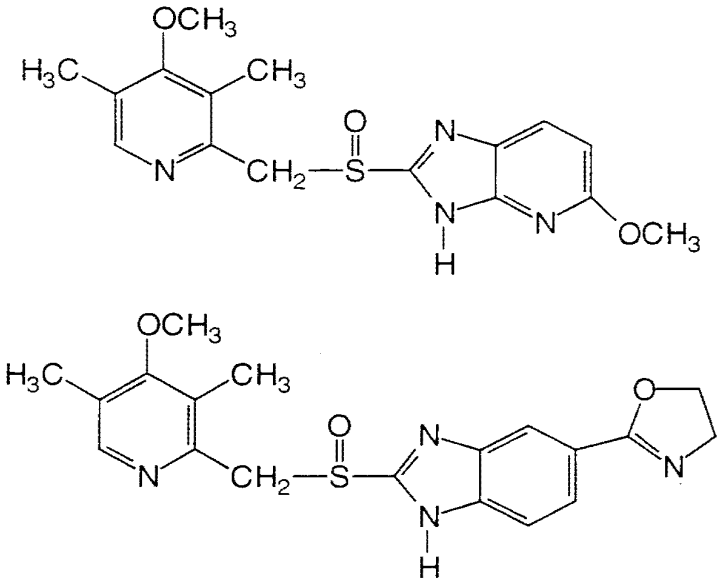


Leminoprazole









The acid susceptible proton pump inhibitors used in the dosage forms of the invention may be used in their neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+},Ca^{2+},Na^{+} , K^{+} or Li^{+}salts, preferably the Mg^{2+} salts. Further where applicable, the compounds listed above may be used in racemic form or in the form of the substantially pure enantiomer thereof, or alkaline salts of the single enantiomers.

Suitable proton pump inhibitors are for example disclosed in EP-A1-0005129, EP-A1-174 726, EP-A1-166 287, GB 2 163 747 and WO 90/06925, and further especially suitable compounds are described in WO 95/01977 and WO94/27988.

The proton pump inhibitors used in a combination in accordance with the present invention, are preferably provided as enteric coating layered pellets comprising the acid susceptible proton pump inhibitor. For the composition of the enteric coating layered pellets and its preparation, reference is made to WO 96/01623, which is hereby incorporated by reference.

Suitable combinations in accordance with the present invention are for instance a NO-releasing NSAID of the formula Ia and omeprazole or an alkaline salt of omeprazole, (S)-

omeprazole or an alkaline salt of (S)-omeprazole; or a NO-releasing NSAID of the formula Ii and omeprazole or an alkaline salt of omeprazole, (S)-omeprazole or an alkaline salt of (S)-omeprazole.

The pharmaceutical composition of the invention is filled into single dosage forms suitable for oral administration, such as capsules, drinking ampoules and dose cushions, or may be formulated as other suitable oral dosage forms such as chewable soft pills and chewy-base lozenges.

In a preferred embodiment of the invention, the pharmaceutical composition is filled into hard gelatin capsules, but capsules from alternative materials such as methylcellulose-based shells, and soft gelatine capsules may also be used.

In an alternative embodiment of the invention, the pharmaceutical composition may be dissolved in e.g. a glass of water, thus allowing the pre-concentrate to form an emulsion which may be administered as such. The compositions intended for dissolution prior to administration may be filled e.g. into soft gelatine capsules, plastic or aluminium cushions, or plastic or glass ampoules. This feature is particularly advantageous for high dose compositions which would require a large capsule, for patients who have difficulty in swallowing capsules, and for pediatric patients.

In a preferred embodiment the pharmaceutical composition of the present invention is filled into capsules. Preferred capsules are gelatin capsules which may be soft or hard. The hard gelatine capsule consists of two pieces, a cap and a body, one fitting inside the other. The hard gelatine capsules are produced empty and filled in a separate operation step. The soft gelatin capsule is a capsule which is manufactured and filled in one single operation.

As mentioned above, the emulsion pre-concentrate transforms into an oil-in-water emulsion upon contact with the gastrointestinal fluids, whereby the active drug is released.

Thus, the composition will form an *in situ* oil-in-water emulsion in the gastrointestinal tract (GI tract).

The pharmaceutical composition of the present invention is particularly useful in the treatment of pain and inflammation. The wording "pain" is intended to include, but not limited to, nociceptive and neuropathic pain or combinations thereof; acute, intermittent and chronic pain; cancer pain; migraine and headaches of similar origin. The wording "inflammation" is intended to include, but not limited to, rheumatoid arthritis; ostheoarthritis; and juvenile arthritis.

Methods of preparation

The pharmaceutical composition of the present invention may be prepared mainly by the following alternative methods:

I. Mixing

a) The oily or semi-solid NO-releasing NSAID is put in a vessel, solid or semi-solid surfactant and solid/oily fat (optional) is added. The mixture is heated to the temperature corresponding to the melting point of the excipients , making the formulation fluid, mixed thoroughly until homogenous (visual inspection) and the pre-concentrate is filled into capsules suitable for oral administration.

b) Alternatively, the oily NO-releasing NSAID is put in a vessel and fluid surfactant is added. The mixture is mixed thoroughly until homogenous (visual inspection) and the pre-concentrate is filled into capsules suitable for oral administration.

c) In a further alternative method, the oily NO-releasing NSAID is put in a vessel, finely grinded (particle size < 177 um) solid surfactant is added. The liquid mixture is mixed

thoroughly until homogenous (visual inspection) and the pre-concentrate is filled into capsules suitable for oral administration.

d) In still an alternative method the semi-solid/solid surfactant (s) is put in a vessel, and one or more alcohols are added. The mixture is heated to the temperature corresponding to the melting point of the excipients, making the formulation fluid, mixed thoroughly until homogenous (visual inspection). The NO-NSAID is added, and the mixture is mixed thoroughly until homogenous (visual inspection). The pre-concentrate is filled into capsules suitable for oral administration.

e) In yet a further alternative method the liquid surfactant(s) is put in a vessel, and one or more alcohols are added. The mixture is blended thoroughly until homogenous (visual inspection). The NO-NSAID is added, and the mixture is mixed thoroughly until homogenous (visual inspection). The pre-concentrate is filled into capsules suitable for oral administration.

In order to fill a two-piece capsule or a softgel capsule with a liquid, the formulation must be within a certain viscosity range, as determined by the manufacturer, at the filling temperature suitable for the process. For a two-piece capsule the maximum filling temperature is roughly 70 °C. The viscosity of the formulation should normally be in the range 50-1000 cPoise (=0.05-1 Pas) at the temperature chosen for the filling process. For the filling of the formulation into softgel capsules, process temperature is not allowed to exceed 30-40 °C (the exact temperature depending on the manufacturer). The formulation must be liquid and have a viscosity that allows it to be pumpable at the filling temperature. In order to make the formulation liquid with an acceptable viscosity, several additives may be used, for example Cremophor EL®.

II. Filling

For the filling procedure it is required that the composition is in liquid form at the temperature of filling. Semisolid thermosoftening compositions are therefore filled above

the liqueifying temperature. Soft gelatine capsules are manufactured and filled in one operation, and may be filled at temperatures of up to 40 °C, whereas hard gelatine capsules may be filled at temperatures of up to 70 °C. Hard gelatin capsules filled with compositions that remain liquid at storage temperature require sealing, e.g. by gelatin banding, to prevent leakage. The process of liquid filling of hard gelatin capsules and product requirements are e.g. described in *W.J. Bowtle, Pharmaceutical Technology Europe, October 1998; V.M. Young, Pharmaceutical Manufacturing and Packaging Sourcer, March 1999;* and *E.T. Coole, Pharmaceutical Technology International, September/October 1989.* Using two piece capsules permits filling of more than one phase into a single capsule, which may be desired for bi-or multiphase drug release *(W.J. Bowtle et al.,Int. J. Pharm. 141 (1996), pp. 9-16).* Several phases of solidifying material can be filled in single steps. The final phase may be liquid if required. The number of phases is only restricted by the capsule size, and volume of the single phases. This special feature may also allow controlled release or separation of different drug substances formulated in the same capsule. Additionally, capsules may be processed further, e.g. by enteric coating.

III. Combination with PPI's

The oily or semi-solid NO-releasing NSAID is put in a vessel, solid or semi-solid surfactant and solid/oily fat (optional) is added. The mixture is heated to the temperature corresponding to the melting point of the excipients , making the formulation fluid, mixed thoroughly until homogenous (visual inspection) and prepared enteric coating layered pellets comprising an acid susceptible proton pump inhibitor are added to the mixture. The pre-concentrate with the suspended PPI-pellets is filled into capsules, where it solidifies, suitable for oral administration.

Alternatively the oily or semi-solid NO-releasing NSAID is put in a vessel, solid surfactant and solid/oily fat (optional) is added. The mixture is heated to the temperature corresponding to the melting point of the excipients , making the formulation fluid, mixed thoroughly until homogenous (visual inspection). The pre-concentrate is filled into

capsules suitable for oral administration, where it solidifies. A protective layer of paraffin, or any other inert thermosoftening base suitable for oral administration, is added and allowed to solidify. On top of the paraffin, the prepared PPI-pellets are added.

In still an alternative method, the oily NO-releasing NSAID is put in a vessel and fluid surfactant is added. The mixture is mixed thoroughly until homogenous (visual inspection), and the prepared PPI-pellets are added to the mixture. The pre-concentrate with suspended PPI-pellets is filled into capsules suitable for oral administration.

IV. Characterisation of the formulations

In order to characterise formulations, the time required for the formulation to form an oil-in-water emulsion upon contact with simulated gastric fluid, SGF, (without enzymes), is determined, and the formed emulsion is characterised. SGF comprises of 7 millilitres concentrated hydrochloric acid, 2 grams of sodium chloride and distilled water to give the solution a total volume of 1 L. The "emulsion forming test" is performed in test tubes (beaker) with magnetic stirring. The test tube, containing a small magnet, is filled with 12.5 ml SGF without enzymes, corresponding to one tenth of the average volume of gastric fluid in humans, and formulation corresponding to one tenth of the dose of active compound is added. If the formulation being characterised is a combination with a PPI, the PPI-pellets are checked in order that they are unaffacted by the SGF, which is made by visual inspection. If the enteric coating of the PPI-pellets is affected, the PPI may be affected negatively in pH=1.2, and this can be observed as a marked change in colour.

The time for emulsion formation will vary from 30 seconds and up to 15 minutes, depending on the composition of the formulation. If one or more short-chain alcohols are added, the time for emulsion formation will vary between 2-3 seconds and 3-4 minutes. Also the average particle size of the formed emulsion is studied with Laser Diffraction, LD, or Photon Correlation Spectroscopy, PCS. Depending on particle size either of the two methods may be used.

Detailed description of the invention

The invention will now be described in more detail by the following examples, which are not to be construed as limiting the invention.

The following emulsion pre-concentrates were prepared.

In the Examples1-7 below, the active compound used in the formulations was a compound of the formula (Ia) above.

Example 1

	amount [g]
(i) Compound of formula (Ia)	1000
(ii) Pluronic F127®	1000

A semi-solid formulation was obtained by melting 1 kg of Pluronic F127 ® (Poloxamer 407) by heating to 62 °C. The melt was stirred thoroughly to ensure that no solid particles were present.

1 kg of the compound of formula (Ia) was added to the melted Pluronic F127®, and the mixture was allowed to reach a temperature of 62 °C. The liquid formulation was mixed until homogenous (checked by visual inspection). The resulting liquid formulation was then filled into hard gelatin capsules. The formulation becomes a semi-solid upon cooling (in the capsule).

Characterization

150 milligram of the formulation was put in 12.5 millilitres of SGF (without enzymes) and magnetic stirring. The following results were obtained:

Time to emulsion: 13 minutes

Average particle size: 2-3 μm

The viscosity was measured in a Stress Tech cone and plate viscometer, measurement system C 40 4 PC, at the shear rate 20 s^{-1}. The flow was more or less Newtonian.

Example 2

	amount [g]
(i) Compound of formula (Ia)	1000
(ii) Pluronic L121®	1000

A liquid formulation was prepared by mixing 1 kg of the liquid surfactant Poloxamer 401, with 1 kg of the compound of formula (Ia) at room temperature. The liquid formulation was mixed until homogenous (checked by visual inspection). The resulting liquid formulation was then filled into hard gelatin capsules.

Characterization

150 milligram of the formulation was put in 12.5 millilitres of SGF (without enzymes) and magnetic stirring. The following results were obtained:

Time to emulsion: 20 seconds

Average particle size: 11 μm

Example 3

	amount [g]
(i) Compound of formula (Ia)	1000
(ii) Polyglycol BM 45®	1000
(iii) Sodium dodecyl sulphate	40

A formulation was obtained by mixing 1 kg of Polyglycol BM 45® (Poloxamine 1107), 40 grams of sodium dodecyl sulphate, acting as a co-surfactant, and 1 kg of the compound of formula (Ia). The liquid formulation was mixed until homogenous (checked by visual inspection). The resulting liquid formulation was then filled into hard gelatin capsules.

Characterization

150 milligram of the formulation was put in 12.5 millilitres of SGF (without enzymes) and magnetic stirring. The following results were obtained:

Time to emulsion: 15 minutes

Average particle size: 0.7 µm

Example 4

	amount [g]
(i) Compound of formula (Ia)	1000
(ii) Pluronic F127®	500
(iii) Cremophor EL®	500

To be able to fill the semi-solid formulation into soft gelatin capsules, process temperatures must be below 30-40 °C (the specific temperature depends on manufacturer). This means that the formulation must be fluid and pumpable below 30-40 °C. To obtain a formulation fluid at this temperature, some of the surfactant was replaced with Cremophor EL®. A melt was prepared as described in Example 1, except for the substitution of 0.5 kg surfactant with the same amount of Cremophor EL®.

Characterization

150 milligram of the formulation was put in 12.5 millilitres of SGF (without enzymes) and magnetic stirring. The following results were obtained:

Time to emulsion: 9 minutes

Average particle size: 4-5 µm

Example 5

	amount [g]
(i) Compound of formula (Ia)	1250
(ii) Pluronic F127®	1500
(iii) Fractionated coconut oil	1880

To ensure that low dose formulations will have a good filling precision, and to fill a capsule of a certain volume to minimise the amount of air present, the active compound may be filled up to volume with aliquot part coconut oil. A semi-solid formulation was obtained by melting 1500 kg of Pluronic F127® (Poloxamer 407) by heating to 62 °C. The melt was stirred thoroughly to ensure that no solid particles were present. 1.250 kg of the compounf of formula (Ia) and 1880 kg of fractionated coconut oil were added to the melted Pluronic F127®, and the mixture was allowed to reach a temperature of 62 °C. The liquid formulation was mixed until homogenous (checked by visual inspection). The resulting liquid formulation was then filled into hard gelatin capsules.

Characterization

One tenth of the formulation was put in 12.5 millilitres of SGF (without enzymes) and magnetic stirring. The following results were obtained:

Time to form emulsion: 10 minutes

Average particle size: 5 µm

Example 6

	amount [g]
(i) Compound of formula (Ia)	62.5

(ii) Pluronic F127®	375
(iii) Fractionated coconut oil	312.5

The formulation was prepared as described for Example 5 above.

Characterization

Characterization was performed as for Example 5 above. The following results were obtained:

Time to form emulsion:	10 minutes
Average particle size:	36 μm

Example 7

	amount [g]
(i) Compound of formula (Ia)	62.5
(ii) Pluronic F127®	375
(iii) Fractionated castor oil	312.5

The formulation was prepared as described for Examples 5 above.

Characterization

Characterization was performed as for Example 5 above. The following results were obtained:

Time to form emulsion:	10 minutes
Average particle size:	81 μm

Example 8

The active compound of formula (Ib) above was used in the formulation of the present Example 8.

	amount [g]
(i) Compound of formula (Ib)	75
(ii) Polyglycol BM45®	75

A formulation was prepared in the same way as for the preceding Examples.

Characterization

Time to form emulsion: 1.5 minutes

Average particle size: 5 μm

Example 9

The active compound of formula (Ic) above was used in the formulation of the present Example 9.

	amount [g]
(i) Compound of formula (Ic)	75
(ii) Polyglycol BM45®	75

A formulation was prepared in the same way as for the preceding Examples.

Characterization

Time to form emulsion: 3 minutes

Average particle size: 2 μm

Example 10

The active compound of formula (Id) above was used in the formulation of the present Example 10.

	amount [g]
(i) Compound of formula (Id)	75
(ii) Polyglycol BM45®	75

A formulation was prepared in the same way as for the preceding Examples.

Characterization

Time to form emulsion: 0.5 minutes

Average particle size: 2 µm

Example 11

The active compound of formula (Ie) above was used in the formulation of the present Example 11.

	amount [g]
(i) Compound of formula (Ie)	75
(ii) Polyglycol BM45®	75

A formulation was prepared in the same way as for the preceding Examples.

Characterization

Time to form emulsion: 1 minute

Average particle size: 4 µm

Example 12

The active compound of formula (If) above was used in the formulation of the present Example 12.

	amount [g]
(i) Compound of formula (If)	75
(ii) Polyglycol BM45®	75

A formulation was prepared in the same way as for the preceding Examples.

Characterization

Time to form emulsion: 1 minute

Average particle size: 2 µm

Example 13

The active compound of formula (Ig) above was used in the formulation of the present Example 13.

	amount [g]
(i) Compound of formula (Ig)	75
(ii) Polyglycol BM45®	75

A formulation was prepared in the same way as for the preceding Examples.

Characterization

Time to form emulsion: 3 minutes

Average particle size: 1 µm

Example 14

The active compounds of formulas (Ia) and (Ik) above were used in the formulation of the present Example 14.

	amount [g]
(i) Compound of formula (Ia)	250
(ii) Compound of formula (Ik)	8
(iii) Pluronic L121®	250

A formulation was prepared by dissolving the compound of formula (Ih) in the compound of formula (Ia), whereafter the Pluronic L121® (Poloxamer 401) was added to this mixture. The liquid formulation was mixed until homogenous (checked by visual inspection).

Characterization

The formulation was put in 20 ml of SGF (without enzymes) under magentic stirring. The time to emulsion formation was determined. The following results were obtained:

Time to form emulsion: 5-10 seconds

Example 15

The active compounds of formulas (Ia) and (Ii) above were used in the formulation of the present Example 15.

	amount [g]
(i) Compound of formula (Ia)	250
(ii) Compound of formula (Ii)	8
(iii) Pluronic L121®	250

A formulation was prepared as described for Example 14.

Characterization

Performed as in the previous Example 14 above.

Time to form emulsion: 3 minutes

Example 16

	amount [g]
(i) Compound of formula (Ia)	750
(ii) Pluronic F127®	450
(iii) Omeprazole	20

A semi-solid formulation was obtained by melting 450 g Pluronic F127® (Poloxamer 407) by heating to 62 °C. The melt was stirred thoroughly to ensure that no solid particles were present. 750 g of a compound of formula (Ia) above were added to the melted Pluronic F127®, and the mixture was allowed to reach a temperature of 62 °C. 20 g Omeprazole in the form of prepared enteric coating layered pellets comprising omeprazole Mg salt, prepared as described in WO 96/01623, Example 2, was added. The liquid formulation was mixed until homogenous (checked visual inspection) and filled into hard gelatine capsules. The formulation became a semi-solid upon cooling (in the capsule).

Characterization

120 mg of formulation was put in 12.5 ml of SGF (without enzymes) at 37 °C, and magnetic stirring. The SEDDS formed an emulsion upon contact with SGF, and the PPI-pellets remained unaffected by the SEDDS and the pH=1.2, as seen by no change of colour. The time for emulsion formation was 12 minutes.

Example 17

	amount [g]
(i) Compound of formula (Ia)	750
(ii) Pluronic L121®	450
(iii) Omeprazole	20

A liquid formulation was prepared by mixing 450 g of the liquid surfactant Poloxamer 401, with 750 g of a compound of the formula (Ia) above, at room temperature. 20 g Omeprazole in the form of enteric coating layered pellets comprising omeprazole Mg salt, prepared as described in WO 96/01623, Example 2, was added to the mixture. The liquid formulation was mixed until homogenous (checked by visual inspection) and filled into hard gelatine capsules.

Characterization

120 mg formulation was put in 12.5 ml of SGF (without enzymes) at 37 °C, and magnetic stirring. The SEDDS formed an emulsion upon contact with SGF, and the PPI-pellets remained unaffected by the SEDDS and the pH=1.2, as seen by no change of colour. The time for emulsion formation was 0.5 minutes.

Example 18

	amount [g]
(i) Compound of formula (Ia)	3
(ii) Pluronic L127®	0.843
(iii) sorbitanmonolaurat	0.282
(iv) glycerol	0.375

A semi-solid formulation was obtained by melting 0.843 gram of Pluronic F127® (Poloxamer 407), 0.282 gram of sorbitanmonolaurat and 0.375 gram of glycerol by heating to 62 °C. The melt was stirred thoroughly to ensure that no solid particles were present. 3

Grams of the compound of formula (Ia) was added to the mixture. The mixture was allowed to reach a temperature of 62 °C. The liquid formulation was mixed until homogenous (checked by visual inspection). The resulting liquid formulation was allowed to cool to a temperature of 30 °C, and was then filled into soft gelatin capsules. The formulation becomes a semi-solid upon cooling (in the capsule).

Characterization

112 milligram of the formulation was put in 12.5 millilitres of SGF (without enzymes) and magnetic stirring. The following result was obtained:

Time to emulsion: 2.5-3.5 minutes

Example 19

	amount [g]
(i) Compound of formula (Ia)	3
(ii) Pluronic L127®	0.843
(iii) sorbitanmonolaurat	0.282
(iv) propylene glycol	0.375

A semi-solid formulation was obtained by melting 0.843 gram of Pluronic F127® (Poloxamer 407), 0.282 gram of sorbitanmonolaurat and 0.375 gram of propylene glycol by heating to 62 °C. The melt was stirred thoroughly to ensure that no solid particles were present. 3 Grams of the compound of formula (Ia) was added to the mixture. The mixture was allowed to reach a temperature of 62 °C. The liquid formulation was mixed until homogenous (checked by visual inspection). The resulting liquid formulation was allowed to cool to a temperature of 30 °C, and was then filled into soft gelatin capsules. The formulation stays liquid upon cooling (in the capsule).

Characterization

112 milligram of the formulation was put in 12.5 millilitres of SGF (without enzymes) and magnetic stirring. The following result was obtained:

Time to emulsion: within 20 seconds

Example 20

	amount [g]
(i) Compound of formula (Ia)	3
(ii) Pluronic L101®	0.506
(iii) sorbitanmonolaurat	0.169
(iv) ethanol	0.225

A liquid formulation was prepared. A solution of 0.506 gram of Pluronic L101® (Poloxamer 331), 0.169 gram of sorbitanmonolaurat and 0.225 gram of ethanol, was mixed until homogenous (checked by visual inspection). 3 Grams of the compound of formula (Ia) was added to the mixture, at room temperature. The resulting liquid formulation was then filled into soft gelatin capsules.

Characterization

97 milligram of the formulation was put in 12.5 millilitres of SGF (without enzymes) and magnetic stirring. The following result was obtained:

Time to emulsion: within 20 seconds

In vivo study of formulations in mini pigs

A bioavailability study of formulations according to the present invention was performed after oral administration in fastened minipigs.

6 male Göttingen SPF minipigs were used in the study. At the start of the acclimatization period, the animals were 4 months old and had a weight of from 7.7 to 10.1. kg. The animals were fasted for 12 hours before treatment and until the blood sample at 4 hours post treatment had been taken. A supply of autoclaved hay was given daily as well. Twice daily, the animals were offered domestic quality drinking water.

A pharmaceutical composition of the invention, filled in a suitable unit dosage form according to the invention, was administered to each animal. The dose levels were approximately 15 µmol/kg body weight. 10 ml of tap water was given to facilitate the swallowing of the capsule or corresponding unit dosage.

All visible signs of ill health and any behavioural changes were recorded daily. Any deviation from normal was recorded with respect to time of onset, duration and severity. Included in the daily health check were observations of the consistency of faeces. All animals were weighed on arrival and of the first day of of each treatment.

Blood samples (5 ml) were taken from the jugular vein into Vacutainer tubes containing heparin. Blood samples were taken before treatment (0) and at 15, 30 and 45 minutes; 1, 1.5, 2, 4, 7 and 24 hours after treatment.

Claims

1. A pharmaceutical composition suitable for oral administration, in form of an emulsion pre-concentrate, comprising

(i) one or more NO-releasing NSAID(s);

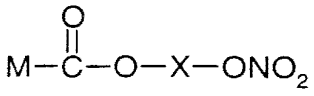
(ii) one or more surfactants;

(iii) optionally an oil or semi-solid fat;

said composition forming an *in-situ* oil-in-water emulsion upon contact with aqueous media such as gastrointestinal fluids.

2. A pharmaceutical composition according to claim 1, further comprising one or more short-chain alcohols.

3. A pharmaceutical composition according to claim 1 or 2, wherein the NO-releasing NSAID is a compound of the formula I

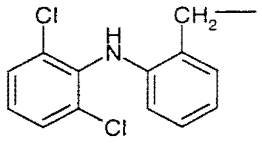


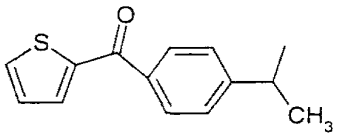
I

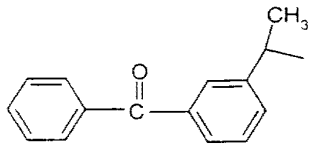
wherein

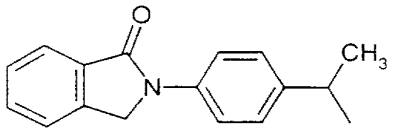
X is a spacer; and

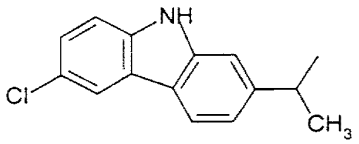
M is selected from anyone of

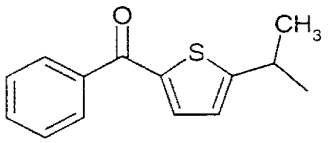


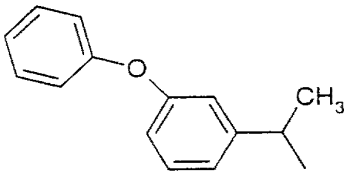


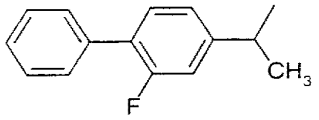


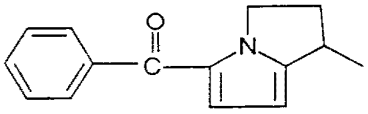


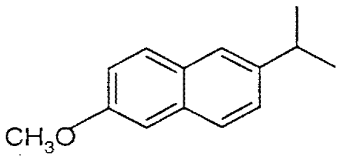


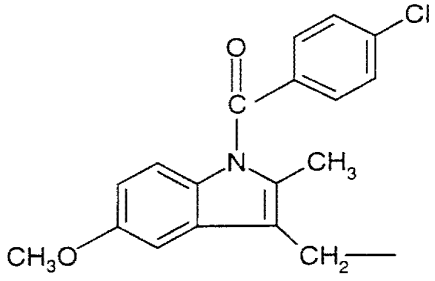


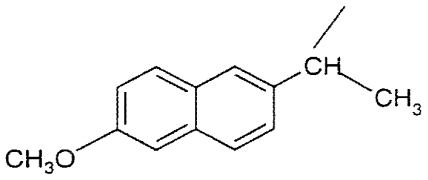


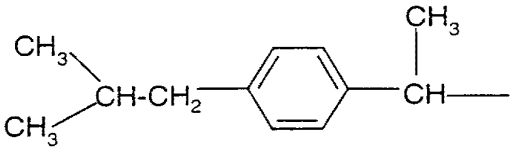












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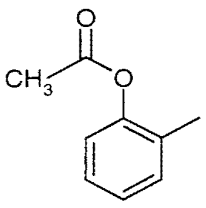
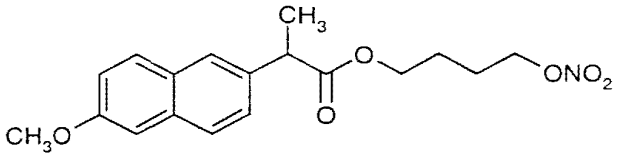


4. A pharmaceutical composition according to claim 3, wherein the spacer X of the NO-releasing NSAID is selected from a linear, branched or cyclic alkylene group $-(CH_2)-_n$ wherein n is an integer of from 2 to 10; $-(CH_2)_m-O-(CH_2)_p-$ wherein m and p are integers of from 2 to 10; and $-CH_2-pC_6H_4-CH_2-$.

5. A pharmaceutical composition according to any one of the preceding claims, wherein the NO-releasing NSAID is any one compound selected from



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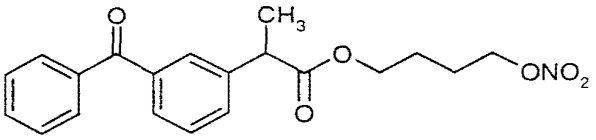
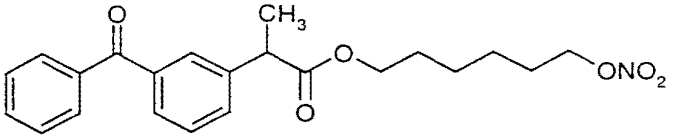


(Ib) ;



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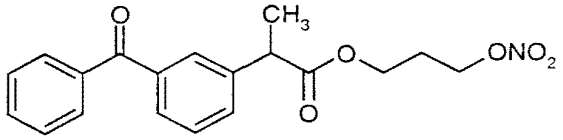
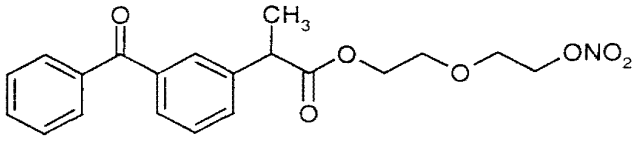
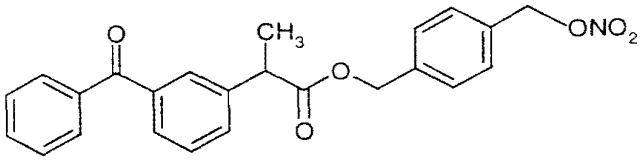


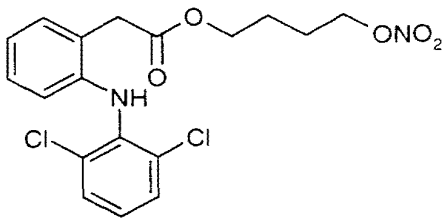
(Ic) ;



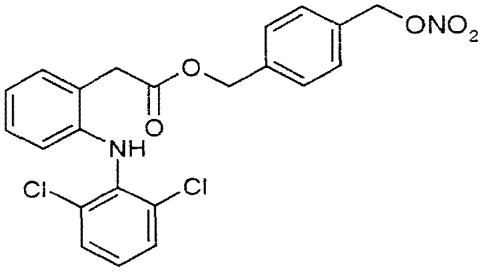
(Ie) ;



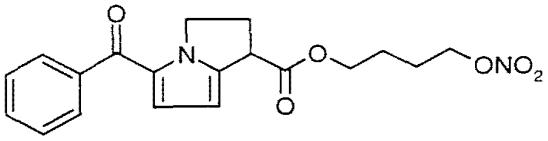
(If) ;



(Ig) ;



(Ii) ;



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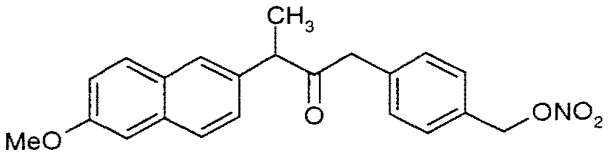

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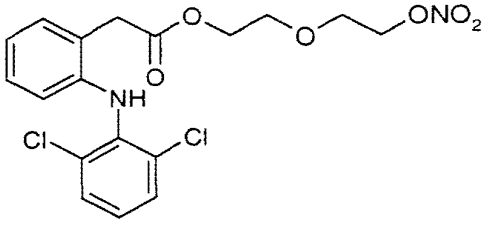
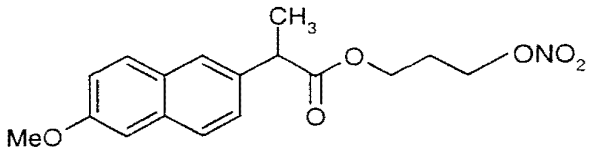
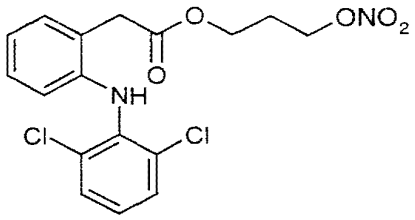


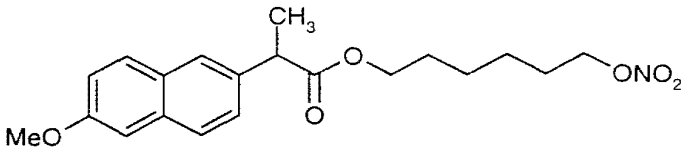
(IL) ;



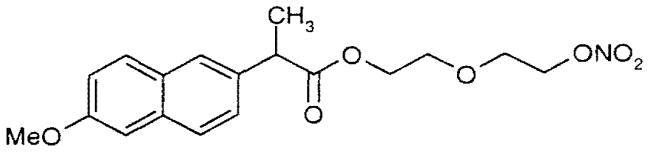
(Im) ;



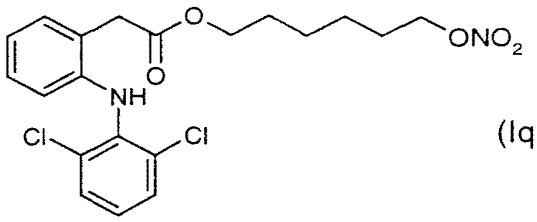
(In) ;



(Io) ;



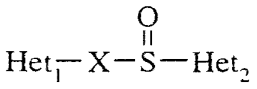
(Ip) ; and



(Iq)

6. A pharmaceutical composition according to any one of the preceding claims, further comprising individually enteric coating layered units of an acid susceptible proton pump inhibitor, or a pharmaceutically acceptable alkaline salt thereof.

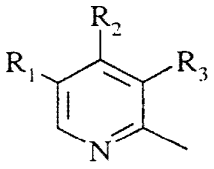
7. A pharmaceutical composition according to claim 6, wherein the acid susceptible proton pump inhibitor is selected from a compound of the general formula I or a pharmaceutically acceptable alkaline salt thereof, or one of its single enantiomer or an alkaline salt of the single enantiomer



I

wherein

Het_1 is



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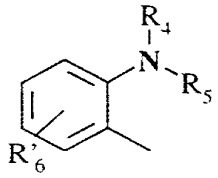

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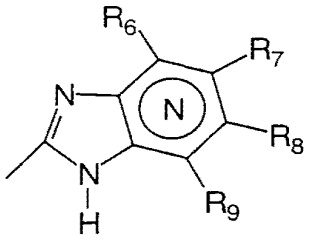

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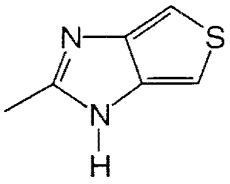
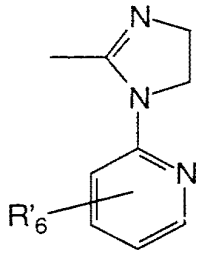


or



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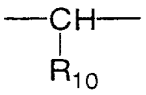

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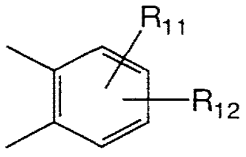


wherein

N in the benzimidazole moiety means that one of the carbon atoms substituted by R_6-R_9 optionally may be exchanged for a nitrogen atom without any substituents;

R_1, R_2 and R_3 are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R_4 and R_5 are the same or different and selected from hydrogen, alkyl and aralkyl;

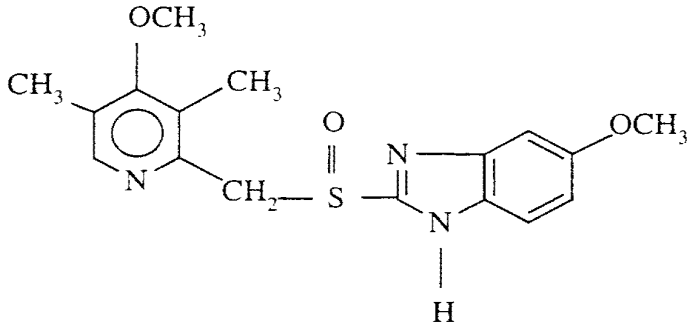
R_6' is hydrogen, halogen, trifluoromethyl, alkyl and alkoxy;

R_6-R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolyl, trifluoroalkyl, or adjacent groups R_6-R_9 form ring structures which may be further substituted;

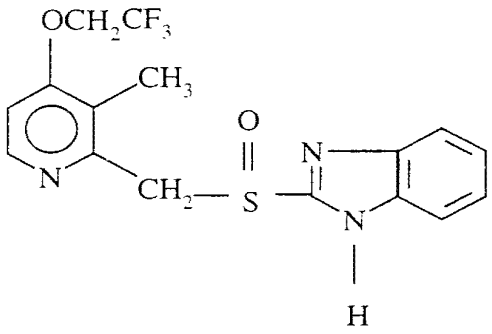
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl;
alkyl groups, alkoxy groups and moities thereof , they may be branched or straight C_1 - C_9 -chains or comprise cyclic alkyl groups, such as cycloalkyl-alkyl.

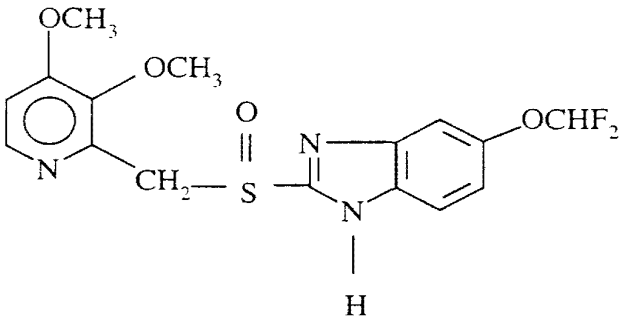
8. A pharmaceutical composition according to claim 7, wherein the acid susceptible proton pump inhibitor is selected from any one of



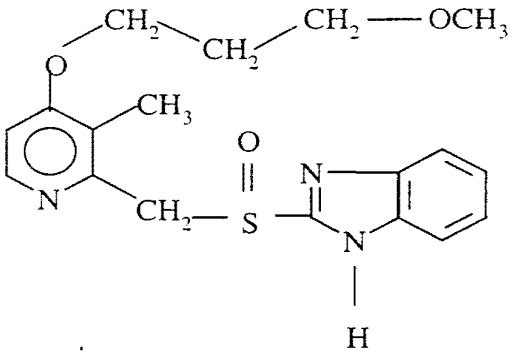
Omeprazole



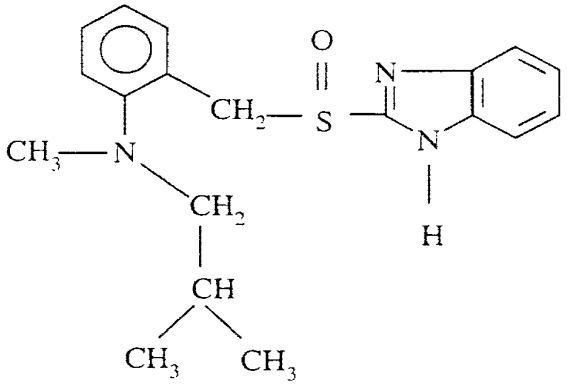
Lansoprazole



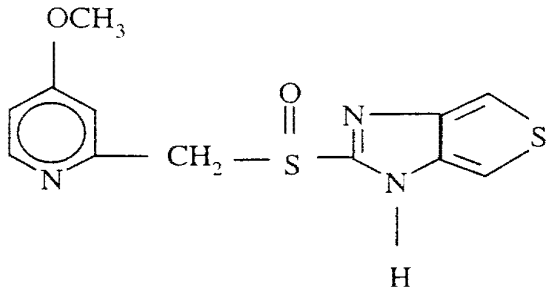
Pantoprazole

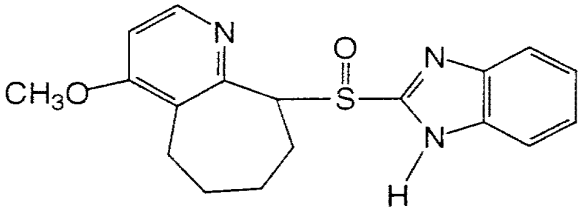


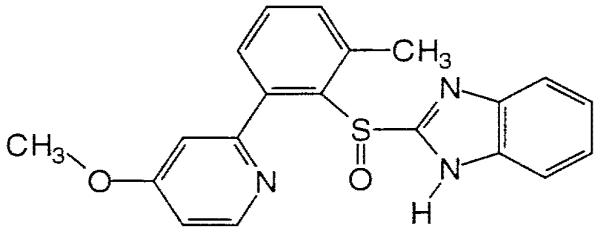
Pariprazole

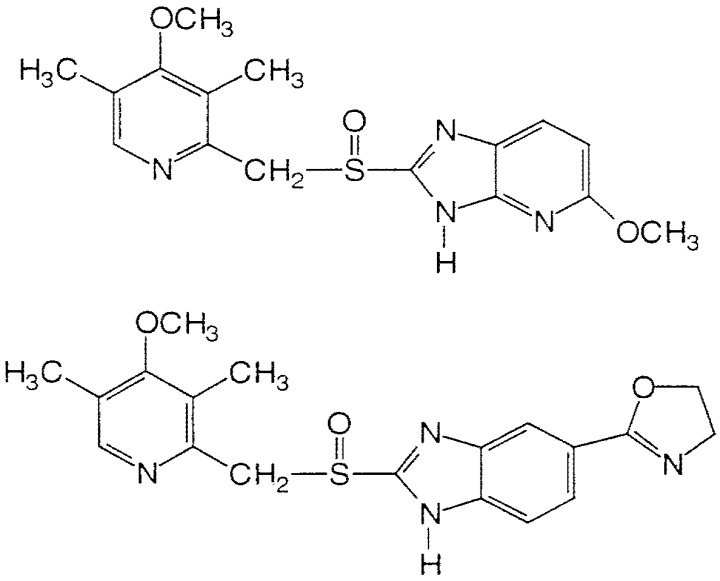


Leminoprazole









9. A pharmaceutical composition according to claim 8, wherein the acid susceptible proton pump inhibitor is selected from omeprazole, an alkaline salt of omeprazole, (S)-omeprazole and an alkaline salt of (S)-omeprazole.

10. A pharmaceutical composition according to claim 9, wherein the alkaline salt of omeprazole or (S)-omeprazole is a magnesium salt.

11. A pharmaceutical composition according to claim 6, wherein the NO-releasing NSAID is a compound of formula Ia and the acid susceptible proton pump inhibitor is selected from omeprazole, an alkaline salt of omeprazole, (S)-omeprazole and an alkaline salt of (S)-omeprazole.

12. A pharmaceutical compositon according to any one of the preceding claims, wherein the amount of the NO-releasing NSAID is from 50-1500 mg per unit dose.

13. A pharmaceutical compositon according to claim 12, wherein the amount of the NO-releasing NSAID is from 125-500 mg per unit dose.

14. A pharmaceutical compositon according to any one of the preceding claims, wherein the surfactant is a block co-polymer.

15. A pharmaceutical compositon according to any one of the preceding claims, wherein the surfactant is a non-ionic surfactant.

16. A pharmaceutical composition according to claim 15, wherein the non-ionic surfactant is a poloxamer.

17. A pharmaceutical compositon according to claim 15, wherein the surfactant is selected from any one of Poloxamer 407; Poloxamer 401; Poloxamer 237; Poloxamer 338; Poloxamer 331; Poloxamer 231; Poloxamine 908; Poloxamine 1307; Poloxamine 1107; and polyoxyethylene polyoxybutylene block copolymer.

18. A pharmaceutical compositon according to any one of the preceding claims, wherein the total amount of surfactant(s) is from 12.5-6000 mg.

19. A pharmaceutical compositon according to claim 18, wherein the total amount of surfactant(s) is from 100-500 mg.

20. A pharmaceutical compositon according to any one of the preceding claims, wherein the ratio NO-releasing NSAID: surfactant is within the range of from 1:0.1 – 1:10.

21. A pharmaceutical compositon according to claim 20 wherein the ratio NO-releasing NSAID: surfactant is within the range of from 1:0.3 –1:3.

22. A pharmaceutical compositon according to any one of the preceding claims, wherein an oil is present.

23. A pharmaceutical compositon according to claim 22, wherein the oil is a vegetable oil.

24. A pharmaceutical compositon according to claim 23, wherein the vegetable oil is selected from coconut oil, corn oil, soybean oil, rape seed oil, safflower oil and castor oil.

25. A pharmaceutical composition according to claim 22, wherein the oil is an animalic oil.

26. A pharmaceutical composition according to claim 25, wherein the animalic oil is a fish oil or one or more mono-, di- or triglycerides.

27. A pharmaceutical composition according to any one of the preceding claims, wherein a semi-solid fat is used as filler.

28. A pharmaceutical composition according to claim 27, wherein the semi-solid fat is selected from mono-, di- and triglycerides.

29. A pharmaceutical composition according to claim 28, wherein the mono-, di- and triglycerides are selected from glyceryl palmitostearate, or a mixture of mono-, di and tri-esters of glycerol, mono- and di-esters of polyethylene glycol or free polyethylene glycol.

30. A pharmaceutical composition according to any one of claims 2-29, wherein the short-chain alcohol is selected from ethanol, propyleneglycol or glycerol.

31. A pharmaceutical composition according to any one of the preceding claims, further comprising a co-surfactant.

32. A unit dosage form filled with a pharmaceutical composition according to any one of the preceding claims.

33. A unit dosage form according to claim 32, selected from any one of capsules, drinking ampoules, dose cushion, chewable soft pill, and chewy-base lozenges.

34. A unit dosage form according to claim 33, in form of a capsule.

35. A unit dosage form according to claim 34, wherein said capsule is a hard gelatine capsule.

36. A unit dosage form according to claim 34, wherein said capsule is a soft gelatine capsule.

37. An oral solution comprising a pharmaceutical composition according to any one of claims 1-31 dissolved in water.

38. A kit comprising a pharmaceutical composition according to claim 1 in a unit dosage form, in combination with an acid susceptible proton pump inhibitor.

39. A kit according to claim 38, wherein the proton pump inhibitor is enteric coated.

40. A kit according to claim 39, wherein the proton pump inhibitor is enteric coated omeprazol.

41. A method for the treatment of pain, whereby a pharmaceutical composition according to any one of the preceding claims, is administered to a patient in need of such treatment.

42. A method for the treatment of inflammation, whereby a pharmaceutical composition according to any one of the preceding claims, is administered to a patient in need of such treatment.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/00467

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 9/113
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)

IPC7: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI DATA, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9509831 A1 (NICOX LIMITED), 13 April 1995 (13.04.95) --	1-42
A	WO 9508983 A1 (GATTEFOSSE S.A.), 6 April 1995 (06.04.95) --	1-42
A	WO 9956727 A2 (ELAN CORPORATION, PLC), 11 November 1999 (11.11.99) -- --------	1-42

☐ Further documents are listed in the continuation of Box C. ☒ 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 application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2001	30 -07- 2001
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carolina Gómez Lagerlöf/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE0100467

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 41-42
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE0100467

Claims 41-42 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/07/01

International application No.
PCT/SE 01/00467

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9509831 A1	13/04/95	AT 168986 T	15/08/98
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		AU 7809294 A	01/05/95
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		EP 0670715 A,B	13/09/95
		ES 2101574 T	01/07/97
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WO 9956727 A2	11/11/99	AU 3843999 A	23/11/99
		EP 1075252 A	14/02/01
		US 5976963 A	02/11/99

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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(43) International Publication Date
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(10) International Publication Number
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(25) Filing Language: English

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(30) Priority Data:
P 200100329 14 February 2001 (14.02.2001) ES

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(74) Agent: **GIDDINGS, Peter, John**; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/066002 A2

(54) Title: PHARMACEUTICAL FORMULATION

(57) Abstract: The present invention provides a pharmaceutical formulation which comprises a core comprising a first active ingredient, a coating comprising a second active ingredient which is incompatible with the first active ingredient and a barrier between the core and the coating which prevents physical contact between the core and the coating, characterised in that the barrier is formed on the core by film-coating and the coating is formed on the barrier by press-coating.

Pharmaceutical Formulation

The present invention relates to improvements in the formulation of pharmaceutical compositions. In particular, it relates to improvements in the formulation of pharmaceutical compositions wherein two or more active ingredients are present in the composition and wherein at least two of the active ingredients are incompatible with one another.

In the context of the present application, the term "incompatible", when applied to active ingredients, means that the active ingredients cannot normally be formulated into a pharmaceutical composition wherein the active ingredients are in physical contact. The incompatibility is usually, but not necessarily, the result of a chemical reaction between the active ingredients which results in a reduction of the therapeutic activity of at least one of the active ingredients.

It will be appreciated by a person skilled in the art that many pharmaceutical compositions which comprise incompatible active ingredients may be formulated as described herein. However, the present invention is particularly directed to compositions which comprise acetylsalicylic acid or a physiologically acceptable salt of acetylsalicylic acid and ranitidine or a physiologically acceptable salt of ranitidine, such as ranitidine hydrochloride.

Systemic non-steroidal anti-inflammatory drugs such as acetylsalicylic acid are known to give undesirable side effects. In particular they are known to be ulcerogenic and can therefore give rise to gastric ulceration when administered orally over a period of time to a patient.

Ranitidine is the approved name for N-[2-[[[5-(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl-N'-methyl-2-nitro-1,1-ethanediamine which is described and claimed in British Patent No 1,565,966. It is known to be a potent histamine H_2-antagonist which may be used in the treatment of conditions where there is an advantage in lowering gastric acidity, particularly in gastric and peptic ulceration.

It is also known from British Patent No 2,105,193 that mucosal lesions of the gastrointestinal tract caused by systemic non-steroidal anti-inflammatory drugs can be significantly reduced by co-administering ranitidine. British Patent No 2,105,193 discloses pharmaceutical compositions comprising a systemic non-steroidal anti-inflammatory drug and ranitidine or a physiologically acceptable salt thereof. However, experiments show that there is a clear chemical incompatibility between ranitidine hydrochloride (the most preferred physiologically acceptable salt of ranitidine) and acetylsalicylic acid. These two active ingredients react chemically with each other to produce degradation products. The reaction becomes manifest in a matter of days and implies a serious stability problem for pharmaceutical compositions containing both active ingredients.

The present invention addresses the problems outlined above and provides a pharmaceutical formulation which comprises a core comprising a first active ingredient, a coating comprising a second active ingredient which is incompatible with the first active ingredient and a barrier between the core and the coating which prevents physical contact between the core and the coating, characterised in that the barrier is formed on the core by film-coating and the coating is formed on the barrier by press-coating.

It will be appreciated by those skilled in the art that further barriers and coatings may be formed on the composition if so desired. This may be necessary if, for example, more than two active ingredients are present and each active ingredient is incompatible with all or some of the other active ingredients.

In one embodiment of the present invention the core comprises ranitidine or a physiologically acceptable salt thereof and the coating comprises acetylsalicylic acid or a physiologically acceptable salt thereof.

In a preferred embodiment, ranitidine or a physiologically acceptable salt thereof is present in the core in an amount sufficient to reduce gastrointestinal distress caused by acetylsalicylic acid. In a more preferred embodiment, ranitidine is present in the core in an amount of from 10 to 200 mg or a physiologically acceptable salt of ranitidine is present in the core in an amount which is

equivalent to from 10 to 200 mg of ranitidine. In a more preferred embodiment, ranitidine is present in the core in an amount of from 50 to 100 mg or a physiologically acceptable salt of ranitidine is present in the core in an amount which is equivalent to from 50 to 100 mg of ranitidine. In a more preferred embodiment, ranitidine is present in the core in an amount of from 70 to 80 mg or a physiologically acceptable salt of ranitidine is present in the core in an amount which is equivalent to from 70 to 80 mg of ranitidine.

It is preferable that the ranitidine be present in the form of a physiologically acceptable salt. Such salts include salts of inorganic or organic acids such as the hydrochloride, hydrobromide, sulphate, acetate, maleate, succinate and fumarate salts. In a particularly preferred embodiment, ranitidine is present in the form of ranitidine hydrochloride.

As well as the first active ingredient, the core may also comprise one or more pharmaceutical excipients, disintegrants, lubricants, anti-adhesion agents, flow agents, diluents or taste-masking agents.

In a preferred embodiment, the one or more lubricants are present in the core in an amount of from 0.1 to 5 % by weight based on the total weight of the core. In a more preferred embodiment, the one or more lubricants are present in the core in an amount of from 0.1 to 3 % by weight based on the total weight of the core. In a still more preferred embodiment, the one or more lubricants are present in the core in an amount of from 0.5 to 1.0 % by weight based on the total weight of the core. Examples of suitable lubricants include magnesium stearate, calcium stearate, zinc stearate, stearic acid, palmitic acid and sodium stearyl fumarate. A preferred lubricant is magnesium stearate.

In a preferred embodiment, the one or more diluents are present in the core in an amount of from 10 to 90 % by weight based on the total weight of the core. In a more preferred embodiment, the one or more diluents are present in the core in an amount of from 30 to 70 % by weight based on the total weight of the core. In a still more preferred embodiment, the one or more diluents are present in the core in an amount of from 40 to 60 % by weight based on the total weight of the core. Examples of suitable diluents include microcrystalline cellulose, powdered

cellulose, lactose, mannitol, sucrose and calcium phosphate. A preferred diluent is microcrystalline cellulose.

In a preferred embodiment, the one or more disintegrants are present in the core in an amount of from 0.1 to 10 % by weight based on the total weight of the core. In a more preferred embodiment, the one or more disintegrants are present in the core in an amount of from 0.1 to 5 % by weight based on the total weight of the core. In a still more preferred embodiment, the one or more disintegrants are present in the core in an amount of from 1 to 3 % by weight based on the total weight of the core. An example of a suitable disintegrant is sodium croscaramelose.

In a preferred embodiment, acetylsalicylic acid is present in the coating in an amount of from 50 to 1000 mg or a physiologically acceptable salt of acetylsalicylic acid is present in the core in an amount which is equivalent to from 50 to 1000 mg of acetylsalicylic acid. In a more preferred embodiment, acetylsalicylic acid is present in the coating in an amount of from 300 to 700 mg or a physiologically acceptable salt of acetylsalicylic acid is present in the coating in an amount which is equivalent to from 300 to 700 mg of acetylsalicylic acid. In a more preferred embodiment, acetylsalicylic acid is present in the coating in an amount of from 450 to 550 mg or a physiologically acceptable salt of acetylsalicylic acid is present in the coating in an amount which is equivalent to from 450 to 550 mg of acetylsalicylic acid. In an embodiment the acetylsalicylic acid or the physiologically acceptable salt of acetylsalicylic acid may be microencapsulated with ethyl cellulose. An example of a commercially available microencapsulated acetylsalicylic acid product is Rhodine NCR-P™.

As well as the second active ingredient, the coating may also comprise one or more pharmaceutical excipients, disintegrants, lubricants, anti-adhesion agents, flow agents, diluents or taste-masking agents.

In a preferred embodiment, the one or more diluents are present in the coating in an amount of from 5 to 90 % by weight based on the total weight of the coating. In a more preferred embodiment, the one or more diluents are present in the coating in an amount of from 5 to 50 % by weight based on the total weight of

the coating. In a still more preferred embodiment, the one or more diluents are present in the coating in an amount of from 10 to 20 % by weight based on the total weight of the coating. Examples of suitable diluents include copovidone, microcrystalline cellulose, powdered cellulose, maize starch, lactose, Cellactose™80 (a compound formed from 25% powdered cellulose and 75% lactose monohydrate) and Ludipress™ (a compound formed from 93% lactose monohydrate, 3.5% povidone and 3.5% crospovidone). A preferred diluent is Cellactose™80.

In a preferred embodiment, the one or more disintegrants are present in the coating in an amount of from 0.1 to 10 % by weight based on the total weight of the coating. In a more preferred embodiment, the one or more disintegrants are present in the coating in an amount of from 0.1 to 5 % by weight based on the total weight of the coating. In a still more preferred embodiment, the one or more disintegrants are present in the coating in an amount of from 1 to 3 % by weight based on the total weight of the coating. Examples of suitable disintegrants include maize starch, crospovidone, sodium starch glycolate, bentonite, aluminium magnesium silicate and sodium croscaramelose. A preferred disintegrant is sodium croscaramelose.

In a preferred embodiment, the one or more lubricants are present in the coating in an amount of from 0.1 to 10 % by weight based on the total weight of the coating. In a more preferred embodiment, the one or more lubricants are present in the coating in an amount of from 0.1 to 5 % by weight based on the total weight of the coating. In a still more preferred embodiment, the one or more lubricants are present in the coating in an amount of from 0.1 to 1.0 % by weight based on the total weight of the coating. Examples of suitable lubricants include hydrogenated vegetable oil, stearic acid, palmitic acid and sodium stearyl fumarate. A preferred lubricant is sodium stearyl fumarate.

In a preferred embodiment, the one or more anti-adhesion agents are present in the coating in an amount of from 0.1 to 10 % by weight based on the total weight of the coating. Examples of suitable anti-adhesion agents are talc and hydrogenated vegetable oil.

In a preferred embodiment, the one or more flow agents are present in the coating in an amount of from 0.01 to 5 % by weight based on the total weight of the coating. In a more preferred embodiment, the one or more flow agents are present in the coating in an amount of from 0.01 to 1 % by weight based on the total weight of the coating. In a still more preferred embodiment, the one or more flow agents are present in the coating in an amount of from 0.01 to 0.5 % by weight based on the total weight of the coating. An example of a suitable flow agent is colloidal anhydrous silica.

The barrier is present in order to prevent physical contact between the core and the coating and therefore prevent reaction between the first and second active ingredients which are present in the core and the coating respectively. Preferably the barrier also reduces the transmission of moisture between the core and the coating. More preferably the barrier is substantially impermeable to the transmission of moisture between the core and the coating.

In a preferred embodiment the barrier is present in an amount of from 1 to 20 % by weight based on the total weight of the core. In a more preferred embodiment the barrier is present in an amount of from 3 to 15 % by weight based on the total weight of the core. In a still more preferred embodiment the barrier is present in an amount of from 5 to 10 % by weight based on the total weight of the core.

In general terms any material that reduces water transmission and is compatible with the active ingredients contained in the core and the coating can be used to physically separate them. Thus, a barrier material which comprises one or more of stearic acid, polyvinyl alcohol, ethyl cellulose, microcrystalline cellulose, hydroxypropyl cellulose and methacrylic acid copolymer type C, can be used.

An example of a suitable barrier material is OPADRY™ Aqueous Moisture Barrier (AMB) produced by the Colorcon Company (Reference OY-B-28920). OPADRY™ AMB is made up of polyvinyl alcohol, titanium dioxide, purified talc, lecithin and xanthan gum. The formula is supplied as a powder which is reconstituted using purified cold water before it is sprayed on the core. The actual solids content of the coating suspensions can be varied according to the

atomising capabilities of the spraying equipment. Preferably, the solids content is approximately 20% w/w.

Another example of a suitable barrier material is SEPIFILM™ Low Permeability (LP) produced by Seppic. SEPIFILM™ LP is made up of hydroxypropylmethyl cellulose, microcrystalline cellulose, stearic acid and pigments and/or lakes (if required).

Another example of a suitable barrier material is LUSTRECLEAR™ produced by FMC Corporation. LUSTRECLEAR™ is made up of microcrystalline cellulose, carrageenan, polyethylene glycol, hydroxyethyl cellulose, maltodextrin and pigments and/or lakes (if required).

Another example of a suitable barrier material is EUDRAGIT™ L 30D-55 produced by Degussa. If this barrier material is chosen, it should not be applied in an amount greater than approximately 1 mg/cm^2 of barrier material on the tablet surface. If more is used there is a danger of forming an enteric coating around the core which could reduce the bioavailability of the active ingredient in the core. EUDRAGIT™ L 30D-55 is made up of methacrylic acid – ethyl acrylate copolymer as a 30% dispersion in water. The mean relative molecular mass of the copolymer is approximately 250 000 and the ratio of carboxylic groups to ester groups is approximately 1:1. The material may also comprise surface-active agents such as sodium dodecyl sulphate and polysorbate 80. It contains not less than 46.0% m/m and not more than 50.6% m/m of methacrylic acid units, calculated with reference to the residue on evaporation.

Methods of manufacturing by press coating, also known as dry coating or compression coating are well known in the pharmaceutical industry. See for example; Pharmaceutics, the Science of Dosage Form Design, edited by M E Aulton, Published by Churchill Livingstone (part of the Longman Group) 1988, ISBN 0-443-03643-8. In particular pages 675 to 676 explain the method of press coating as follows. Press coating involves the compaction of granular material around an already preformed core using compressing equipment similar to that used for the core itself, e.g. Manesty Drycota. It is used mainly to separate chemically incompatible materials, one or more being placed in the core and the

other(s) in the coating layer. However, there is still an interface of contact left between the two layers. In cases where even this is important then the process of press coating can be taken one step further. It is possible to apply two press coatings to a tablet core using suitable equipment, e.g. Manesty Bicota. This equipment produces press coated tablets with perfect separation between the active core and the coating as these two can be separated by an inert coating. The technique is also described in Reminton: The Science and Practice of Pharmacy 19th Edition 1995, published by Mack Publishing Company, ISBN 0-912734-04-3. See in particular pages 1616 and 1631 which explain the method of manufacture by press coating as follows. Press coated tablets, also referred to as dry-coated, are prepared by feeding previously compressed tablets into a special tableting machine and compressing another granulation layer around the preformed tablets. They have all the advantages of compressed tablets, i.e. slotting, monogramming, speed of disintegration, etc, while retaining the attributes of sugar-coated tablets in masking the taste of the taste drug substance in the core tablets. An example of a press-coated tablet press is the Manesty Drycota. Press coated tablets can also be used to separate incompatible drug substances; in addition, they can provide a means to give an enteric coating to the core tablets.

The following journal articles also provide some discussion of the technique of press-coating:

Press-coated tablets for the sequential pulsed administration of two different drugs, International Journal of Pharmaceutics, Volume 99, Issues 2-3, 1993, pages 173-179, Maggi L, *et al.*

Press-coated tablets for time-programmed released of drug, Biomaterials, Volume 14, Issue 13, 1993 1017-1023, Conte U, *et al.*

The technique of film-coating is also well known in the pharmaceutical industry and is described for example in Pharmaceutics, the Science of Dosage Form Design, edited by M E Aulton, Published by Churchill Livingstone (part of the Longman Group) 1988, ISBN 0-443-03643-8. In particular pages 672 to 675 explain the method of film coating as follows. Film coating involves the

deposition, usually by a spray method, of a thin film of polymer surrounding the tablet core. It is possible to utilize conventional panning equipment but more usually specialized equipment is employed to take advantage of fast coating times and a high degree of automation is possible. The coating solution contains a polymer in a suitable liquid medium together with other ingredients such as pigments and plasticizers. This solution is sprayed on to a rotated mixed tablet bed. The drying conditions permit the removal of the solvent so as to leave a thin deposition of coating material around each tablet core. Typically the coating solution formulation comprises: polymer, solvent, plasticizer and colorants. The technique is also described in Reminton: The Science and Practice of Pharmacy 19th Edition 1995, published by Mack Publishing Company, ISBN 0-912734-04-3. See in particular pages 1652 to 1659 which explain the method of film coating as follows. Film coating involves the deposition of a thin, but uniform, film onto the surface of the substrate. Unlike sugar coating, the flexibility afforded in film coating allows additional substrates other than just compressed tablets, to be considered (eg, powders, granules, nonpareils, capsules). Coatings are essentially applied continuously to a moving bed of material by means of a spray technique, although manual application procedures have also been used.

The following are examples of formulations which are representative of the present invention. They are intended to illustrate the invention but are not intended to be limiting on the scope of the invention which is defined by the claims.

Example 1

A double tablet having the following specifications for the core, barrier and coating was manufactured. The first active ingredient is ranitidine hydrochloride and the second active ingredient is acetylsalicylic acid:

Core

Core Ingredient	Weight per tablet (mg)	%w/w (based on total core weight)	Function
Granulated Ranitidine Hydrochloride	84.000	56.00	Active Ingredient
Microcrystalline Cellulose	64.875	43.25	Diluent
Magnesium Stearate	1.125	0.75	Lubricant

Barrier

Barrier Ingredient	Weight per tablet (mg)	%w/w (based on total core weight)	Function
Opadry AMB ™	12.000	8.00	Moisture Barrier

Coating

Coating Ingredient	Weight per tablet (mg)	%w/w (based on total coating weight)	Function
Acetylsalicylic acid	500.000	82.40	Active Ingredient
Cellactose™ 80	91.020	15.00	Diluent
Sodium Croscaramelose	12.140	2.00	Disintegrant
Sodium Stearyl Fumarate	3.030	0.50	Lubricant
Colloidal Anhydrous Silica	0.610	0.10	Flow Promoter

The manufacturing method was as follows, the steps being numbered sequentially:

A) Manufacture of the ranitidine tablet cores:

Mixture of the ranitidine tablet core ingredients

1) The selected amount of granulated ranitidine hydrochloride, microcrystalline cellulose and magnesium stearate were weighed out according to the batch size to be manufactured.

2) The granulated ranitidine hydrochloride and the microcrystalline cellulose were added to a drum blender or equivalent mixing equipment.

3) The mixture was blended for 10 minutes at a speed of rotation of 15 rpm to provide a homogenous mixture. Note that the mixing parameters may be varied according to the equipment used and batch size intended for manufacture.

4) To the homogenous mixture of ranitidine hydrochloride and microcrystalline cellulose was added the magnesium stearate. Mixing was continued in the same drum blender or equivalent mixing equipment for 5 minutes at a speed of rotation of 15 rpm. Again, the mixing parameters may be varied according to the equipment used and batch size intended for manufacture.

Compression of the powder mixture to produce the Ranitidine tablet core

5) A tableting machine was used to compress the previous powder mixture into tablet cores in compliance with the following specifications:

Weight:	150 mg
Uniformity of Mass:	In compliance with European Pharmacopeia
Hardness:	greater than 8 Kp
Friability:	less than 1% w/w
Disintegration time:	less than 15 minutes

The punches used were standard concave, 8 mm diameter.

B) Film-coating the ranitidine tablet cores:

6) The coating suspension of Opadry AMB was prepared as follows. The required amount of Opadry AMB and purified water to prepare a 20% w/w dispersion of Opadry AMB in purified water were measured out. Note that the recommended solids level is 20% w/w, but the actual solids level in the suspension can be changed to allow for the atomising capabilities of the spraying equipment. Opadry AMB was reconstituted as follows. The total quantity of cold water was poured into a suitable container. A propeller or similar type of stirrer was placed in the water, and rotated so that a vortex was produced, but without drawing air into the liquid. The Opadry AMB powder was added to the vortex as quickly as possible so that undispersed powder did not float on the surface of the liquid. During the addition step, the suspension viscosity rose, thus it was necessary to increase the stirrer speed in order to maintain the vortex. After all the Opadry AMB powder had been added, the stirrer speed was reduced until the vortex was nearly eliminated and stirring continued for a further 45 minutes, after which time the coating suspension was ready for use. It was preferable to provide gentle agitation to the coating suspension while it was being sprayed.

7) The selected amount of ranitidine tablet cores were placed into a suitable film coating equipment e.g. ACCELA-COTA or similar equipment. 12 mg of Opadry AMB film was coated on the ranitidine tablet cores using the following film coating parameters:

Inlet air temperature:	≥ 90°C
Product temperature before spraying:	≥ 70°C
Drum speed:	10 rpm
Spray equipment:	Manesty spray gun
Atomising air pressure:	3.5 Bar

The spraying parameters may be varied according to the equipment used and batch size intended for manufacture.

C) Press coating the ranitidine film coated cores:

Mixture of the acetyl salicylic acid (ASA) tablet coat ingredients

8) The selected amounts of ASA, Cellactose™ 80, sodium croscaramelose, sodium stearyl fumarate and colloidal anhydrous silica were weighed out.

9) The ASA, Cellactose™ 80, sodium croscaramelose, sodium stearyl fumarate and colloidal anhydrous silica were added to a drum blender or equivalent mixing equipment.

10) The mixture was blended for 10 minutes at 15 rpm to obtain a homogenous mixture. Note that these parameters are intended as a guide only. The proper parameters will depend upon the equipment and the batch size intended for manufacture.

Press coating the ASA powder mixture onto the film coated ranitidine cores

11) A tableting machine which is capable of producing double compressed tablets e.g. Manesty Drycota or similar equipment was used to provide a tablet in compliance with the following specifications:

Weight:	768.8 mg
Uniformity of Mass:	compliant with European Pharmacopeia
Hardness:	greater than 10 Kp
Friability:	less than 1% w/w

The punches used were standard concave, 12 mm diameter

The press coating process can be summarised in the following steps. Approximately half of the ASA powder mixture was filled into a tablet die. Then the filmed-coated ranitidine tablet was fed into the tablet die. Afterwards, the rest of the ASA mixture was filled into the die. The punches compressed the ASA coat onto the filmed-coated ranitidine tablet, producing a double compressed tablet where the tablet core is the filmed-coated ranitidine tablet and the external

coat is the ASA. This cycle was repeated by the tableting machine as more film coated ranitidine tablets and ASA mixture (dry coating material) were fed into the dies from the hoppers.

This formulation was subjected to a stability study under the following conditions: 25°C/60% relative humidity and 40°C/75% relative humidity for 1, 2, 3 and 6 months. It was found that the ranitidine remains stable for 6 months at 25°C/60% relative humidity and at 40°C/75% relative humidity. The acetylsalicylic acid is stable for 6 months at 25°C/60% relative humidity and is stable for 2 months at 40°C/75% relative humidity.

Example 2

A double tablet having the following specifications for the core, barrier and coating was manufactured:

Core

Core Ingredient	Weight per tablet (mg)	%w/w (based on total core weight)	Function
Granulated Ranitidine Hydrochloride	84.000	56.00	Active Ingredient
Microcrystalline Cellulose	64.875	43.25	Diluent
Magnesium Stearate	1.125	0.75	Lubricant

Barrier

Barrier Ingredient	Weight per tablet (mg)	%w/w (based on total core weight)	Function
Opadry AMB ™	12.000	8.00	Moisture Barrier

Coating

Coating Ingredient	Weight per tablet (mg)	%w/w (based on total coating weight)	Function
Acetylsalicylic Acid micro-encapsulated with Ethyl Cellulose (Rhodine NCR-P™)	507.6 - 526.3[(1)]	82.7 – 85.7	Active Ingredient
Cellactose™ 80	73.7 – 92.4[(2)]	12.0 - 15.0	Diluent
Sodium Croscaramelose	12.3	2.0	Disintegrant
Sodium Stearyl Fumarate	1.2	0.2	Lubricant
Colloidal Anhydrous Silica	0.6	0.1	Flow Promoter

(1) The purity of acetylsalicylic acid micro-encapsulated with ethyl cellulose varies between 95% and 98.5% w/w. Therefore the quantity of acetylsalicylic acid micro-encapsulated with ethyl cellulose that has to be included in each tablet can vary between 507.6 and 526.3 mg in order to provide a dose of 500 mg of acetylsalicylic acid.

(2) The amount of Cellactose™ 80 added can vary between 73.7 and 92.4 mg so as to provide a total of 600 mg for the combined weight of Cellactose™ 80 and acetylsalicylic acid micro-encapsulated with ethyl cellulose.

The manufacturing method was the same as for Example 1 above except that the weight of acetylsalicylic acid micro-encapsulated with ethyl cellulose has to be adjusted to provide 500mg of acetylsalicylic acid and the difference in the final tablet weight is compensated with the amount of Cellactose™ 80.

This formulation was subjected to a stability study under the following conditions: 25°C/60% relative humidity and 40°C/75% relative humidity for 1, 2, 3 and 6 months. It was found that the ranitidine remains stable for 6 months at 25°C/60% relative humidity and at 40°C/75% relative humidity. The acetylsalicylic acid is stable for 6 months at 25°C/60% relative humidity and is stable for 2 months at 40°C/75% relative humidity.

Claims

1. A pharmaceutical formulation which comprises a core comprising a first active ingredient, a coating comprising a second active ingredient which is incompatible with the first active ingredient and a barrier between the core and the coating which prevents physical contact between the core and the coating, characterised in that the barrier is formed on the core by film-coating and the coating is formed on the barrier by press-coating.

2. A pharmaceutical formulation as claimed in claim 1 wherein the core further comprises one or more pharmaceutical excipients, disintegrants, lubricants, anti-adhesion agents, flow agents or diluents.

3. A pharmaceutical formulation as claimed in claim 1 or claim 2 wherein the coating further comprises one or more pharmaceutical excipients, disintegrants, lubricants, anti-adhesion agents, flow agents or diluents.

4. A pharmaceutical formulation as claimed in any one of claims 1 to 3 wherein the core comprises ranitidine or a physiologically acceptable salt thereof and the coating comprises acetylsalicylic acid or a physiologically acceptable salt thereof.

5. A pharmaceutical formulation as claimed in claim 4 wherein the ranitidine is present in the core in an amount of from 10 to 200 mg or a physiologically acceptable salt of ranitidine is present in the core in an amount which is equivalent to from 10 to 200 mg of ranitidine.

6. A pharmaceutical formulation as claimed in claim 4 or claim 5 wherein the ranitidine is present in the form of ranitidine hydrochloride.

7. A pharmaceutical formulation as claimed in any one of claims 4 to 6 wherein acetylsalicylic acid is present in the coating in an amount of from 50 to 1000 mg or a physiologically acceptable salt of acetylsalicylic acid is present in the core in an amount which is equivalent to from 50 to 1000 mg of acetylsalicylic acid.

8. A pharmaceutical formulation as claimed in any one of claims 4 to 7 wherein the acetylsalicylic acid or the physiologically acceptable salt of acetylsalicylic acid is microencapsulated with ethyl cellulose.

9. A pharmaceutical formulation as claimed in any one of claims 1 to 8 wherein the barrier also reduces the transmission of moisture between the core and the coating.

10. A pharmaceutical formulation as claimed in any one of claims 1 to 9 wherein the barrier is present in an amount of from 1 to 20 % by weight based on the total weight of the core.

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(54) **Title:** PHARMACEUTICAL FORMULATION

(57) **Abstract:** The present invention provides a pharmaceutical formulation which comprises a core comprising a first active ingredient, a coating comprising a second active ingredient which is incompatible with the first active ingredient and a barrier between the core and the coating which prevents physical contact between the core and the coating, characterised in that the barrier is formed on the core by film-coating and the coating is formed on the barrier by press-coating.

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INTERNATIONAL SEARCH REPORT

Inte ıal Application No
PC.,.P 02/01668

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61P1/04 A61K31/616 A61K31/60
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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)
IPC 7 A61K A61P

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, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 0 105 065 A (MATHUR KISHAN NARAIN) 11 April 1984 (1984-04-11) page 1, line 1 -page 4, line 18; claims 1-11	1-3,9,10 4-8
X Y	US 5 425 950 A (DANDIKER YOGENDRA ET AL) 20 June 1995 (1995-06-20) column 2, line 33 -column 5, line 13; claims 1-15	1-3,9,10 4-8
X	US 5 702 723 A (GRIFFIN DAVID) 30 December 1997 (1997-12-30) claims 1-5	1-3,9,10
Y	EP 0 546 593 A (GLAXO GROUP LTD) 16 June 1993 (1993-06-16) page 4, line 5 -page 5, line 52; claims 1-13; examples 12-15	1-10

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

[X] Patent family members are listed in 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
21 November 2002	29/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Kling, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 874 586 A (UPJOHN CO) 10 August 1961 (1961-08-10) page 3, right-hand column, line 76 -page 4, right-hand column, line 93; claims 1-14; examples 1-7	1-10
A	GB 1 037 689 A (ABBOTT LAB) 3 August 1966 (1966-08-03) claims 1-13	1-10

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 -3, 9, 10 relate to an extremely large number of possible compounds being active ingredients. In fact, the claims contain so many options, variables, possible permutations and provisos that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely the subject-matter of claims 4 to 8, e.g those pharmaceutical formulation which comprises the compounds recited in the examples (ranitidine and acetylsalicylic acid) and closely related homologous compounds, and those mentioned in the description at pages 1 and 2, and the examples 1 and 2.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/EP 02/01668

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/01668

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(54) Title: PHARMACEUTICAL FORMULATIONS CONTAINING A NON-STEROIDAL ANTIINFLAMMATORY DRUG AND A PROTON PUMP INHIBITOR

(57) Abstract: An oral solid dosage form includes a therapeutically effective amount of an NSAID and a proton pump inhibitor in an amount effective to inhibit or prevent gastrointestinal side effects normally associated with the NSAID. Also disclosed is a method of treating a human patient in need of antiinflammatory, analgesic and/or antipyretic therapy, comprising orally administering to the patient an oral pharmaceutical dosage form which includes a therapeutically effective amount of an NSAID and an amount of a proton pump inhibitor effective to substantially inhibit gastrointestinal side effects of the NSAID. The invention is further related to a method of prophylactically treating a human patient who is on a therapy known to have significant gastrointestinal side effects or is about to begin such a therapy, via concurrent administration of an NSAID and a proton pump inhibitor in a combination (single) oral dosage form.

PHARMACEUTICAL FORMULATIONS CONTAINING A NON-STEROIDAL ANTIINFLAMMATORY DRUG AND A PROTON PUMP INHIBITOR

FIELD OF THE INVENTION

The present invention is related to the combination of a non-steroidal antiinflammatory drug ("NSAID") or one of its single enantiomers or salt of the NSAID, and a proton pump inhibitor or one of its single enantiomers, or an alkaline salt of the proton pump inhibitor or one of its single enantiomers, in a single oral pharmaceutical dosage form.

BACKGROUND

Although NSAIDs are often used for their antiinflammatory, analgesic, and/or antipyretic effects, it is well known that NSAIDs have the potential to cause gastrointestinal (GI) bleeding through a variety of mechanisms related to their topical and systemic effects. The GI bleeding may depend on the length of the treatment and on the particular drug. This problem is important in cases where the therapy must be continued for a long period of time. For example, osteoarthritis and rheumatoid arthritis in the elderly is often treated with long-term NSAID therapy, as chronic treatment is needed to control pain and inflammation and to improve quality of life.

Additionally it is well known that because of their side-effects on the GI tract, NSAIDs are invariably administered after meals or, generally, when the stomach is not empty. This pharmacological principle is confirmed by the recommendations found in the labeling of these medications. Patients who have an ulcer or who are susceptible to developing ulcers are commonly advised to avoid taking NSAIDs for pain, inflammation, and/or fever.

Other measures which can be taken to decrease GI side affects associated with NSAID therapy is to coadminister an H_2 blocker e.g. ranitidine, or a prostaglandin analogue, e.g. misoprostol, with the NSAID. In fact, a combination tablet containing diclofenac sodium and misoprostol (Arthrotec®, Pharmacia Corp.) has had FDA approval since 1988.

There is a continuing need for analgesic medications able to provide high efficacy pain relief while reducing the possibility of undesirable effects. Non-steroidal anti-inflammatory drugs, including compounds such as ibuprofen, ketoprofen and diclofenac, have anti-inflammatory actions and are effective on pain associated with the release of prostaglandins and other mediators of inflammation. For example, diclofenac and pharmaceutically acceptable salts thereof, e.g. diclofenac sodium, are considered to be extremely potent and effective as an analgesic and anti-inflammatory agent. Diclofenac is approved in the United States for the long-term symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. It is also considered to be useful for the short-term treatment of acute musculoskeletal injury, acute shoulder pain, postoperative pain and dysmenorrhea. However, NSAIDs such as diclofenac produce side effects in about 20% of patients that require cessation of medication. Side effects include, for example, gastrointestinal bleeding and the abnormal elevation of liver enzymes.

Non-steroidal anti-inflammatory drugs (NSAIDs) exert most of their anti-inflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Inhibition of COX-1 causes a number of side effects including inhibition of platelet aggregation associated with disorders of coagulation, and gastrointestinal side effects with the possibility of ulcerations and of hemorrhage. It is believed that the gastrointestinal side effects are due to a decrease in the biosynthesis of prostaglandins which are cytoprotective of the gastric mucosa.

A high incidence of side effects has historically been associated with chronic use of classic cyclooxygenase inhibitors, all of which are about equipotent for COX-1 or COX-2, or which are COX-1-selective. While renal toxicity occurs, it usually becomes evident in patients who already exhibit renal insufficiency (D. Kleinknecht, Sem. Nephrol. 15: 228, 1995). By far, the most prevalent and morbid toxicity is gastrointestinal. Even with relatively nontoxic drugs such as piroxicam, up to 4 % of patients experience gross bleeding and ulceration (M.J.S. Langman et al, Lancet 343: 1075, 1994). In the United States, it is estimated that some 2000 patients with rheumatoid arthritis and 20,000 patients with osteoarthritis die each year due to gastrointestinal side effects related to the use of COX inhibitors. In the UK, about 30 % of the annual 4000 peptic ulcer-related deaths are attributable to COX inhibitors (Scrip 2162, p.17). COX inhibitors cause gastrointestinal and renal toxicity due to the inhibition of synthesis of homeostatic prostaglandins responsible for epithelial mucus production and renal blood flow, respectively.

The second form of cyclooxygenase, COX-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxins, hormones, cytokines and growth factors. It has been proposed that COX-2 is mainly responsible for the pathological effects of prostaglandins, which arise when rapid induction of COX-2 occurs in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Selective inhibitors of COX-2 have anti-inflammatory, antipyretic and analgesic properties similar to those of a conventional non-steroidal anti-inflammatory drug (NSAID), but COX-2 inhibitors have been touted as providing a reduced potential for gastrointestinal toxicity, among other side effects. Nevertheless, experience with selective COX-2 inhibitors is limited relative to experience with non-selective COX inhibitors (which non-selectively inhibit COX-1 and COX-2). Non-selective COX inhibitors are widely used, and it is expected that these drugs will continue to be widely used. Further, there has been recent suggestions that COX-2 inhibitors have serious but previously unrecognized side effects, including increased intraocular pressure and the risk of glaucoma, as well as possible effects on

For years, neutralization of gastric acid with antacids was the only relief from the pain of ulcers. However, more recently, a class of antisecretory agents that do not exhibit anticholinergic or H_2 histamine antagonistic properties, but that suppress gastric acid secretion by the specific inhibition of the H^+, K^+ - ATPase enzyme system at the secretory surface of the gastric parietal cell, has been developed. These agents (hereinafter "proton pump inhibitors") provide a more specific class of inhibitors of gastric acid secretion in mammals and man by blocking the final step of acid production.

Generally, proton pump inhibitors, their single enantiomers or alkaline salts thereof, are used for the prevention and treatment of gastric acid related diseases including, but not limited to, reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. These proton pump inhibitors may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre- and postoperatively to prevent acid aspiration of gastric acid and to prevent and treat stress ulceration. Also, they may be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections and diseases related to these. Additionally, these proton pump inhibitors may be used for the treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable, such as patients with Non Ulcer Dyspepsia, in patients with symptomatic gastro-esophageal reflux disease, in patients with gastrinomas, and in particular in patients on NSAID therapy.

U.S. Patent No. 5,817,338 (Bergstrand, et al.) describes multiple unit tableted dosage forms of omeprazole, a proton pump inhibitor commercially available for inhibiting gastric acid secretion in humans. Therein, it is suggested that omeprazole may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable, e.g., in patients on NSAID therapy. However, this patent does not describe pharmaceutical formulations combining a proton pump inhibitor such as omeprazole with an NSAID.

SUMMARY OF THE INVENTION

It is an object of this invention to provide a method for the treatment of pain, inflammation, and/or fever with the use of a NSAID without the undesirable stomach discomfort and other side effects typically associated with NSAID therapy.

It is a further object of the invention to decrease the risk of the development and/or exacerbation of ulcers which may occur during NSAID therapy.

It is a further object of the invention to promote patient compliance and thereby increase efficacy of NSAID treatment in patients who are being chronically treated with NSAIDs.

It is a further object of the invention to provide prophylactic treatment to a human patient who is on NSAID therapy or is about to begin NSAID therapy, in order to avoid or minimize gastrointestinal side-effects.

It is a further object of the invention to provide prophylactic treatment to a human patient who is on a therapy known to have significant gastrointestinal side effects or is about to begin such a therapy, in order to avoid or minimize such side effects.

It is a further object of the invention to provide cost effective therapy to decrease the risk of the development and/or exacerbation of ulcers which may occur during NSAID therapy.

In view of the above-mentioned objects and others, the invention is directed to an oral solid dosage form comprising a therapeutically effective amount of an NSAID and a proton pump inhibitor in an amount effective to inhibit or prevent gastrointestinal side effects normally associated with the NSAID treatment.

The invention is further directed to a solid oral dosage form comprising

a) an NSAID (e.g. diclofenac or a pharmaceutically acceptable salt thereof) extended release tablet and

b) an enterically coated proton-pump inhibitor without a separating layer between the proton pump inhibitor and the enteric coat.

The invention is further directed to a (non-steroidal) antiinflammatory, analgesic, and antipyretic oral therapy which does not possess any substantial gastrointestinal side-effects, comprising an orally administrable dosage form comprising a therapeutically effective amount of an NSAID and an amount of a proton pump inhibitor effective to substantially inhibit gastrointestinal side effects of the NSAID, together with one or more pharmaceutically acceptable excipients.

The invention is further directed to a dosage form comprising a therapeutically effective amount of an NSAID and an amount of a proton pump inhibitor effective to substantially inhibit gastrointestinal side effects of the NSAID, wherein said proton pump inhibitor is coated with a material suitable to prevent contact of said proton pump inhibitor with acidic gastric juice (e.g. an enteric coating). In preferred embodiments, the material is directly coated onto the proton pump inhibitor without a separating layer between the material and the proton pump inhibitor.

The invention is further directed to the prophylactic treatment of a human patient who is on NSAID therapy or is about to begin NSAID therapy, via the concurrent administration of a proton pump inhibitor.

The invention is further directed to the prophylactic treatment of a human patient who is on a therapy known to have significant gastrointestinal side effects or is about to begin such a therapy, via the concurrent administration of a proton pump inhibitor.

The invention is further related to a method of treating a human patient in need of antiinflammatory, analgesic and/or antipyretic therapy, comprising orally administering to the patient an oral pharmaceutical dosage form comprising a therapeutically effective amount of an NSAID and an amount of a proton pump inhibitor effective to substantially inhibit gastrointestinal side effects of the NSAID.

In certain preferred embodiments, the dosage form is an oral tablet comprising the NSAID, the proton pump inhibitor, and one or more pharmaceutically acceptable excipients. In other preferred embodiments, the NSAID and the proton pump inhibitor comprise a mixture of tablets, powders, pellets, granules, or inert nonpareil beads coated with the drugs, contained within a gelatin capsule.

The inventive formulations and methods described herein promote patient compliance and thereby increase efficacy of NSAID treatment in patients who are being chronically treated with NSAIDs. In other words, the inventive formulations increase the likelihood that a patient on NSAID therapy who is noncompliant due to gastrointestinal side effects, or who forgets or refuses to take both medications separately will be more accepting of a single composition combining the NSAID and proton pump inhibitor, particularly due to the avoidance of gastrointestinal side effects.

Proton pump inhibitors are known to be highly acid labile, and therefore it is preferred that the proton pump inhibitor(s) contained in the dosage forms of the invention be protected from contact with acidic gastric juice.

In certain preferred embodiments, the proton pump inhibitor is omeprazole.

In certain preferred embodiments, the NSAID is diclofenac, more preferably diclofenac

For purposes of this disclosure, all references to proton pump inhibitors and NSAIDs include their single enantiomers and their pharmaceutically acceptable salts.

For purposes of this disclosure, the phrase "substrates" is meant to encompass inert pharmaceutically acceptable beads, particles, granules or pellets.

For purposes of this disclosure, the phrase "combination pharmaceutical" shall be understood to include any drug composition containing at least two therapeutically active components of which at least one is a non-steroidal antiinflammatory drug. The term "pain-alleviating" shall be understood herein to include the expressions "pain-suppressing" and "pain-inhibiting" as the invention is applicable to the alleviation of existing pain as well as the suppression or inhibition of pain which would otherwise ensue from an imminent pain-causing event.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG.1 is a graph of in vitro dissolution data which shows the dissolution profile of omeprazole from the initial formulation of Example 1 and the formulation of Example 1 after exposure to accelerated storage conditions of 40°C and 75% relative humidity for 2 weeks. The dissolution medium is a 0.5 M Phosphate buffer at a pH 6.8.

FIG. 2 is a graph of in vitro dissolution data which shows the dissolution profile of diclofenac from the initial formulation of Example 1 and the formulation of Example 1 after exposure to accelerated storage conditions of 40°C and 75% relative humidity for 2 weeks. The dissolution medium is a 0.5 M Phosphate buffer at a pH 6.8.

FIG. 3 is a graph of in vitro dissolution data which shows the dissolution profile of diclofenac from the initial formulation of Example 2, the formulation of Example 2 after

exposure to accelerated storage conditions of 40°C and 75% relative humidity for 2 weeks and the formulation of Example 2 after exposure to accelerated storage conditions of 40°C and 75% relative humidity for 1 month. The dissolution medium is a 0.5 M Phosphate buffer at a pH 6.8.

FIG. 4 is a graph of in vitro dissolution data which shows the dissolution profile of omeprazole from the initial formulation of Example 2, the formulation of Example 2 after exposure to accelerated storage conditions of 40°C and 75% relative humidity for 2 weeks and the formulation of Example 2 after exposure to accelerated storage conditions of 40°C and 75% relative humidity for 1 month. The dissolution medium is a 0.5 M Phosphate buffer at a pH 6.8.

DETAILED DESCRIPTION OF THE INVENTION

The term "NSAID," as used herein, refers to any compound acting as a non-steroidal anti-inflammatory agent identifiable as such by one of ordinary skill in the art. For many years NSAIDs have been used for treating pain and/or inflammation. "Treating" includes prophylaxis of a physical and/or mental condition or amelioration or elimination of the developed condition once it has been established, or alleviation of the characteristic symptoms of such condition. The term "pain" includes all types of pain. Pain includes, but is not limited to, chronic pains, such as arthritis pain (e.g. pain associated with osteoarthritis and rheumatoid arthritis), neuropathic pain, and post-operative pain, chronic lower back pain, cluster headaches, herpes neuralgia, phantom limb pain, central pain, dental pain, neuropathic pain, opioid-resistant pain, visceral pain, surgical pain, bone injury pain, pain during labor and delivery, pain resulting from burns, including sunburn, post partum pain, migraine, angina pain, and genitourinary tract-related pain including cystitis, the term also refers to nociceptive pain or nociception.

The Merck Manual, 16th Edition, Merck Research Laboratories (1990) pp 1308-1309 provide well known examples of NSAIDs. The term NSAID includes, but is not limited to, the group consisting of salicylates, indomethacin, flurbiprofen, diclofenac, ketorolac, naproxen,

piroxicam, tebufelone, ibuprofen, etodolac, nabumetone, tenidap, alcofenac, antipyrine, aminopyrine, dipyrone, aminopyrone, phenylbutazone, clofezone, oxyphenbutazone, prexazone, apazone, benzydamine, bucolome, cinchopen, clonixin, ditrazol, epirizole, fenoprofen, floctafeninl, flufenamic acid, glaphenine, indoprofen, ketoprofen, meclofenamic acid, mefenamic acid, niflumic acid, phenacetin, salidifamides, sulindac, suprofen and tolmetin. The salicylates may include acetylsalicylic acid, sodium acetylsalicylic acid, calcium acetylsalicylic acid, salicylic acid, and sodium salicylate.

NSAIDs have been widely used in arthritis therapy for several years. The following references, hereby incorporated by reference, describe various NSAIDs suitable for use in the invention described herein, and processes for their manufacture: U.S. Pat. No. 3,558,690 to Sallmann and Pfister, (assigned to Ciba Geigy), issued 1971; U.S. Pat. No. 3,843,681 (assigned to American Home Products), issued 1974; U.S. Pat. No. 3,766,263 to Godfrey, (assigned to Reckitt and Colman) issued 1973; U.S. Pat. No. 3,845,215 to Godfrey (assigned to Reckitt and Colman) issued 1974; U.S. Pat. No. 3,600,437 to Marshall (assigned to Eli Lilly), issued 1971; U.S. Pat. No. 3,228,831 to Nicholson and Adams, (assigned to Boots Pure Drug), issued 1966; (U.S. Pat. No. 3,385,886 to Nicholson and Adams, (assigned to Boots Pure Drug) issued 1968; U.S. Pat. No. 3,161,654 to Shen, (assigned to Merck & Co.), issued 1964; U.S. Pat. No. 3,904,682 to Fried and Harrison, (assigned to Syntex), issued 1975; U.S. Pat. No. 4,009,197 to Fried and Harrison, (assigned to Syntex), issued 1977; U.S. Pat. No. 3,591,584 to Lombardino (assigned to Pfizer) issued 1971; U.S. Pat. No. 5,068,458 to Dales et al., (assigned to Beecham Group, PLC.), issued Nov. 26, 1991; U.S. Pat. No. 5,008,283 to Blackburn et al. (assigned to Pfizer, Inc.), issued Apr. 16, 1991; and U.S. Pat. No. 5,006,547 to Loose (assigned to Pfizer), issued Apr. 9, 1991. All of the above patents are hereby incorporated by reference.

Proton pump inhibitors (PPI) are potent inhibitors of gastric acid secretion, inhibiting H^+, K^+- ATPase, the enzyme involved in the final step of hydrogen ion production in the parietal cells. The term proton pump inhibitor includes, but is not limited to, omeprazole, lansoprazole,

rabeprazole, pantoprazole and leminoprazole, including isomers, enantiomers and tautomers thereof, and alkaline salts thereof. Proton pump inhibitors typically include benzimidazole compounds. The following patents describe various benzimidazole compounds suitable for use in the invention described herein: U.S. Pat. No. 4,045,563, U.S. Pat. No. 4,255,431, U.S. Pat. No. 4,359,465, U.S. Pat. No. 4,472,409, U.S. Pat. No. 4,508,905, JP-A-59181277, U.S. Pat. No. 4,628,098, U.S. Pat. No. 4,738,975, U.S. Pat. No. 5,045,321, U.S. Pat. No. 4,786,505, U.S. Pat. No. 4,853,230, U.S. Pat. No. 5,045,552, EP-A-295603, U.S. Pat. No. 5,312,824, EP-A-166287, EP-A-519365, EP5129, EP 174,726, EP 166,287 and GB 2,163,747. All of the above patents are hereby incorporated by reference. Proton pump inhibitors, e.g. omeprazole and its pharmaceutically acceptable salts, which are used in accordance with the invention are known compounds and can be produced by known processes. In certain preferred embodiments, the proton pump inhibitor is omeprazole, either in racemic mixture or only the (-)enantiomer of omeprazole (i.e. esomeprazole), as set forth in U.S. Patent No. 5,877,192, hereby incorporated by reference.

Omeprazole is typically administered in a 20 mg dose/day for active duodenal ulcer for 4-8 weeks; in a 20 mg dose/day for gastro-esophageal reflux disease (GERD) or severe erosive esophagitis for 4-8 weeks; in a 20 mg dose/twice a day for treatment of Helicobacter pylori (in combination with other agents); in a 60 mg dose/day for active duodenal ulcer for 4-8 weeks and up to 120 mg three times/day; and in a 40 mg dose/day for gastric ulcer for 4-8 weeks. Such dosages are contemplated to be within the scope of the invention. Thus, in certain embodiments of the invention, the amount of proton pump inhibitor which is included in the dosage form is an amount which is considered to be therapeutically effective, in accordance with the dosages set forth above for a variety of disease states. In other preferred embodiments of the invention, the dose of proton pump inhibitor is sub-therapeutic. For example, when the drug is omeprazole, the dosage form may contain from about 0.1 mg to about 120 mg omeprazole.

Lansoprazole is typically administered about 15-30 mg/day; rabeprazole is typically administered 20 mg/day and pantoprazole is typically administered 40 mg/day. However, any therapeutic or sub-therapeutic dose of these agents is considered within the scope of the present invention.

The proton pump inhibitor(s) included in the dosage forms of the invention are preferably protected from contact with acidic gastric juice, and preferably is transferred without exposure to gastric fluid until the dosage form reaches a part of the gastrointestinal tract where the pH is near neutral and where rapid absorption of omeprazole can occur.

In preferred embodiments of the invention, the pharmaceutical compositions containing the proton pump inhibitors and NSAIDs set forth herein are administered orally. Such oral dosage forms may contain one or both of the drugs in immediate or sustained release form. The oral dosage forms may be in the form of tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, multiparticulate formulations, syrups, elixirs, and the like.

The combination of proton pump inhibitor and a NSAID can be employed in admixtures with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for oral, parenteral, nasal, intravenous, subcutaneous, enteral, or any other suitable mode of administration, known to the art. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelate, carbohydrates such as lactose, amylose or starch, magnesium stearate talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or aromatic substances and the like. They can

also be combined where desired with other active agents, e.g., other analgesic agents. For oral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules, caplets and gelcaps. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically excipients which are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay the release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

Aqueous suspensions containing the above-identified combination of drugs and that mixture have one or more excipients suitable as suspending agents, for example pharmaceutically acceptable synthetic gums such as hydroxypropylmethylcellulose or natural gums. Oily suspensions may be formulated by suspending the above-identified combination of drugs in a vegetable oil or mineral oil. The oily suspensions may contain a thickening agent such as beeswax or cetyl alcohol. A syrup, elixir, or the like can be used wherein a sweetened vehicle is employed.

As is well known in the art, proton pump inhibitors are susceptible to degradation and/or transformation in acidic and neutral media. For example, the half-life of degradation of omeprazole in water solutions at pH-values less than three is shorter than ten minutes. The degradation of proton pump inhibitors is catalyzed by acidic compounds and is stabilized in mixtures with alkaline compounds. The stability of this class of antisecretory compounds is also affected by moisture, heat, organic solvents and to some degree by light. With respect to the stability properties of the proton pump inhibitors, it is preferable that in an oral solid dosage form they be protected from contact with the acidic gastric juice and the active substance must be

transferred in intact form to that part of the gastrointestinal tract where pH is near neutral and where rapid absorption of the medication can occur. Formulations which address the degradation of proton pump inhibitors in acidic media are described in U.S. Patent No. 4,786,505, 5,817,338; and 5,798,120, each of which is hereby incorporated by reference, and each of the described formulations in those patents can be modified to include one or more NSAIDs pursuant to the present invention.

One preferred embodiment of the invention is a combination pharmaceutical composition having two active ingredients, comprising a proton pump inhibitor and a NSAID in a single composition, in which the proton pump inhibitor is in the form of individually enteric coated substrates layered onto an NSAID tablet. The enteric coating layer(s) covering the substrates of the proton pump inhibitor (with or without the NSAID) is preferably sufficient to provide acid resistance to the substrates. Preferably, the enteric coating layer covering the substrates disintegrates/dissolves rapidly in near neutral or alkaline media.

In formulations prepared using multiparticulate substrates comprising enterically coated proton pump inhibitor, such multiparticulates may be mixed with NSAID (e.g., in particulate or powder form) and then separated into unit doses. Alternatively, the enterically coated substrates containing the proton pump inhibitor may thereafter by coated with the NSAID (with or without further optional overcoatings are described in more detail below). Alternatively, two separate populations of substrates may be used, one population of substrates being coated with the proton pump inhibitor and thereafter enteric-coated, the other population of substrates comprising the NSAID. The NSAID-containing substrates may comprise inert beads coated with the NSAID, or may comprise a plurality of immediate release matrices containing the NSAID. Thereafter, requisite amounts of each of the two populations of substrates could be incorporated into tablets, or into gelatin capsules, for example.

In embodiments where the substrates comprise inert pharmaceutically acceptable beads, the drug(s) may be mixed with further ingredients prior to being coated onto the beads. Ingredients include, but are not limited to, binders, surfactants, fillers, disintegrating agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures. Binders include, for example, celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants include pharmaceutically acceptable non-ionic or ionic surfactants. An example of a suitable surfactant is sodium lauryl sulfate. The inert beads may be first coated with the proton pump inhibitor, overcoated with an enteric coating, and thereafter coated with the NSAID (with or without further optional overcoatings are described in more detail below). Alternatively, two separate populations of beads may be used, one population of beads being coated with the proton pump inhibitor and thereafter enteric-coated, the other population of beads being coating with the NSAID. Thereafter, requisite amounts of each of the two populations of beads could be incorporated into tablets, or into gelatin capsules, for example.

Alternatively, the proton pump inhibitor may be optionally mixed with alkaline compounds and further mixed with suitable ingredients (with or without the NSAID) as set forth above and then formulated into the substrate. Such substrates may be manufactured via extrusion/spheronization, balling or compression utilizing different process equipments. The size of the substrates may be, for example, from about 0.1 to about 4 mm, and preferably from about 0.1 to about 2 mm. Alternatively, the substrates may include additional ingredients, optionally comprising the NSAID. Such suitable ingredients include fillers, binders, lubricants, disintegrating agents, surfactants and other pharmaceutically acceptable additives. The alkaline compound may be selected from substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminum, calcium and magnesium hydroxides;

magnesium oxide or composite substances, such as $Al_2O_3.6MgO.CO_2 12H_2O$, (Mg_6Al_2 $(OH)_{16}$ $CO_3.4H_2O$), $MgO.Al_2O_3.2SiO_2.nH_2O$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids and their salts or other similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned substrate can be prepared by using spray drying or spray congealing technique.

The proton pump inhibitor omeprazole has an asymmetric centre in the sulfur atom, i.e. exists as two optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two enantiomers are suitable for the pharmaceutical formulation according to the present invention. A suitable form of omeprazole for preparation of multiparticulate dosage forms in accordance with the invention can be the magnesium salt of omeprazole with a specific degree of crystallinity and other physical properties disclosed in WO 95/01977, hereby incorporated by reference. Other suitable forms of the active substance are the sodium, potassium, magnesium and calcium salts of the single enantiomers of omeprazole, especially in their crystalline form described in WO 94/27988, hereby incorporated by reference.

Before applying enteric coating layer(s) onto the substrate, the substrates may optionally be covered with one or more separating (intermediate) layers, however, in preferred embodiments, the enteric coating is applied directly onto the proton pump inhibitor without the need for a separating layer.

Preferably, one or more enteric coating layers are applied onto the substrate using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more,

separately or in combination, of the following can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethylethylcellulose, shellac or other suitable enteric coating layer polymer(s).

The enteric coating layers preferably contain effective amounts of pharmaceutically acceptable plasticizers to obtain the desired mechanical properties, such as flexibility and hardness of the enteric coating layers. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, polysorbates or other plasticizers. The amount of plasticizer is optimized for the particular situation. The amount of plasticizer is usually above 10% by weight of the enteric coating layer polymer(s), preferably 15-50%, and more preferably 20-50%. Additives such as dispersants, colorants, pigments, polymers e.g. poly(ethylacrylate, methylmethacrylate), anti-tacking and anti-foaming agents may also be included into the enteric coating layer(s). Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the add susceptible material.

Overcoatings may be applied to the substrates coated as set forth above, e.g., by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. Suitable overcoating materials include sugar, polyethylene glycol, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose sodium and the like. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the over-coating layer(s).

The enteric coated substrates may then be mixed with tablet excipients (and with the NSAID in certain embodiments) and compressed into a multiple unit tableted dosage form according to the present invention, or alternatively incorporated as unit doses in appropriately sized gelatin capsules. Compressed tablets prepared in accordance with the invention are optionally covered with a film-forming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance. The compaction process (compression) for formulating the multiple unit tableted dosage form must not significantly affect the acid resistance of the enteric coated substrates. In other words the mechanical properties, such as the flexibility and hardness as well as the thickness, of the enteric coating layer(s) must secure that the requirements on enteric coated articles in the United States Pharmacopeia are accomplished and that the acid resistance does not decrease more than 10% during the compression of pellets into tablets.

In certain preferred embodiments, where the NSAID is incorporated into the formulation after the enteric coating of the proton pump inhibitor substrates, the addition of the NSAID after the addition of the enteric coating to the substrates allows for rapid release of the NSAID and delayed release of proton pump inhibitor. The NSAID may be present in an outer coating in a form that does not retard its release, or may be separately incorporated into the formulation as set forth above.

Optionally soft gelatin capsules can be manufactured by filling a composition comprising the active ingredients as mentioned above and a known vegetable oil into capsules. Hard gelatin capsules can also be manufactured by filling into capsules the tablet, granules or pellets, each comprising an active ingredient as mentioned above, and a solid particulate carrier such as

lactose, sucrose, sorbitol, mannitol, potato starch, corn starch, amylopectin, a cellulose derivative or gelatin.

It is often considered desirable to administer NSAIDs in sustained release form in order to reduce the number of NSAID doses per day, thereby improving patient compliance and efficacy. Proton pump inhibitors are generally administered on a once- or twice-a-day basis, and it has not generally been contemplated to incorporated proton pump inhibitors into a sustained release dosage form. The details of how to achieve slowing or delaying of the release are familiar to the skilled worker on the basis of his expert knowledge. The skilled worker is likewise familiar with suitable ancillary substances and vehicles for the required dosage forms (pharmaceutical formulations). Besides solvent, tablet auxiliary substances and other active ingredient excipients it is possible to use, for example, tablet-coating compositions, plasticizers, antioxidants, preservatives, and dyes. Where incompatibilities between the active ingredients or between the active ingredients and ancillary substances are expected, suitable separating layers are provided where appropriate (for example in layered or multi-layer tablets).

In certain embodiments in which the NSAID is incorporated into the dosage form in a sustained release form designed to slowly release the NSAID over time, the proton pump inhibitor may be formulated in the dosage form to release via a different mechanism, e.g., via an enteric coating. However, in view of the rationale for administration of the proton pump inhibitors in accordance with the invention (prophylaxis as opposed to treatment of existing disease states), it is contemplated that in certain preferred embodiments, the proton pump inhibitor is incorporated into the dosage form in a sustained release state together with the NSAID.

In certain embodiments, the NSAID (and optionally the proton pump inhibitor) can be formulated as a sustained release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The sustained release dosage form

may optionally include a sustained released carrier which is incorporated into a matrix along with the drug(s), or the sustained release carrier can be applied as a sustained release coating. The sustained release dosage form may comprise a plurality of substrates which include the NSAID and/or the NSAID and the proton pump inhibitor. The substrates may comprise matrix spheroids or may comprise inert pharmaceutically acceptable beads which are coated with the drug(s). The coated beads may then be overcoated with a sustained release coating comprising the sustained release carrier. The matrix spheroid may include the sustained release carrier in the matrix itself; or the matrix may comprise a normal release matrix containing the drugs, the matrix having a coating applied thereon which comprises the sustained release carrier. In yet other embodiments, the oral solid dosage form comprises a tablet core containing the drugs within a normal release matrix, with the tablet core being coated with a sustained release coating comprising the sustained release carrier. In yet further embodiments, the tablet contains the drugs within a sustained release matrix comprising the sustained release carrier. In yet further embodiments, the tablet contains the NSAID within a sustained release matrix and the proton pump inhibitor coated into the tablet in an enteric coated layer. In yet further embodiments, the dosage form comprises a plurality of multiparticulates comprising the NSAID in sustained release form (e.g., prepared in any of the manners set forth above) together with a population of a plurality of multiparticulates comprising the proton pump inhibitor in an acid-protected form (e.g., enteric coated).

The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release, e.g., when exposed to gastrointestinal fluid. A pH-dependent coating serves to release the proton pump inhibitor in desired areas of the gastro-intestinal (GI) tract, e.g., the small intestine, such that an absorption profile is provided which is capable of providing at least about twelve hour and preferably up to twenty-four hour relief to a patient. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible and preferable to formulate

compositions which release a portion of the dose, preferably the NSAID, in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose, preferably the proton pump inhibitor, in another area of the GI tract, e.g., the small intestine.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug, preferably the NSAID, is coated over the enteric coat and is released in the stomach, while the remainder, preferably containing the proton pump inhibitor, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention, including shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing the proton pump inhibitor (with or without the NSAID) is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2 to about 25% of the substrate in order to obtain a desired sustained release profile.

In certain preferred embodiments, the oral dosage form of the present invention comprises a compressed matrix comprising the NSAID or a salt thereof and a retardant material in an effective amount to provide a controlled release of the NSAID for at least about 24 hours; a proton pump inhibitor coated on the surface of the matrix, wherein the proton pump inhibitor is in an amount effective to inhibit gastrointestinal side effects normally associated with oral administration of the NSAID; and an overcoat with a material suitable to prevent contact of said proton pump inhibitor with acidic gastric juice after oral administration. Preferably, the NSAID

is diclofenac or a pharmaceutically acceptable salt thereof and the proton pump inhibitor is omeprazole or a pharmaceutically acceptable salt thereof.

The retardant material which may be included in the matrix with the NSAID can include one or more pharmaceutically acceptable hydrophobic materials and/or hydrophilic materials which are capable of imparting controlled release of the active agent in accordance with the present invention.

The hydrophobic material is preferably selected from the group consisting of waxes, alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, hydrogenated castor oil, hydrogenated vegetable oil, gums, protein derived materials, aliphatic alcohols or mixtures thereof.

In certain embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cynaoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as alkylcelluloses, e.g. methylcellulose or ethylcellulose. In other embodiments, the hydrophobic material is an aliphatic alcohol, e.g. lauryl alcohol, myristyl alcohol, or stearyl alcohol.

An example of a suitable retardant material having hydrophilic properties is a hydroxyalkylcellulose, e.g. hydroxypropylmethylcellulose.

This list is not meant to be exclusive, and any pharmaceutically acceptable hydrophobic material and/or hydrophilic material which are capable of imparting controlled release of the active agent may be used in accordance with the present invention.

In addition to the above ingredients, the matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation. Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986), incorporated by reference herein.

A further ingredient which can be added to the matrix is a pH modifying agent which is defined for purposes of the present invention to mean any substance which decreases the ionization of the medicament, whereby the release of the drug from the matrix and into solution is facilitated. Suitable pH modifying agent are organic acids such as citric acid, succinic acid, fumaric acid, malic acid, maleic acid, glutaric acid or lactic acid.

Prior to coating the matrix with the proton pump inhibitor, the matrix can be coated with a pharmaceutically acceptable film-coating, e.g., for stability purposes (e.g., coated with a moisture barrier), etc. For example, the matrix may be overcoated with a film coating, preferably containing a pigment and a barrier agent, such as hydroxypropylmethylcellulose and/or a polymethylmethacrylate. An example of a suitable material which may be used for such a hydrophilic coating is hydroxypropylmethylcellulose (e.g., Opadry®, commercially available from Colorcon, West Point, Pa.). Any pharmaceutically acceptable manner known to those skilled in the art may be used to apply the coatings. For example, the coating may be applied using a coating pan or a fluidized bed. An organic, aqueous or a mixture of an organic and aqueous solvent is used for the hydrophobic polymer or enteric coating. Examples of suitable

organic solvents are, e.g., isopropyl alcohol, ethanol, and the like, with or without water. Aqueous solvents are preferred for the overcoating procedures.

The proton pump inhibitor is coated onto the tablet. Preferably, a solution of the proton pump inhibitor is spray dried onto the surface of the tablet using any spray technique known to those skilled in the art. This coating can also be applied using a coating pan or a fluidized bed using an organic, aqueous or a mixture of an organic and aqueous solvent for the proton pump inhibitor. Preferably, aqueous solvents are preferred for the proton pump inhibitor coating.

The material suitable to prevent contact of said proton pump inhibitor with acidic gastric juice after oral administration is then overcoated onto the proton pump inhibitor coated matrix. This material preferably contains an enteric polymer. Examples of suitable enteric polymers include cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing. A suitable commercially available enteric material, for example is sold under the trademark Eudragit™ L 100–555. as defined above. This coating can be spray coated onto the substrate as previously mentioned with respect to the other layers of this embodiment of the invention. Preferably, the coating to prevent contact of said proton pump inhibitor with acidic gastric juice is applied directly over the proton pump inhibitor without an intermediate separating layer.

In another preferred embodiment of the invention, the oral solid dosage form comprises a compressed matrix comprising (i) an NSAID or a salt thereof and a retardant material in an effective amount to provide a controlled release of the NSAID for at least about 24 hours and (ii) a plurality of particles comprising a proton pump inhibitor in a sufficient amount to provide an effective dose of the proton pump inhibitor to inhibit or prevent gastrointestinal side effects associated with diclofenac treatment. Preferably, the NSAID is diclofenac or a pharmaceutically

acceptable salt thereof and the proton pump inhibitor is omeprazole or a pharmaceutically acceptable salt thereof.

The compressed matrix of this embodiment can be prepared in accordance with the compressed matrix described in the immediately preceding embodiment. For example, the retardant material can be an aliphatic alcohol, such as a stearyl alcohol and can be combined with the NSAID to form a matrix.

The plurality of particles comprising the proton pump inhibitor can be in the form of substrates coated with the proton pump inhibitor and then overcoated with a material suitable to prevent contact of said proton pump inhibitor with acidic gastric juice after oral administration, e.g. an enteric coating. Preferably, the coating to prevent contact of said proton pump inhibitor with acidic gastric juice is applied directly over the proton pump inhibitor without an intermediate separating layer.

In embodiments where the substrates comprise a plurality of inert pharmaceutically acceptable beads, the proton pump inhibitor can be mixed with further ingredients prior to being coated onto the beads. Ingredients include, but are not limited to, binders, surfactants, fillers, disintegrating agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures. Binders include, for example, celluloses such as hydroxypropyl methylcellulose, hydroxypropyl cellulose and carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants include pharmaceutically acceptable non-ionic or ionic surfactants. An example of a suitable surfactant is Polysorbate-80.

The NSAID matrix and the proton pump inhibitor particles are then encapsulated in a pharmaceutically acceptable capsule.

In embodiments where the NSAID is included in sustained release form, the amount of NSAID included will generally be based upon a multiple of the amount administered in immediate release form, depending of course upon the dosage frequency. In general, when the proton pump inhibitor is incorporated in sustained release form as well as the NSAID, the amount of proton pump inhibitor will remain within the same limits as set forth above with respect to enteric release forms.

DETAILED DESCRIPTION OF CERTAIN PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

Preparation of

Diclofenac sodium Extended-release/Omeprazole Delayed-release Tablets, 100/20 mg

The above formulation was prepared by preparing diclofenac extended release (ER) granules and compressing the granules into tablets. The tablets are were seal coated, followed by spray coating with an omeprazole suspension. The omeprazole coated tablet was then enteric coated, followed by a color coating.

In particular, the ingredients as set forth below in Table 1 were granulated to form Diclofenac Sodium ER Granules:

TABLE 1

Ingredients		%Weight
Diclofenac Sodium, USP		45.87
Fumaric Acid, NF		1.01
Cetyl Alcohol, NF		6.01
Stearyl Alcohol, NF		6.01
Colloidal Silicon Dioxide (CAB-O-SIL M-5)		1.01
Compressible Sugar (DI-PAC)		40.09
	Total	100.00

The Diclofenac Sodium granules were then compressed with Magnesium Stearate to form Diclofenac Sodium ER Tablets, 100 mg (Uncoated). These uncoated tablets were then seal coated and drug layered with the ingredients set forth in Table 2.

TABLE 2

Ingredients		%Weight
Diclofenac Sodium ER Tablets, 100 mg (uncoated)		78.596
Omeprazole, USP (micronized)		8.217
Opadry Clear YS-1-7006		2.858
L-Arginine Base, USP/FCC		0.146
Polysorbate 80, NF		0.733
D-Mannitol, USP		8.217
Povidone, USP		1.233
Purified Water, USP*		*
	Total	100.000

*Evaporate during the process

For the seal coating, the Opadry Clear was added to the Purified Water, USP and sprayed onto the uncoated tablets. After a 10 minute drying period, an omeprazole suspension with the remaining ingredients were sprayed onto the seal coated tablets to form an immediate release (IR) omeprazole

The Diclofenac Sodium ER/Omeprazole IR tablets, 100/20 mg were then enteric coated with the ingredients set forth in Table 3. The enteric coating was applied directly onto the immediate release omeprazole layer without an intermediate separating layer.

TABLE 3

Ingredients	%Weight
Diclofenac Sodium ER/Omeprazole DR Tablets	90.462
Hydroxypropyl Methylcellulose Phthalate 50, NF	4.637
Talc, USP	4.637
Cetyl Alcohol, NF	0.265
Isopropyl Alcohol, USP*	*
Acetone, NF*	*
Total	100.000

*Evaporated during the coating process

These enteric coated tablets were then color coated with an aqueous solution of Opadry White to form the final product.

The dissolution profile of omeprazole from the Diclofenac Sodium ER/Omeprazole DR tablets in a 0.5 M Phosphate buffer medium at a pH 6.8 is set forth in Figure 1 and Table 4 below:

TABLE 4

Amount Dissolved (% Omeprazole)

Time (min)	V1	V2	V3	V4	V5	V6	Mean	%RSD	Min.	Max
0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	1	0	245	0	1
10	13	16	13	22	25	20	18	27	13	25
20	86	89	81	82	81	88	85	4	81	89
30	92	93	92	90	86	95	91	3	86	95

The dissolution profile of diclofenac from the Diclofenac Sodium ER/Omeprazole DR tablets in a 0.5 M Phosphate buffer medium at a pH 6.8 is set forth in Figure 2 and Table 5 below:

TABLE 5

Amount Dissolved (% Diclofenac sodium)

Time(Hr)	V1	V2	V3	V4	V5	V6	Mean	%RSD	Min.	Max
0	0	0	0	0	0	0	0	0	0	0
0.5	7	7	7	7	7	7	7	4	7	7
1	12	12	12	12	12	12	12	3	12	12
2	20	20	20	20	21	21	20	3	20	21
3	27	27	27	27	28	28	27	2	27	28
4	33	34	34	35	35	34	34	2	33	35
6	43	43	44	45	45	44	44	2	43	45
8	49	49	50	51	50	50	50	2	49	51
12	56	56	57	59	56	57	57	2	56	59

The tablets were then exposed to accelerated storage conditions of 40°C and 75% relative humidity for 2 weeks. The dissolution of omeprazole and diclofenac from the accelerated storage tablets in a 0.5 M Phosphate buffer medium at a pH 6.8 showed the formulation to be stable.

EXAMPLE 2

Preparation of

Diclofenac sodium ER/Omeprazole DR Capsules, 100/20 mg

The above formulation was prepared by preparing diclofenac extended release granules and compressing the granules into tablets, followed by a seal coating. Delayed release enteric coated omeprazole pellets were then prepared and encapsulated with the extended release diclofenac tablet.

In particular, Diclofenac Sodium ER Tablets, 100 mg (Seal Coated) tablets were prepared in accordance with Example 1.

Omeprazole Active Pellets were prepared by coating inert beads with an omeprazole suspension in accordance with the ingredients set forth in Table 6 below:

TABLE 6

Ingredients	%Weight
Sugar Sphere, NF (18/20)	69.700
Omeprazole, USP (micronized)	14.000
Polysorbate 80, NF	1.250
L-Arginine Base, USP	0.250
D-Mannitol, USP	14.000
Povidone, USP (Plasdone K-90)	0.800
Purified Water, USP*	*
Total	100.000

*Evaporated during the coating process

The omeprazole active pellets were then enteric coated with the ingredients set forth in Table 7. The enteric coating was applied directly onto the omeprazole pellets without an intermediate separating layer.

TABLE 7

Ingredients	%Weight
Omeprazole Active Pellets	81.00
Hydroxypropyl Methylcellulose Phthalate 55, NF	9.27
Cetyl Alcohol, NF	0.46
Talc, USP	9.27
Isopropyl Alcohol, USP*	*
Acetone, NF*	*
Total	100.00

*Evaporated during the process

A sufficient amount of enteric coated omeprazole pellets to provide 20 mg omeprazole were then encapsulated with a Diclofenac Sodium ER seal coated tablet to form Diclofenac Sodium ER/Omeprazole DR Capsules, 100/20 mg.

The dissolution profile of diclofenac from the Diclofenac Sodium ER/Omeprazole DR capsules in a 0.5 M Phosphate buffer medium at a pH 6.8 is set forth in Figure 3 and Table 8 below:

TABLE 8

Amount Dissolved (% Diclofenac sodium)

Time (Hr)	V1	V2	V3	V4	V5	V6	Mean	%RSD	Min	Max
0	0	0	0	0	0	0	0	0	0	0
0.5	4	4	4	4	3	4	4	3	3	4
1	7	8	8	8	7	8	8	2	7	8
2	15	16	16	15	15	16	16	2	15	16
3	23	23	22	22	23	24	23	2	22	24
4	29	29	28	28	28	30	29	3	28	30
6	38	38	36	36	36	38	37	3	36	38
8	44	43	42	42	42	44	43	3	42	44
12	52	51	49	49	49	52	50	3	49	52

The dissolution profile of omeprazole from the Diclofenac Sodium ER/Omeprazole DR capsules in a 0.5 M Phosphate buffer medium at a pH 6.8 is set forth in Figure 4 and Table 9 below:

TABLE 9

Amount Dissolved (% Omeprazole)

Time (min)	V1	V2	V3	V4	V5	V6	Mean	%RSD	Min.	Max
0	0	0	0	0	0	0	0	0	0	0
5	3	3	5	6	4	10	5	50	3	10
10	59	58	66	71	55	71	64	11	55	71
20	86	86	87	89	82	88	86	3	82	89
30	87	87	86	89	82	88	87	3	82	89

Capsules were then exposed to accelerated storage conditions of 40°C and 75% relative humidity for 2 weeks. The dissolution of diclofenac from the accelerated storage capsules in a 0.5 M Phosphate buffer medium at a pH 6.8 showed the formulation to be stable.

EXAMPLES 3-7

In Example 3, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 1. These seal coated tablets are then sprayed with an aqueous lansoprazole solution or suspension and enteric coated in accordance with the drug layering and enteric coating procedures of Example 1. The final dosage form contains 100 mg diclofenac sodium and 15 mg lansoprazole.

In Example 4, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 1. These seal coated tablets are then sprayed with an aqueous pantoprazole solution or suspension and enteric coated in accordance with the drug layering and enteric

coating procedures of Example 1. The final dosage form contains 100 mg diclofenac sodium and 40 mg pantoprazole.

In Example 5, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 1. These seal coated tablets are then sprayed with an aqueous rabeprazole solution or suspension and enteric coated in accordance with the drug layering and enteric coating procedures of Example 1. The final dosage form contains 100 mg diclofenac sodium and 20 mg rabeprazole.

In Example 6, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 1. These seal coated tablets are then sprayed with an aqueous esomeprazole solution or suspension and enteric coated in accordance with the drug layering and enteric coating procedures of Example 1. The final dosage form contains 100 mg diclofenac sodium and 20 mg esomeprazole.

In Example 7, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 1. These seal coated tablets are then sprayed with an aqueous (+) omeprazole solution or suspension and enteric coated in accordance with the drug layering and enteric coating procedures of Example 1. The final dosage form contains 100 mg diclofenac sodium and 20 mg (+) omeprazole.

EXAMPLE 8-12

In Example 8, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 2. Lansoprazole Active Pellets are prepared and enteric coated in accordance with the bead layering and enteric coating procedures of Example 2. A sufficient amount of enteric coated pellets to provide 15 mg lansoprazole are then encapsulated with the Diclofenac Sodium ER seal coated tablet to form Diclofenac Sodium ER/Lansoprazole DR Capsules, 100/15 mg.

In Example 9, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 2. Pantoprazole Active Pellets are prepared and enteric coated in accordance with the bead layering and enteric coating procedures of Example 2. A sufficient amount of enteric

coated pellets to provide 40 mg pantoprazole are then encapsulated with the Diclofenac Sodium ER seal coated tablet to form Diclofenac Sodium ER/Pantoprazole DR Capsules, 100/40 mg.

In Example 10, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 2. Rabeprazole Active Pellets are prepared and enteric coated in accordance with the bead layering and enteric coating procedures of Example 2. A sufficient amount of enteric coated pellets to provide 20 mg rabeprazole are then encapsulated with the Diclofenac Sodium ER seal coated tablet to form Diclofenac Sodium ER/Rabeprazole DR Capsules, 100/20 mg.

In Example 11, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 2. Esomeprazole Active Pellets are prepared and enteric coated in accordance with the bead layering and enteric coating procedures of Example 2. A sufficient amount of enteric coated pellets to provide 20 mg esomeprazole are then encapsulated with the Diclofenac Sodium ER seal coated tablet to form Diclofenac Sodium ER/Esomeprazole DR Capsules, 100/20 mg.

In Example 12, Diclofenac Sodium ER Tablets are prepared and seal coated in accordance with Example 2. (+) Omeprazole Active Pellets are prepared and enteric coated in accordance with the bead layering and enteric coating procedures of Example 2. A sufficient amount of enteric coated pellets to provide 20 mg (+) omeprazole are then encapsulated with the Diclofenac Sodium ER seal coated tablet to form Diclofenac Sodium ER/(+) omeprazole DR Capsules, 100/20 mg.

In Examples 1 and 2, the specified proton pump inhibitor is in the arginine salt form. Equivalent amounts of other forms of the proton pump inhibitor such as the free base, pharmaceutically acceptable salts thereof (e.g., the sodium, potassium, magnesium, calcium and amino acid salts, or mixtures thereof) or mixtures thereof, can be utilized as well.

WHAT IS CLAIMED IS:

1. A solid oral dosage form comprising
   a) a diclofenac extended release tablet and
   b) an enterically coated proton-pump inhibitor without a separating layer between the proton pump inhibitor and the enteric coat.

2. The solid oral dosage form of claim 1 wherein said proton pump inhibitor is coated onto the surface of the tablet.

3. The solid dosage form of claim 1 further comprising a film coating over said enteric coat.

4. The solid dosage form of claim 2 wherein said proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, pantoprazole, leminoprazole, single enantiomers thereof, alkaline salts thereof and mixtures thereof.

5. The solid dosage form of claim 4 wherein said proton pump inhibitor is omeprazole or a pharmaceutically acceptable salt thereof.

6. The solid dosage form of claim 1 wherein said proton pump inhibitor coated onto a plurality of inert beads.

7. The solid dosage form of claim 6 wherein a sufficient amount of proton pump inhibitor enteric coated beads to provide a therapeutic effect and the diclofenac tablet are contained within a capsule.

8. The solid dosage form of claim 6 wherein said proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, pantoprazole, leminoprazole, single enantiomers thereof, alkaline salts thereof and mixtures thereof.

9. The solid dosage form of claim 8 wherein said proton pump inhibitor is omeprazole or a pharmaceutically acceptable salt thereof.

10. An solid dosage form for oral administration comprising

a compressed matrix tablet comprising diclofenac or a pharmaceutically acceptable salt thereof and a retardant material in an effective amount to provide a controlled release of diclofenac in an amount sufficient to provide a therapeutic effect for at least about 24 hours; and

a proton pump inhibitor coated on the surface of said matrix in an amount effective to inhibit gastrointestinal side effects associated with oral administration of said diclofenac;

said coated matrix overcoated with a material suitable to prevent contact of said proton pump inhibitor with acidic gastric juice after oral administration.

11. The solid dosage form of claim 10 wherein said proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, pantoprazole, leminoprazole, single enantiomers thereof, alkaline salts thereof and mixtures thereof.

12. The solid dosage form of claim 11 wherein said proton pump inhibitor is omeprazole or an alkaline salt thereof.

13. The solid dosage form of claim 12 wherein said omeprazole or alkaline salt thereof is spray coated onto said matrix.

14. The solid dosage form of claim 10 wherein said material suitable to prevent contact of said proton pump inhibitor with acidic gastric juice is an enteric coating.

15. The solid dosage form of claim 14 comprising a film coating or color coating over said enteric coating.

16. The solid dosage form of claim 10 wherein said retardant material is an aliphatic alcohol.

17. The solid dosage form of claim 16 wherein said aliphatic alcohol is selected from the group consisting of stearyl alcohol, cetyl alcohol and mixtures thereof.

18. The solid dosage form of claim 10 wherein said diclofenac and said retardant material are in granular form prior to compression.

19. The oral dosage form of claim 10 further comprising a film coating between said matrix and said proton pump inhibitor.

20. An solid dosage form for oral administration comprising

a compressed matrix tablet comprising diclofenac or a pharmaceutically acceptable salt thereof and a retardant material in an effective amount to provide a controlled release of diclofenac in an amount sufficient to provide a therapeutic effect for at least about 24 hours; and

a plurality of particles comprising a proton pump inhibitor coated onto the surface of a plurality of inert beads and overcoated with a material suitable to prevent contact of said proton pump inhibitor with acidic gastric juice after oral administration; said dosage form containing a sufficient amount of said particles to provide an effective dose of said proton pump inhibitor to inhibit gastrointestinal side effects associated with oral administration of said diclofenac;

said compressed matrix and said dose of proton pump inhibitor contained within a capsule.

21. The solid dosage form of claim 20 wherein said proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, pantoprazole, leminoprazole, single enantiomers thereof, alkaline salts thereof and mixtures thereof.

22. The solid dosage form of claim 21 wherein said proton pump inhibitor is omeprazole or a pharmaceutically acceptable salt thereof.

23. The dosage form of claim 20 wherein said material suitable to prevent contact of said omeprazole or pharmaceutically acceptable salt thereof with acidic gastric juice is an enteric material.

24. The solid dosage form of claim 20 wherein said retardant material is an aliphatic alcohol.

25. The solid dosage form of claim 24 wherein said aliphatic alcohol is selected from the group consisting of stearyl alcohol, cetyl alcohol and mixtures thereof.

26. The solid dosage form of claim 20 wherein said diclofenac and said retardant material are in granular form prior to compression.

27. A method of treating patients with diclofenac comprising administering the solid dosage form of claim 1.

28. A method of treating patients with diclofenac comprising administering the solid dosage form of claim 10.

29. A method of treating patients with diclofenac comprising administering the solid dosage form of claim 20.

30. A solid dosage form for oral administration comprising

a compressed matrix tablet comprising an NSAID or a pharmaceutically acceptable salt thereof and a retardant material in an effective amount to provide a controlled release of said NSAID in an amount sufficient to provide a therapeutic effect for at least about 24 hours; and

a proton pump inhibitor a plurality of particles comprising coated on the surface of said matrix in an amount effective to inhibit gastrointestinal side effects associated with oral administration of said NSAID;

said coated matrix overcoated with a material suitable to prevent contact of said proton pump inhibitor with acidic gastric juice after oral administration.

31. A solid dosage form for oral administration comprising

a compressed matrix tablet comprising an NSAID or a pharmaceutically acceptable salt thereof and a retardant material in an effective amount to provide a controlled release of said NSAID in an amount sufficient to provide a therapeutic effect for at least about 24 hours; and

a plurality of particles comprising a proton pump inhibitor coated onto the surface of a plurality of inert beads and overcoated with a material suitable to prevent contact of said proton pump inhibitor with acidic gastric juice after oral administration; said dosage form containing a sufficient amount of said particles to provide an effective dose of said proton pump inhibitor to inhibit gastrointestinal side effects associated with oral administration of said diclofenac;

said compressed matrix and said dose of particles contained within a capsule.

32. The dosage form of claim 30, wherein the NSAID is selected from the group consisting of salicylates, indomethacin, flurbiprofen, diclofenac, ketorolac, naproxen, piroxicam, tebufelone, ibuprofen, etodolac, nabumetone, tenidap, alcofenac, antipyrine, aminopyrine, dipyrone, aminopyrone, phenylbutazone, clofezone, oxyphenbutazone, prexazone, apazone, benzydamine, bucolome, cinchopen, clonixin, ditrazol, epirizole, fenoprofen, floctafeninl, flufenamic acid, glaphenine, indoprofen, ketoprofen, meclofenamic acid, mefenamic acid, niflumic acid, phenacetin, salidifamides, sulindac, suprofen, tolmetin, pharmaceutically acceptable salts thereof, and mixtures thereof.

33. The dosage form of claim 30, wherein the proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, pantoprazole, leminoprazole, single enantiomers thereof, alkaline salts thereof, and mixtures thereof.

34. The dosage form of claim 31, wherein the NSAID is selected from the group consisting of salicylates, indomethacin, flurbiprofen, diclofenac, ketorolac, naproxen, piroxicam, tebufelone, ibuprofen, etodolac, nabumetone, tenidap, alcofenac, antipyrine, aminopyrine, dipyrone, aminopyrone, phenylbutazone, clofezone, oxyphenbutazone, prexazone, apazone, benzydamine, bucolome, cinchopen, clonixin, ditrazol, epirizole, fenoprofen, floctafeninl, flufenamic acid, glaphenine, indoprofen, ketoprofen, meclofenamic acid, mefenamic acid, niflumic acid, phenacetin, salidifamides, sulindac, suprofen, tolmetin, pharmaceutically acceptable salts thereof, and mixtures thereof.

35. The dosage form of claim 31, wherein the proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, pantoprazole, leminoprazole, single enantiomers thereof, alkaline salts thereof, and mixtures thereof.

FIGURE 1

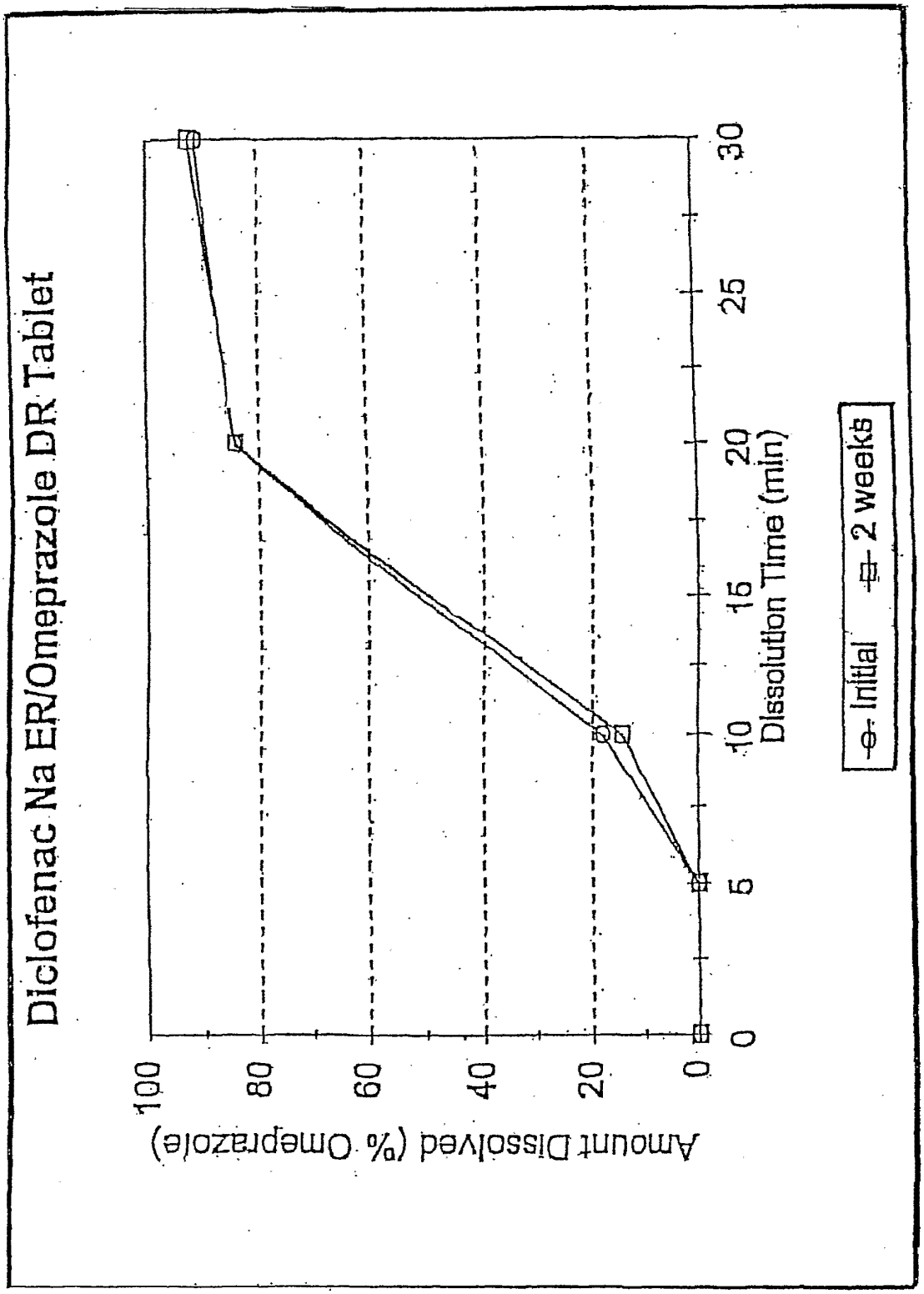

Diclofenac Na ER/Omeprazole DR Tablet
Amount Dissolved (% Omeprazole)
0
20
40
60
80
100
0
5
10
15
20
25
30
Dissolution Time (min)
Initial
2 weeks

FIGURE 2

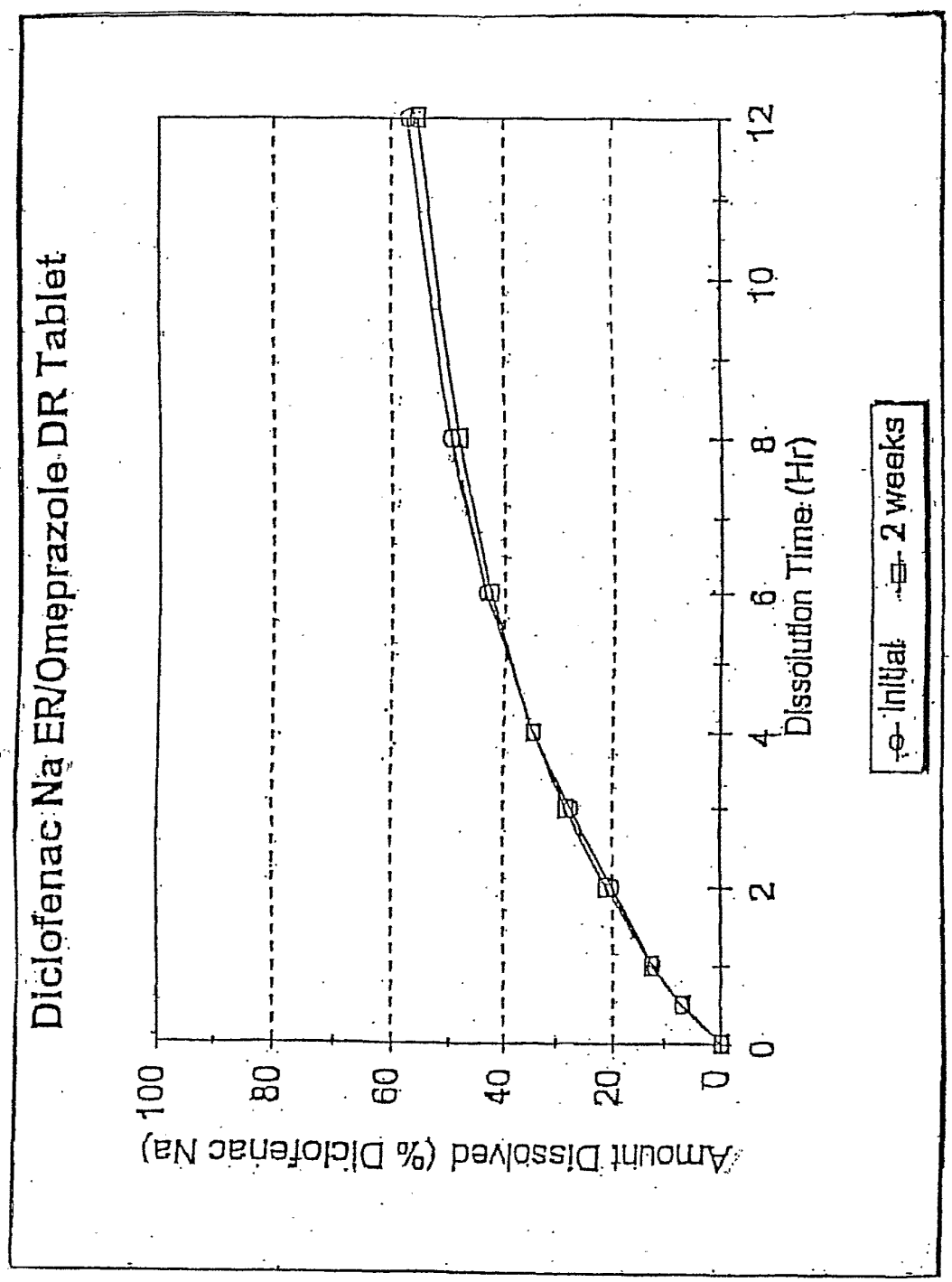

Diclofenac Na ER/Omeprazole DR Tablet
Amount Dissolved (% Diclofenac Na)
0
20
40
60
80
100
0
2
4
6
8
10
12
Dissolution Time (Hr)
Initial
2 weeks

FIGURE 3

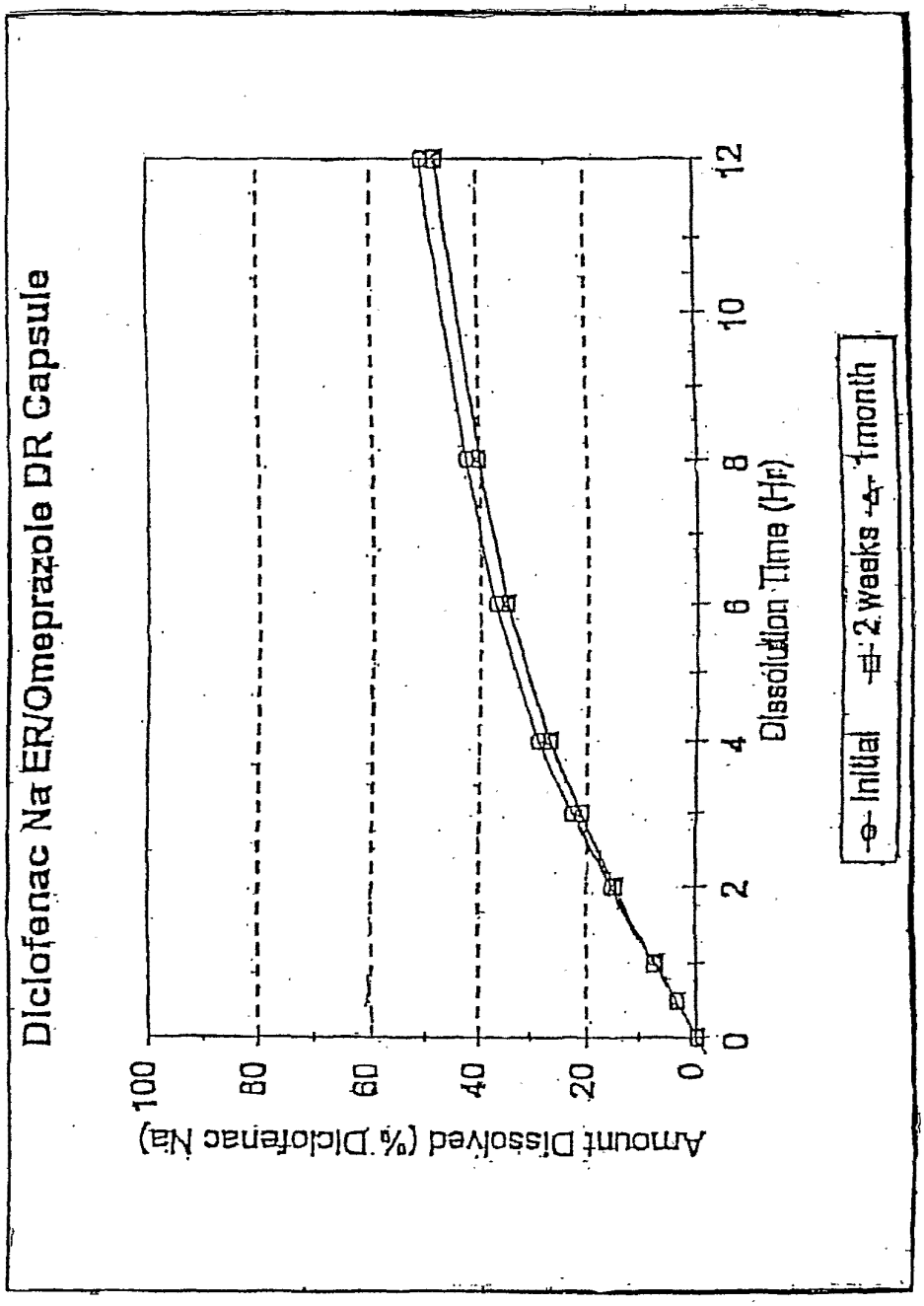
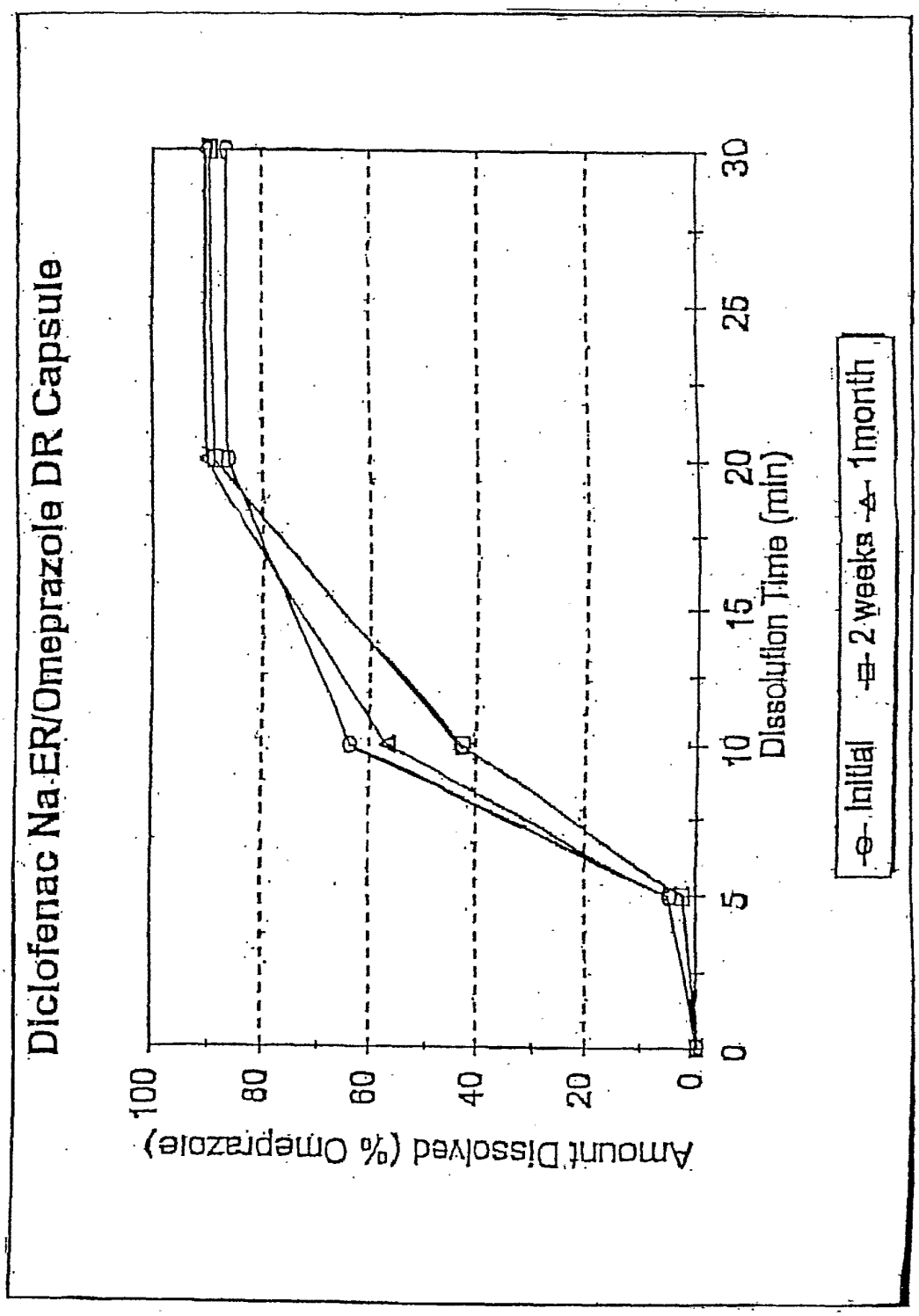

Diclofenac Na ER/Omeprazole DR Capsule
Amount Dissolved (% Diclofenac Na)
0
20
40
60
80
100
0
2
4
6
8
10
12
Dissolution Time (Hr)
Initial
2 weeks
1month

FIGURE 4


Diclofenac Na ER/Omeprazole DR Capsule
Amount Dissolved (% Omeprazole)
100
80
60
40
20
0
0
5
10
15
20
25
30
Dissolution Time (min)
Initial
2 weeks
1month

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/28331

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/32, 9/34, 9/36, 9/54, 9/58, 9/60, 9/62

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/451, 455, 456, 464, 468, 469, 470, 477, 480, 481, 482, 489, 493, 494, 495, 496, 497,

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,417,980 A (GOLDMAN et al) 23 May 1995, see entire document, especially examples 11-14, claims 1-4, 6 and 7.	1-35
Y	WO 97/25064 A1 (DEPUI et al) 17 July 1997, pages 4-13, examples 7, 10, claims 1-36.	1-35

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 12 NOVEMBER 2001	Date of mailing of the international search report 28 DEC 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JAMES M. SPEAR Telephone No. (703) 308-1235

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PCT/US01/28331

A. CLASSIFICATION OF SUBJECT MATTER:
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424/451, 455, 456, 464, 468, 469, 470, 477, 480, 481, 482, 489, 493, 494, 495, 496, 497,

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

WEST 2.0 search terms: proton, proton pump inhibitor, NSAID, antiinflammatory, diclofenac, naproxen, ibuprofen, flurbiprofen, piroxicam, omeprazole, lemiprazole, lansoprazole, rabeprazole, indomethacin, ketorolac, etodolac, salicylate,

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Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/017980 A1

(54) Title: STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING ACID LABILE BENZIMIDAZOLES

(57) Abstract: This invention provides a solid preparation without enteric coating which contains an acid labile active ingredient, particularly, a benzimidazole compound having an antiulcer action, and can neutralize the acid in stomach quickly, and exerts quickly the pharmacological effect of the active ingredient and suppresses the generation of a carbon dioxide gas as much as possible. A gastric disintegrable solid preparation contains an acid labile active ingredient, particularly, a benzimidazole compound, and at least one component selected from metal oxides and metal hydroxides. The preparation does not enteric-coated, but has a disintegration time of 7 minutes or less.

DESCRIPTION

STABLE PHARMACEUTICAL COMPOSITIONS COMPRISING ACID LABILE BENZIMIDAZOLES

Technical Field

The present invention relates to a solid preparation, further in detail, to a medical solid preparation containing an acid labile active ingredient, particularly, an acid labile active ingredient such as a benzimidazole compound useful as an antiulcer agent.

Background Art

Benzimidazole compounds such as lansoprazole, omeprazole, rabeprazole and the like are widely used as a digestive ulcer therapeutic agent because of its gastric acid secretion suppressing action and gastric mucous membrane preventing action and the like.

However, these compounds have poor stability, and unstable to humidity, temperature and light. They are particularly unstable to an acid, and become extremely unstable in aqueous solution or suspension as the pH of the solution or suspension lowers.

In a preparation, namely, a tablet, powder, fine particles, capsule and the like, benzimidazole compounds become unstable since mutual interaction with other components of the preparation is stronger in a preparation

than that of the compounds alone, and consequently, coloration change or decomposition is observed in production and storage. For stabilization of them, JP-A 10-36290 discloses enteric granules or enteric fine particles obtained by compounding a stabilizer composed of an inorganic base salt of magnesium and/or calcium for a medical solid composition, then, applying an enteric coating.

However, for producing such an enteric preparation, a process is required in which fine particles or granules containing a benzimidazole compound are produced, then, an enteric coating is applied. Further, since it takes a longer time until an enteric film is dissolved and a medicine is absorbed in a digestive tract after administration, a quick pharmacological effect can not be expected in the early stages after administration.

On the other hand, USP 5,840,737 and WO 00/26185 disclose a solution, suspension, tablet and capsule obtained by combining omeprazole or lansoprazole, which is not enteric-coated, with an alkali metal salt of bicarbonate.

However, since these preparations are combined with a bicarbonate, they react with an acid in stomach to evolve carbon dioxide gas which causes burping, and therefore they are not preferable from the viewpoint of compliance.

Objects of the Invention

An object of the present invention is to provide a solid preparation having no enteric coating which is capable of neutralizing quickly an acid in stomach, realizing quick occurrence of pharmacological effect of an active ingredient, and suppressing the evolution of carbon dioxide gas as much as possible, by solving the above-mentioned problems in medical solid preparations containing an acid labile active ingredient typically including benzimidazole compounds.

Summary of the Invention

The present inventors have found that a metal oxide and/or metal hydroxide is suitable for a gastric acid neutralizing agent in a solid preparation containing an acid labile active ingredient and having no enteric coating, and further investigation resulted in completion of the present invention.

Namely, the present invention provides:

(1) A gastric disintegrable solid preparation comprising an acid labile active ingredient and at least one component selected from metal oxides and metal hydroxides;

(2) A solid preparation according to the above-

mentioned (1), wherein the disintegration time is within 7 minutes;

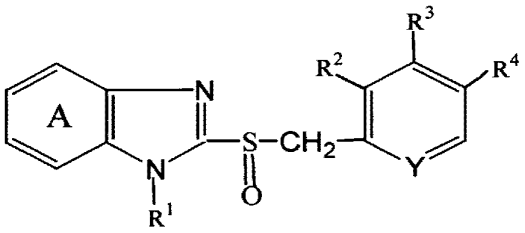
(3) A solid preparation according to the above-mentioned (1), which is the preparation without enteric coating;

(4) A solid preparation according to the above-mentioned (1), which comprises further at least one component selected from carbonates of alkali earth metal and basic additives having high water-solubility;

(5) A solid preparation according to the above-mentioned (1), wherein an acid labile active ingredient is a proton pump inhibitor (hereinafter, referred to as "PPI");

(6) A solid preparation according to the above-mentioned (5), wherein the PPI is a benzimidazole compound;

(7) A solid preparation according to the above-mentioned (6), wherein a benzimidazole compound is a compound represented by the formula (I):



(I)

wherein ring A is an optionally substituted benzene ring, R^1 is hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R^2, R^3 and R^4 are the

same or different and each represent a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH, or a salt thereof;

(8) A solid preparation according to the above-mentioned (6), wherein a benzimidazole compound is lansoprazole, omeprazole, rabeprazole or pantoprazole, or an optically active compound thereof;

(9) A solid preparation according to the above-mentioned (1), wherein the metal oxides and the metal hydroxides are those of which 1% aqueous solution or 1% aqueous suspension has a pH of 8.0 or more;

(10) A solid preparation according to the above-mentioned (1) which comprises at least one metal oxide selected from the group consisting of magnesium oxide, magnesium silicate, dry aluminum hydroxide gel and magnesium metasilicate aluminate;

(11) A solid preparation according to the above-mentioned (1) which comprises at least one metal hydroxide selected from the group consisting of magnesium hydroxide, aluminum hydroxide, synthetic Hydrotalcite, coprecipitate of aluminum hydroxide and magnesium hydroxide, coprecipitate of aluminum hydroxide, magnesium carbonate and calcium carbonate, and coprecipitate of aluminum

hydroxide and sodium bicarbonate;

(12) A solid preparation according to the above-mentioned (4), wherein the carbonate of alkali earth metal is calcium carbonate or magnesium carbonate;

(13) A solid preparation according to the above-mentioned (4), wherein the basic additive having high water-solubility is trometamol, disodium succinate, sodium hydrogen phosphate, trisodium phosphate, dipotassium phosphate or L-arginine;

(14) A solid preparation according to the above-mentioned (1) which contains magnesium oxide;

(15) A solid preparation according to the above-mentioned (1) which contains magnesium hydroxide;

(16) A solid preparation according to the above-mentioned (1) which contains magnesium oxide and magnesium hydroxide;

(17) A solid preparation according to the above-mentioned (14) or (16), wherein the magnesium oxide is one obtained by calcination at a temperature ranging from about 500°C to about 1000°C and of purity higher than 95%;

(18) A solid preparation according to the above-mentioned (14), wherein the magnesium oxide has a BET specific surface area of about $10m^2/g$ to about $50m^2/g$.

(19) A solid preparation according to the above-mentioned (6), which contains at least one component

selected from metal oxides and metal hydroxides at a ratio of 0.1 to 1500 parts by weight relative to 1 part by weight of the benzimidazole compound;

(20) A solid preparation according to the above-mentioned (6), which contains at least one component selected from metal oxides and metal hydroxides together with a salt of alkali earth metal at a total ratio thereof of 0.1 to 1800 parts by weight relative to 1 part by weight of the benzimidazole compound;

(21) A solid preparation according to the above-mentioned (1), which is a tablet, a granule or a capsule;

(22) A solid preparation according to the above-mentioned (1), wherein a group containing an acid labile active ingredient and a group containing a metal oxide or a metal hydroxide but containing no active ingredient are separately compounded; and

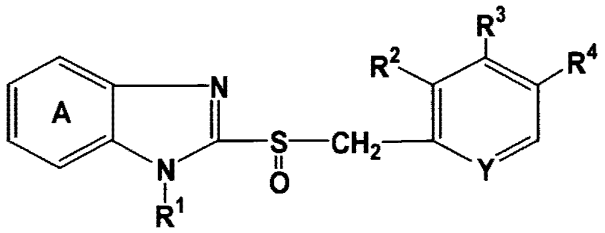
(23) A solid preparation according to the above-mentioned (4), wherein (1) a group containing both an active ingredient and at least one component selected from metal oxides, metal hydroxides, carbonates of alkali earth metal and basic additives having high water-solubility and (2) a group not containing an acid labile active ingredient but containing at least one component selected from metal oxides, metal hydroxides, carbonates of alkali earth metal and basic additives having high water-solubility are

separately compounded.

Detailed Description of the Invention

The acid labile active ingredient in the present invention is not particularly restricted, and any active components becoming unstable when exposed to gastric acid can be applied. Examples of the acid labile active ingredient include PPIs, erythromycin antibacterial compounds, anti-inflammatory enzymatic agents such as serrapeptase, semialkali proteinase and the like. Particularly, the present invention is suitable for PPIs. Such PPIs include benzimidazole compounds and similar compounds such as imidazopyridine compounds, e.g. tenatoprazole. Examples of benzimidazole compounds will be described below, however, the present invention is not limited to them and can be also applied to other active components unstable to an acid.

The benzimidazole compound which is a PPI, used in the present invention, includes a compound represented by the formula (I):



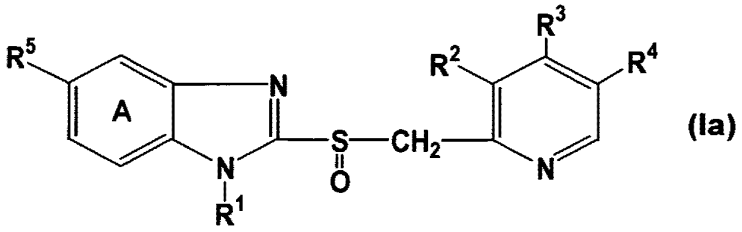
(I)

wherein, ring A represents an optionally substituted

benzene ring, R^1 represents a hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R^2, R^3 and R^4 are the same or different and each represent a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH, or a salt thereof.

In the formula (I), the compound is preferably a compound wherein ring A is a benzene ring which may optionally have a substituent group selected from a halogen atom, an optionally halogenated C_{1-4} alkyl group, an optionally halogenated C_{1-4} alkoxy group and 5 or 6-membered heterocyclic group, R^1 is a hydrogen atom, R^2 is a C_{1-6} alkyl group, C_{1-6} alkoxy group, C_{1-6} alkoxy-C_{1-6} alkoxy group or di-C_{1-6} alkylamino group, R^3 is a hydrogen atom, C_{1-6} alkoxy-C_{1-6} alkoxy group or optionally halogenated C_{1-6} alkoxy group, R^4 is a hydrogen atom or C_{1-6} alkyl group, and Y is a nitrogen atom.

Particularly preferable is the compound represented by the formula (Ia):



(Ia)

wherein, R^1 is a hydrogen atom, R^2 is a C_{1-3} alkyl group or

C_{1-3} alkoxy group, R^3 is a C_{1-3} alkoxy group which may be halogenated or substituted by C_{1-3} alkoxy group, R^4 is a hydrogen atom or C_{1-3} alkyl group, and R^5 is a hydrogen atom, optionally halogenated C_{1-3} alkoxy group or pyrrolyl group (e.g., 1-, 2- or 3-pyrrolyl group).

In the formula (Ia), particularly preferable is the compound wherein R^1 is a hydrogen atom, R^2 is a C_{1-3} alkyl group, R^3 is an optionally halogenated C_{1-3} alkoxy group, R^4 is a hydrogen atom, and R^5 is a hydrogen atom or an optionally halogenated C_{1-3} alkoxy group.

In the compound represented by the formula (I) above (hereinafter, referred to as compound (I)), the "substituent groups" in "an optionally substituted benzene ring" represented by ring A include, for example, a halogen atom, cyano group, nitro group, an optionally substituted alkyl groups, hydroxyl group, optionally substituted alkoxy group, aryl group, aryloxy group, carboxyl group, acyl group, acyloxy group, 5 to 10-membered heterocyclic group and the like, and 1 to 3 of these substituent groups may be substituted on a benzene ring. When the number of substituent groups is 2 or more, each substituent groups may be the same or different. Among these substituents, a halogen atom, an optionally substituted alkyl group and an optionally substituted alkoxy group are preferable.

As the halogen atom, a fluorine atom, chlorine atom,

bromine atom and the like are exemplified, among which a fluorine atom is preferable.

Examples of "alkyl group" in "an optionally substituted alkyl group" include C_{1-7} alkyl group (for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl and the like). Examples of "substituent group" in "an optionally substituted alkyl group" include a halogen atom, hydroxy group, C_{1-6} alkoxy group (for example, methoxy, ethoxy, propoxy, butoxy, etc.), C_{1-6} alkoxy-carbonyl group (for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, etc.), carbamoyl group and the like, and the number of these substituent groups may be 1 to 3. When the number of substituent groups is 2 or more, each substituent groups may be the same or different.

Examples of "alkoxy group" in "an optionally substituted alkoxy group" include C_{1-6} alkoxy group (for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, etc.). Examples of "substituent group" in "an optionally substituted alkoxy group" include groups identical with the "substituent group" of the "optionally substituted alkyl group" described above, and the number of substituent groups is also the same as that of the "optionally substituted alkyl group".

The "aryl group" includes, for example, C_{6-14} aryl

group (e.g., phenyl, 1-naphtyl, 2-naphthyl, biphenyl, 2-anthryl, etc.) and the like.

The "aryloxy group" includes, for example, C_{6-14} aryloxy group (e.g., phenyloxy, 1-naphtyloxy, 2-naphthyloxy, etc.) and the like.

The "acyl group" includes, for example, formyl, alkylcarbonyl, alkoxycarbony, carbamoyl, alkylcarbamoyl, alkylsulfinyl, alkylsulfonyl and the like.

The "alkylcarbonyl group" includes, for example, C_{1-6} alkyl-carbonyl group (e.g., acetyl, propionyl, etc.) and the like.

The "alkoxycarbonyl group" includes, for example, C_{1-6} alkoxy-carbonyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, etc.) and the like.

The "alkylcarbamoyl group" includes N-C_{1-6} alkyl-carbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl, etc.), N,N-diC_{1-6} alkyl-carbamoyl group (e.g., N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, etc.) and the like.

The "alkylsulfinyl group" includes, for example, C_{1-7} alkylsulfinyl group (e.g., methylsulfinyl, ethylsulfinyl, propylsulfinyl, isopropylsulfinyl, etc.) and the like.

The "alkylsulfonyl group" includes, for example, C_{1-7} alkylsulfonyl group (e.g., methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, etc.) and the like.

The "acyloxy group" includes, for example, alkylcarbonyloxy group, alkoxycarbonyloxy group, carbamoyloxy group, alkylcarbamoyloxy group, alkylsulfinyloxy group, alkylsulfonyloxy group and the like.

The "alkylcarbonyloxy group" includes C_{1-6} alkyl-carbonyloxy group (e.g., acetyloxy, propionyloxy, etc.) and the like.

The "alkoxycarbonyloxy group" includes, for example, C_{1-6} alkoxy-carbonyloxy group (e.g., methoxycarbonyloxy, ethoxycarbonyloxy, propoxycarbonyloxy, butoxycarbonyloxy, etc.) and the like.

The "alkylcarbamoyloxy group" includes C_{1-6} alkyl-carbamoyloxy group (e.g., methylcarbamoyloxy, ethylcarbamoyloxy, etc.) and the like.

The "alkylsulfinyloxy group" includes, for example, C_{1-7} alkyl-sulfinyloxy group (e.g., methylsulfinyloxy, ethylsulfinyloxy, propylsulfinyloxy, isopropylsulfinyloxy, etc.) and the like.

The "alkylsulfonyloxy group" includes, for example, C_{1-7} alkyl-sulfonyloxy group (e.g., methylsulfonyloxy, ethylsulfonyloxy, propylsulfonyloxy, isopropylsulfonyloxy, etc.) and the like.

The "5 to 10-membered heterocyclic group" includes, for example, 5 to 10-membered (preferably, 5 or 6-membered) heterocyclic group having 1 or more (for example, 1 to 3)

hetero atoms selected from a nitrogen atom, sulfur atom and oxygen atom in addition to a carbon atom, and specific examples thereof include 2- or 3-thienyl group, 2-, 3- or 4-pyridyl group, 2- or 3-furyl group, 1-, 2- or 3-pyrrolyl group, 2-, 3-, 4-, 5- or 8-quinolyl group, 1-, 3-, 4- or 5-isoquinolyl group, 1-, 2- or 3-indolyl group and the like. Among them, preferable are 5 or 6-membered heterocyclic group such as 1-, 2- or 3-pyrrolyl group.

Preferably, ring A is a benzene ring which may have one or two substituent groups selected from a halogen atom, an optionally halogenated C_{1-4} alkyl group, an optionally halogenated C_{1-4} alkoxy groups and 5 or 6-membered heterocyclic group.

Examples of "aralkyl group" in "an optionally substituted aralkyl group" represented by R^1 include, for example, C_{7-16} aralkyl group (e.g., C_{6-10} aryl C_{1-6} alkyl group such as benzyl, phenetyl, etc.) and the like. Examples of "substituent group" in "an optionally substituted aralkyl group" include the same substituent groups as those of the "optionally substituted alkyl group" described above, and the number of substituent groups is 1 to 4. When the number of substituent groups is 2 or more, each substituent groups may be the same or different.

The "acyl group" represented by R^1 includes, for example, the "acyl group" exemplified as the substituent

group on ring A described above.

The "acyloxy group" represented by R^1 includes, for example, the "acyloxy group" exemplified as the substituent group on ring A described above.

Preferably, R^1 is a hydrogen atom.

The "optionally substituted alkyl group" represented by R^2, R^3 or R^4 includes the "optionally substituted alkyl group" exemplified as the substituent group on ring A described above.

The "optionally substituted alkoxy group" represented by R^2, R^3 or R^4 includes the "optionally substituted alkoxy group" exemplified as the substituent group on ring A described above.

The "optionally substituted amino group" represented by R^2, R^3 or R^4 includes, for example, amino group, mono-C_{1-6} alkylamino group (e.g., methylamino, ethylamino, etc.), mono-C_{6-14} arylamino group (e.g., phenylamino, 1-naphthylamino, 2-naphthylamino, etc.), di-C_{1-6} alkylamino group (e.g., dimethylamino, diethylamino, etc.), di-C_{6-14} arylamino group (e.g., diphenylamino, etc.) and the like.

Preferably, R^2 is a C_{1-6} alkyl group, C_{1-6} alkoxy group, C_{1-6} alkoxy-C_{1-6} alkoxy group or di-C_{1-6} alkylamino group. More preferably, R^2 is a C_{1-3} alkyl group or C_{1-3} alkoxy group.

Preferably, R^3 is a hydrogen atom, C_{1-6} alkoxy-C_{1-6}

alkoxy group or optionally halogenated C_{1-6} alkoxy group. More preferably, R^3 is a C_{1-3} alkoxy group which is halogenated or may be substituted with a C_{1-3} alkoxy group.

Preferably, R^4 is a hydrogen atom or C_{1-6} alkyl group. More preferably, R^4 is a hydrogen atom or C_{1-3} alkyl group (particularly, hydrogen atom).

Preferably, Y is a nitrogen atom.

Specific examples of the compound (I) include the following compounds.

2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole, 2-[[3,5-dimethyl-4-methoxy-2-pyridinyl)methyl]sulfinyl]-5-methoxy-1H-benzimidazole, 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole•sodium salt, 5-difluoromethoxy-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole and the like.

Among these compounds, 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole(Lansoprazole) is preferable.

The above-mentioned compound (I) may be a racemic compound, or may be an optically active compound such as R-compound, S- compound and the like. For example, optically active substances such as (R)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole (sometimes referred to as Lansoprazole R

enantiomer) may also be permissible and preferable.

The salt of the compound (I) is preferably a pharmaceutically acceptable salt, and examples thereof include salts with inorganic bases, salts with organic bases, salts with basic amino acids, and the like.

Suitable examples of the salt with an inorganic base include, for example, alkali metal salts such as sodium salts, potassium salts, etc.; alkaline earth metal salts such as calcium salts, magnesium salts, etc.; ammonium salts, and the like.

Suitable examples of the salt with an organic base include, for example, salts with alkylamines (trimethylamine, triethylamine, etc.), heterocyclic amines (pyridine, picoline, etc.), alkanolamines (ethanolamine, diethanolamine, triethanolamine, etc.), dicyclohexylamine, N,N'-dibenzylethylenediamine and the like.

Suitable examples of the salt with a basic amino acid include, for example, salts with alginine, lysine, ornithine and the like.

Among these salts, alkali metal salts or alkaline earth metal salts are preferable. Particularly, sodium salts are preferable.

The compound (I) can be produced by a method known per se, and produced by methods described, for example, JP-A 61-50978, USP 4,628,098, JP-A 10-195068, WO 98/21201 and

the like, or methods according to these methods. The optically active compound (I) can be obtained by optical resolution methods (fractional re-crystallization method, chiral column method, diastereomer method, method using microorganism or enzyme, etc.), asymmetric oxidation and the like. For example, in the case of Lansoprazole R enantiomer, it can also be produced in accordance with the methods described in WO 00-78745, WO 01-83473, WO 01-87874 and WO 02-44167.

As the PPIs used in the present invention, the benzimidazole compound having an antiulcer action such as lansoprazole, omeprazole, rabeprazole and pantoprazole and the imidazopyridine compound such as tenatoprazole or optically active compounds thereof and pharmaceutically acceptable salts thereof are preferable.

The compounding amount of the benzimidazole compound used in the present invention varies depending on the kind and dosage of an active ingredient, and for example, the amount is from 0.001 to 0.3 parts by weight, preferably from 0.002 to 0.2 parts by weight relative to 1 part by weight of the solid preparation of the present invention.

The metal oxide and metal hydroxide used in the present invention are preferably those of which 1% aqueous solution or 1% aqueous suspension has a pH of 8.0 or more, and examples of the metal oxide include medical magnesium

oxide, magnesium silicate ($2MgO \cdot 3SiO_2 \cdot xH_2O$), dry aluminum hydroxide gel ($Al_2O_3 \cdot xH_2O$), magnesium metasilicate aluminate ($Al_2O_3 \cdot MgO \cdot 2SiO_2 \cdot xH_2O$) and the like. Particularly, magnesium oxide can be suitably used.

Preferable magnesium oxides are those that are available for medical use and that have an excellent reactivity to acid and neutralization ability. As these magnesium oxides, magnesium oxide obtained by a usual production method and commercially available magnesium oxide can be used, and preferable is one obtained by calcination at low temperature, so-called, calcining magnesia. The magnesium oxide calcined at a temperature of about 500 to about 1000°C is generally preferable, and particularly from the viewpoint of neutralization ability the magnesium oxide calcined at a temperature of about 600 to about 900°C is preferable, and the magnesium oxide calcined at about 800°C is most preferable. Among these magnesium oxides, favorable is the one that neutralizes the environment prior to the release of the acid labile active ingredient by the disintegration of the preparation in stomach and has the function to enhance the remaining ratio of the active ingredient. Such magnesium oxide is preferably the one that has usually a BET specific surface area of about $10m^2/g$ to about $50m^2/g$, preferably about $20m^2/g$ to about $50m^2/g$.

Hereupon, a BET specific surface area means the specific surface area measured by nitrogen gas adsorption method, and the specific surface area containing the surface of given amount magnesium oxide and its cavity in which nitrogen gas can enter is determined by the amount of adsorbed nitrogen gas.

The magnesium oxide includes, for example, commercially available heavy magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K.), heavy magnesium oxide (Tomita Pharmaceutical Co. Ltd.), heavy N magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K.), light magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K.) and the like. Particularly heavy N magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K.) is preferable.

The metal hydroxide includes, for example, medical magnesium hydroxide, aluminum hydroxide, synthetic hydrotalcite ($Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O$), co-precipitate of aluminum hydroxide and magnesium hydroxide, co-precipitate of aluminum hydroxide, magnesium carbonate and calcium carbonate, and co-precipitate of aluminum hydroxide and sodium hydrogen carbonate. Among these compounds, magnesium hydroxide is particularly preferable from the viewpoint of the disintegrating property and dissolution property of a preparation.

These may be used alone or in combination of two or

more. Some of metal oxides and metal hydroxides may whittle the surface of a preparation apparatus in production. As a result of such whittling, the resulting tablets sometimes become partially or wholly darkish or blackish and are imparted with black spots, lines or surfaces. Sticking of the resulting preparations on a die in production of tablets is also sometimes caused, depending on the metal hydroxides or metal oxides used. These properties deteriorate remarkably the productivity. It has been found that, when metal oxides or metal hydroxides having whittling property and adhesiveness on a die are used, the whittling action and adhesiveness on a die can be suppressed by wet or dry granulation using metal oxides or metal hydroxides having no such properties or pharmaceutically acceptable additives described bellow (excipients, binders, disintegrants, etc.) in combination. In the case of preparations of PPIs, preferred are magnesium hydroxides, magnesium oxides and combination of a magnesium hydroxide and magnesium oxide from the viewpoint of compatibility with PPIs, dissolution property, and disintegrating property of a preparation.

These metal oxides and/or metal hydroxides are compounded in such an amount that they are quickly dissolved and neutralize gastric acid simultaneously with disintegration of a solid preparation in stomach,

preferably, prior to dissolution of an active ingredient, in order to prevent unstabilization of substantial parts of an active ingredient by being exposed to gastric acid. Metal oxides and metal hydroxides are compounded usually in an amount of about 0.05 to 2000 parts by weight, preferably about 0.1 to 1000 parts by weight, more preferably about 0.1 to 800 parts by weight relative to 1 part by weight of an acid labile active ingredient, though the amount varies depending on the gastric acid neutralization ability of each metal oxide and metal hydroxide. For example, metal oxides and metal hydroxides are compounded in an amount of about 0.1 to 1500 parts by weight, preferably about 0.5 to 800 parts by weight, more preferably 0.1 to 400 parts by weight relative to 1 part by weight of a benzimidazole compound. When the active ingredient is a benzimidazole compound, the pH in stomach usually increases simultaneously with initiation of dosing, and they are compounded preferably in an amount that pH increases to 4 or more within about 60 minutes, more preferably within 40 minutes after administration, in stomach of usual pH range.

Usually, metal oxides and metal hydroxides are compounded preferably in an amount that pH increases to 7 or more within 10 minutes, more preferably within 7 minutes, by a measuring method as shown in the following experiment example.

In the present invention, at least one component selected from carbonates of alkaline earth metals and basic additives having high water-solubility may be compounded, in addition to these metal oxides and/or metal hydroxides, if necessary. The carbonates of alkaline earth metals include, for example, calcium carbonate and magnesium carbonate for medical use. The basic additives having high water-solubility include medical additives having an antacid action such as trometamol, disodium succinate, sodium hydrogen phosphate, trisodium phosphate, dipotassium phosphate, L-arginine and the like. These may also be used alone or in combination of two or more.

These are also compounded in such an amount that they are quickly dissolved and neutralize gastric acid simultaneously with disintegration of a solid preparation in stomach, preferably, prior to dissolution of an active ingredient, in order to prevent unstabilization of substantial parts of an active ingredient by being exposed to gastric acid, and are compounded usually in a total amount with metal oxides and metal hydroxides of about 0.05 to 2000 parts by weight, preferably about 0.1 to 1200 parts by weight, more preferably about 0.1 to 800 parts by weight relative to 1 part by weight of a acid labile active ingredient, though the amount varies depending on the gastric acid neutralization ability of each additives.

Usually, neutralization agents are compounded in a total amount of 0.1 to 1800 parts by weight, preferably about 0.5 to 1000 parts by weight, more preferably 1 to 800 parts by weight relative to 1 part by weight of a benzimidazole compound. Preferably, they are compounded in an amount that pH increases to 4 or more within about 60 minutes, more preferably within 40 minutes after administration, in stomach of usual pH range.

In the solid preparation of the present invention, additives can be further used such as excipients for preparation (e.g., glucose, fructose, lactose, sucrose, D-mannitol, erythritol, maltitol, trehalose, sorbitol, corn starch, potato starch, wheat starch, rice starch, microcrystalline cellulose (crystalline cellulose), anhydrous silic acid, anhydrous calcium phosphate, precipitated calcium carbonate, calcium silicate, etc.), binder (e.g., hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, methylcellulose, polyvinyl alcohol, carboxymethylcellulose sodium, partial α-starch, α-starch, sodium alginate, pullulan, gum Arabic powder, gelatin, etc.), disintegrating agent (e.g., low-substituted hydroxypropylcellulose, calmellose, calmellose calcium, carboxymethyl starch sodium, cross calmellose sodium, crospovidone, hydroxypropyl starch, etc.), flavoring agent (e.g., citric acid, ascorbic acid,

tartaric acid, malic acid, aspartame, acesulfam potassium, somatin, saccharin sodium, dipotasium glycirrhizinate, sodium glutamate, sodium 5'-inosinate, sodium 5'-guanylate, etc), surfactant (e.g., polysorbate, polyoxyethylene•polyoxypropylene copolymer, sodium laurylsulfate, etc.), aromatics (e.g., lemon oil, orange oil, menthol, peppermint oil, etc.), lubricant (e.g., magnesium stearate, sucrose fatty acid ester, stearyl sodium fumarate, stearic acid, talc, polyethylene glycol, etc.), coloring agent (e.g., edible yellow No. 5, edible blue No. 2, ferric oxide, yellow ferric oxide, etc.) and antioxidant (e.g., sodium ascorbate, L-cysteine, sodium sulfite, etc.).

The particle size of a raw material used in them is not particularly restricted, and preferably 500 μm or less from the standpoint of a production property and dosing property.

The method of producing the solid preparation of the present invention may be a method known per se, and for example, benzimidazole compounds, metal oxides and/or metal hydroxides, if necessary, carbonates of alkaline earth metals and/or basic additives having higher water-solubility and an antacid action, excipients, further, binders, disintegrating agents, lubricants, flavoring agents, coloring agents, aromatics are combined suitably to

give a tablet, powder, granule, capsule, fine particles and the like. These can be produced by a method described in the preparation general rule of The Pharmacopoeia of Japan, 14th revision.

Particularly, the granulation by wet granulation is preferred.

Herein, the wet granulation means a method for obtaining granulated materials or powders such as granules and fine granules by granulating a dispersion or solution of the mixture of a drug and excipient in water, binder or solvent and then drying, and the granulation mechanism may be any type such as extrusion, fluidization, rolling, centrifuging, stirring, spraying etc.

Further, these preparations may be coated with a coating agent (for example, coating film containing hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinyl alcohol, polyvinyl pyrrolidone, etc.), however, an enteric coating is not applied.

In the present invention, preparation raw materials may be formulated in one portion, or may be divided into two or more groups and formulated (for example, layer separation, granulations having different disintegrating properties, etc.). In any case, metal oxides and/or metal hydroxides, further, carbonates of alkaline earth metals and/or basic additives having higher water-solubility and

an antacid property are quickly dissolved and neutralize gastric acid simultaneously with disintegration of a solid preparation in stomach, preferably, prior to dissolution of an active ingredient, and prevent unstabilization of substantial parts of an active ingredient by being exposed to gastric acid. For example, a method in which a group containing an active ingredient is compounded near the nucleus of a preparation and a metal oxide and/or metal hydroxide is compounded in an outer layer of the preparation are exemplified.

Also in either case of one-group formulation or divided or separate-groups formulation, it is possible to neutralize gastric acid by compounding a basic additive having high water solubility and dissolving it quickly.

Further, by dividing preparation raw materials into a group containing an acid labile active ingredient and a group containing no active ingredient and compounding them separately in the preparation to give a time difference of disintegration of components, the group containing no active component can be formulated to disintegrate more quickly. A metal oxide and/or metal hydroxide may be compounded in both groups or in the group containing no active ingredient. Further, a carbonate of an alkaline earth metal and/or a basic additive having high water solubility and an antacid action may be compounded in

either group or both groups.

Furthermore, a preparation containing a group which contains neither an active ingredient nor a metal oxide and metal hydroxide but contains mainly a carbonate of an alkaline earth metal and/or a basic additive having high water solubility and an antacid action, may also be formulated. Particularly, this preparation is suitable to increase the pH in stomach by dissolving this group more quickly.

Further, when the components are grouped and formulated separately, an additive having bonding ability to a group containing an active ingredient (e.g., hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polyvinylpyrrolidone, methylcellulose, polyvinyl alcohol, carboxymethylcellulose sodium, partial α-starch, α-starch, sodium alginate, pullulan, gum Arabic powder, gelatin, polyethylene oxide, carboxymethylethylcellulose, carboxyvinyl polymer, ethylcellulose, ethyl acrylate•methyl methacrylate•trimethylammoniumethyl methacrylate copolymer, etc.) may be compounded to delay the dissolution of the active ingredient. Further, a group containing an active component may be coated to delay the dissolution with a component containing hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinyl alcohol,

polyvinylpyrrolidone, ethylcellulose or ethyl acrylate•methyl methacrylate•trimethylammoniumethyl methacrylate copolymer.

More specifically, a tablet can be produced, for example, by several methods such that a benzimidazole compound, metal hydroxide, excipient, binder, disintegrating agent and lubricant are mixed and compressed directly into tablets; a benzimidazole compound, a metal hydroxide, excipient and additive having high water solubility and an antacid action are mixed, then, a binder is added to the mixture to form granules, and a disintegrating agent and lubricant are added to the granules, and then the resultant mixture is compressed into tablets; and a benzimidazole compound, a metal hydroxide and excipient are mixed, then, a binder is added to the mixture to obtain granules, and separately, a metal hydroxide, additive having high water solubility and an antacid action and excipent are mixed, then, a binder is added to the mixture to obtain granules, and these obtained granules, disintegrating agent and lubricant are mixed and compressed into tablets.

Further, in the case of production of two or more kinds of granules, it is also possible that one or more kinds of binders are added to a group containing a benzimidazole compound to suppress its dissolution.

Granules can be produced by an ordinary method. For example, granules can be produced by the same methods as the production methods of a tablet, or by an extrusion granulation method. For obtaining granules having higher sphericity and smaller particle size distribution, for example, nucleus-containing granules may be produced by a method described in JP-A 63-301816. Nucleus-containing granules are obtained by coating a powdery spray agent containing a benzimidazole compound having an antiulcer action, metal hydroxide, excipient, disintegrating agent and the like while spraying binding liquid such as hydroxypropylcellulose on a sugar nucleus. The nucleus granule includes, for example, Nonparell obtained by coating sucrose (75 parts by weight) with corn starch (25 parts by weight) by a method known per se, and spherical nucleus granules using crystalline cellulose, and further, the nucleus granule itself may be the active ingredient component mentioned above. The average particle size of the nucleus granule is generally 14 to 80 mesh.

In the case of a capsule, it can be obtained by filling with a simply mixed powder or the particles for a tablet or granule obtained above.

The solid preparation obtained in the present invention is a gastric disintegrable solid preparation without enteric coating having an disintegration time of 7

minutes or less, preferably 5 minutes or less, more preferably 4 minutes or less, by the measurement of disintegrating time based on the method described in United States Pharmacopoeia <701> Disintegration.

The solid preparation of the present invention can be itself administered orally. The solid preparation of the present invention can be taken in the form of liquid or semisolid by dispersing or dissolving it previously in water, juice, yoghurt and the like.

In the solid preparation of the present invention, when the active ingredient is, for example, a benzimidazole compound represented by the formula (I) such as lansoprazole and optically active compounds thereof, these compounds are useful as a medicine since they have excellent antiulcer action, gastric acid secretion-suppressing action, mucous membrane protecting action, anti-Helicobacter pylori action and the like, and have low toxicity. In this case, the solid preparation of the present invention can be orally administered to mammal animals (for example, human, monkey, sheep, horse, dog, cat, rabbit, rat, mouse, etc.), for the purpose of treating and preventing peptic ulcer (for example, gastric ulcer, duodenal ulcer, stomal ulcer, Zollinger-Ellison syndrome, etc.), gastritis, Gastroesophageal Reflux Diseases (GERD) e.g. reflux esophagitis, Symptomatic GERD, erosive

esophagitis; NUD (Non Ulcer Dyspepsia), stomach cancer (including stomach cancer caused by promotion of production of interleukin-1ß by gene polymorphism of interleukin-1), stomach MALT lymphoma and the like, removing Helicobacter pylori, suppression of upper digestive canal hemorrhage caused by peptic ulcer, acute stress ulcer, and hemorrhagic gastritis, suppressing upper digestive canal hemorrhage caused by invasive stress (stress caused by cerebral vascular disorder requiring major operation or intensive care needing intensive management after operation, head trauma, multi-organ disorder, wider range heat injury), treating and preventing ulcer ascribed to nonsteroidal anti-inflammatory agent; and treating and preventing gastric hyperacidity and ulcer by stress after operation. For removal of Helicobacter pylori, it is preferable to use the solid preparation and, penicillin antibiotics (e.g., amoxicillin) and erythromycin antibiotics (e.g., clarithromycin), together.

The preparation of this invention is especially applicable for GERD (e.g., Symptomatic GERD and erosive esophagitis).

The daily dose differs depending on severity of symptom, age, sex and body weight of the patient, period and interval of administration, kind of the active ingredient employed and the like, and is not particularly

restricted, and for example, the solid preparation can be administered as an antiulcer agent to an adult (60 kg) at an oral daily dose of about 0.5 to 1500 mg/day, preferably about 5 to 150 mg/day as an active ingredient. These benzimidazole compound-containing preparations may be administered once or in two or three divided portions a day.

Examples

Hereinafter, the present invention is further detailed by the following Examples, which are not intended to restrict the present invention.

Example 1

Production of active ingredient group

240 g of lansoprazole, 1160 g of magnesium hydroxide, 616 g of D-mannitol and 264 g of corn starch were charged into a fluidized bed granulator, and 8% aqueous solution prepared by dissolving 120 g of hydroxypropylcellulose in 1380 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2188 g of granules.

Production of outer layer group

870 g of magnesium hydroxide, 1107 g of D-mannitol and 474 g of corn starch were charged in a fluidized bed granulator, and 750 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2199 g

of granules.

300 g of a active ingredient group, 408.5 g of an outer layer group, 37.5 g of crospovidone and 11 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (750 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 2

Production of active ingredient group

120 g of lansoprazole, 200 g of magnesium hydroxide, 580 g of D-mannitol and 240 g of corn starch were charged into a fluidized bed granulator, and 8% aqueous solution prepared by dissolving 60 g of hydroxypropylcellulose in 690 g of purified water was sprayed, and these materials were granulated, and dried to obtain 1161.1 g of granules.

Production of outer layer group

720 g of magnesium hydroxide, 259.5 g of D-mannitol, 225 g of microcrystalline cellulose (Ceolus KG-801) and 112.5 g of crospovidone were charged in a fluidized bed granulator, and 500 g of purified water was sprayed, and these materials were granulated, and dried to obtain 1138.8 g of granules.

300 g of a active ingredient group, 439 g of an outer layer group and 11 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (750 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 3

Production of active ingredient group

120 g of lansoprazole, 580 g of magnesium hydroxide, 332 g of D-mannitol and 108 g of corn starch were charged into a fluidized bed granulator, and 8% aqueous solution prepared by dissolving 60 g of hydroxypropylcellulose in 690 g of purified water was sprayed, and these materials were granulated, and dried to obtain 982.1 g of granules.

Production of outer layer group

108.8 g of magnesium hydroxide, 453.8 g of trometamol, 52.5 g of D-mannitol, 127.5 g of microcrystalline cellulose (Ceolus KG-801) and 63.7 g of crospovidone were charged in a fluidized bed granulator, and 400 g of purified water was sprayed, and these materials were granulated, and dried to obtain 758.7 g of granules.

270 g of a active ingredient group, 483.8 g of an outer layer group and 11.2 g of magnesium stearate were

mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (850 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 4

150 g of lansoprazole, 500 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., grade: heavy N), 725 g of magnesium hydroxide, 1390 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and 2.8% aqueous solution prepared by dissolving 70 g of hydroxypropylcellulose in 2430 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2771.5 g of granules.

2614.5 g of the obtained granules, 315 g of microcrystalline cellulose (Ceolus KG-801), 157.5 g of crospovidone and 63 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 5

60 g of lansoprazole, 120 g of magnesium oxide, 406 g of magnesium hydroxide and 584 g of D-mannitol were charged into a fluidized bed granulator, and 5.6% aqueous solution prepared by dissolving 28 g of hydroxypropylcellulose in 472 g of purified water was sprayed, and these materials were granulated, and dried to obtain 1144.3 g of granules.

581 g of the granules, 70 g of microcrystalline cellulose (Ceolus KG-801), 35 g of crospovidone and 14 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 6

150 g of lansoprazole, 500 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 725 g of magnesium hydroxide, 1316.5 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose and 3.5 g of yellow ferric oxide in 2256.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2817.7 g of granules.

2614.5 g of the granules, 315 g of microcrystalline cellulose (Ceolus KG-801), 157.5 g of crospovidone and 63 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 7

105 g of lansoprazole, 525 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 761.3 g of magnesium hydroxide, 1300.3 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose and 3.5 g of yellow ferric oxide in 2376.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2754.6 g of granules.

2573 g of the granules, 310 g of microcrystalline cellulose (Ceolus KG-801), 155 g of crospovidone and 62 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (1000 mg per tablet) by a die having a 16 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled

powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 8

75 g of lansoprazole, 500 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 725 g of magnesium hydroxide, 1391.5 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose, 1.75 g of yellow ferric oxide and 1.75 g of ferric oxide in 2256.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2828.0 g of granules.

2614.5 g of the granules, 315 g of microcrystalline cellulose (Ceolus KG-801), 157.5 g of crospovidone and 63 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 9

52.5 g of lansoprazole, 525 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 761.3 g

of magnesium hydroxide, 1352.8 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose, 1.75 g of yellow ferric oxide and 1.75 g of ferric oxide in 2376.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2771.6 g of granules.

2573 g of the granules, 310 g of microcrystalline cellulose (Ceolus KG-801), 155 g of crospovidone and 62 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (1000 mg per tablet) by a die having a 16 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 10

300 g of lansoprazole, 500 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 725 g of magnesium hydroxide, 1166.5 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose, 2.5 g of yellow ferric oxide and 1 g of ferric oxide in 2256.5 g of purified water was sprayed, and these materials were granulated, and dried

to obtain 2783.0 g of granules.

2614.5 g of the granules, 315 g of microcrystalline cellulose (Ceolus KG-801), 157.5 g of crospovidone and 63 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 11

210 g of lansoprazole, 525 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 761.3 g of magnesium hydroxide, 1195.3 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose, 2.45 g of yellow ferric oxide and 1.05 g of ferric oxide in 2376.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2823.7 g of granules.

2573 g of the granules, 310 g of microcrystalline cellulose (Ceolus KG-801), 155 g of crospovidone and 62 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (1000 mg per tablet) by a die having a 16 mmΦ flat bevel

edge using tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Example 12

150 g of lansoprazole, 700 g of magnesium oxide (manufactured by Kyowa Kagaku Kogyo K.K., N grade), 435 g of magnesium hydroxide, 1406.5 g of D-mannitol and 70 g of aspartame were charged into a fluidized bed granulator, and an aqueous solution prepared by dispersing and dissolving 140 g of hydroxypropylcellulose and 3.5 g of yellow ferric oxide in 1906.5 g of purified water was sprayed, and these materials were granulated, and dried to obtain 2756.4 g of granules.

2614.5 g of the granules, 350 g of microcrystalline cellulose (Ceolus KG-801), 175 g of crospovidone and 70 g of magnesium stearate were mixed in a bag to obtain a mixture. The resultant mixture was compressed into tablets (700 mg per tablet) by a die having a 13 mmΦ flat bevel edge using a tabletting machine. No darkishness by whittled powders or sticking of the mixture on the die was observed in the resulting tablets.

Experiment Example 1

Disintegration test

The disintegration time was measured according to a method described in USP <701> Disintegration.

Condition: purified water 1000 mL, no disk

The results are shown in Table 1.

Table 1

	Example 1	Example 2	Example 3
Average disintegration time (min)	0.92	0.70	0.45

Measurement of pH change

Test solution of 0.05 mol hydrochloric acid 100 mL (37 ℃) was charged into a 100 mL beaker, and each one tablet obtained in example 1, example 2 and example 3 was added and a test was carried out under the condition of 100 revolutions per minute using a basket according to the dissolution test method of USP. pH change by time was measured.

As shown in Table 2, pH of the test solution increased quickly, and pH of 7 or more could be reached over 3 minutes.

Table 2

	1 min	2 min	3 min	4 min	5 min	10 min
Example 1	1.42	3.12	7.63	8.83	9.04	9.15
Example 2	2.01	6.77	7.97	8.46	8.64	8.85
Example 3	3.08	6.99	7.49	7.72	7.83	8.06

Measurement of dissolution profile

One tablet obtained in example 1, example 2 or example 3, or one Takepron capsule (30 mg) filled with lansoprazole granules with an enteric coating was added to 900 mL of phosphate buffer solution having a pH of 6.8 at 37℃, and the amount of dissolved lansoprazole was measured under rotation at 75 rpm by the absorbancy at 286 nm in the ultraviolet range, and the dissolution ratio was calculated.

The results are shown in Table 3.

The dissolution profile was quick as compared with the dissolution of a capsule.

Table 3

	5 min	10 min	15 min	20 min
Example 1	91.8%	97.9%	98.2%	97.5%
Example 2	99.4%	101.9%	101.1%	100.3%
Example 3	81.5%	87.7%	88.3%	87.7%
Capsule	38.1%	94.2%	96.8%	97.7%

Experiment Example 2

Disintegration test

The disintegration time was measured according to a method described in USP <701> Disintegration.

Condition: purified water 1000 mL, no disk

The results are shown in Table 4.

Table 4

	Example 4	Example 5
disintegration time (min)	1.25	1.28

Measurement of dissolution profile

One tablet obtained in example 4 or example 5 was added to 900 mL of phosphate buffer solution having a pH of 6.8 at 37℃, and the amount of dissolved lansoprazole was measured by the absorbancy at 286 nm in the ultraviolet range under the same conditions as Experiment Example 1, and the dissolution ratio was calculated.

The dissolution profile was quick as compared with that of the above-mentioned Takepron capsule.

The results are shown in Table 5.

Table 5

	5 min	10 min	15 min	20 min
Example 4	86.4%	95.8%	97.5%	97.5%
Example 5	93.3%	96.9%	96.2%	95.7%

Experiment Example 3

Disintegration test

The disintegration time was measured according to a method described in USP <701> Disintegration.

Condition: purified water 1000 mL, no disk

The results are shown in Table 6.

Table 6

	Example 6	Example 7	Example 8	Example 9
disintegration time (min)	1.8	1.98	1.95	1.98

Measurement of dissolution profile

One tablet obtained in example 6, example 7, example 8

or example 9 was added to 900 mL of phosphate buffer solution having a pH of 6.8 at 37℃, and the amount of dissolved lansoprazole was measured by the absorbancy at 286 nm in the ultraviolet range under the same conditions as Experiment Example 1, and the dissolution ratio was calculated.

The dissolution profile was quick as compared with the dissolution of the capsule described above.

The results are shown in Table 7.

Table 7

	5 min	10 min	15 min	20 min
Example 6	78.7%	88.3%	90.0%	90.7%
Example 7	54.9%	81.1%	86.6%	87.6%
Example 8	76.4%	91.8%	96.2%	97.2%
Example 9	78.1%	92.5%	97.6%	96.2%

Experiment Example 4

Disintegration test

The disintegration time was measured according to a method described in USP <701> Disintegration.

Condition: purified water 1000 mL, no disk

The results are shown in Table 8.

Table 8

	Example 10	Example 11	Example 12
disintegration time (min)	1.60	1.28	1.52

Measurement of dissolution profile

One tablet obtained in example 10, example 11 or example 12 was added to 900 mL of phosphate buffer solution having a pH of 6.8 at 37℃, and the amount of dissolved lansoprazole was measured by the absorbancy at 286 nm in the ultraviolet range under the same conditions as Experiment Example 1, and the dissolution ratio was calculated.

The results are shown in Table 9.

The dissolution profile was quick as compared with that of a capsule mentioned above.

Table 9

	5 min	10 min	15 min	20 min
Example 10	73.7%	82.4%	83.7%	83.7%
Example 11	59.1%	72.6%	76.4%	78.8%
Example 12	85.4%	95.2%	96.7%	97.9%

Industrial Applicability

The medical solid preparation of the present invention can be obtained by a simple production method since no enteric coating is applied, though containing an acid labile active ingredient, for example, a benzimidazole compound which is a PPI. Further, since the initial dissolution of an active component from the preparation is quicker as compared with a preparation with an enteric coating, the initiation time of a pharmacological action can be shortened. Furthermore, since a metal oxide and

metal hydroxide is mainly used for neutralization and stabilization in stomach, the generation of carbon dioxide gas which is generated in stomach by the administration of a preparation containing a bicarbonate or carbonate in a large amount can be suppressed, and therefore burp can be suppressed in the preparation.

CLAIMS

1. A gastric disintegrable solid preparation comprising an acid labile active ingredient and at least one component selected from metal oxides and metal hydroxides.

2. A solid preparation according to claim 1, wherein the disintegration time is within 7 minutes.

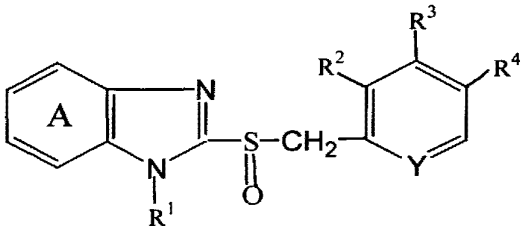
3. A solid preparation according to claim 1, which is the preparation without enteric coating.

4. A solid preparation according to claim 1, which comprises further at least one component selected from carbonates of alkali earth metal and basic additives having high water-solubility.

5. A solid preparation according to claim 1, wherein an acid labile active ingredient is a proton pump inhibitor (PPI).

6. A solid preparation according to claim 5, wherein the PPI is a benzimidazole compound.

7. A solid preparation according to claim 6, wherein a benzimidazole compound is a compound represented by the formula (I):



(I)

wherein ring A is an optionally substituted benzene ring,

R^1 is hydrogen atom, an optionally substituted aralkyl group, acyl group or acyloxy group, R^2, R^3 and R^4 are the same or different and each represent a hydrogen atom, an optionally substituted alkyl group, an optionally substituted alkoxy group or an optionally substituted amino group, and Y represents a nitrogen atom or CH, or a salt thereof.

8. A solid preparation according to claim 6, wherein a benzimidazole compound is lansoprazole, omeprazole, rabeprazole or pantoprazole, or an optically active compound thereof.

9. A solid preparation according to claim 1, wherein the metal oxides and the metal hydroxides are those of which 1% aqueous solution or 1 % aqueous suspension has a pH of 8.0 or more.

10. A solid preparation according to claim 1 which comprises at least one metal oxide selected from the group consisting of magnesium oxide, magnesium silicate, dry aluminum hydroxide gel and magnesium metasilicate aluminate.

11. A solid preparation according to claim 1 which comprises at least one metal hydroxide selected from the group consisting of magnesium hydroxide, aluminum hydroxide, synthetic Hydrotalcite, coprecipitate of aluminum hydroxide and magnesium hydroxide, coprecipitate of aluminum hydroxide, magnesium carbonate and calcium carbonate, and

coprecipitate of aluminum hydroxide and sodium bicarbonate.

12. A solid preparation according to claim 4, wherein the carbonate of alkali earth metal is calcium carbonate or magnesium carbonate.

13. A solid preparation according to claim 4, wherein the basic additive having high water-solubility is trometamol, disodium succinate, sodium hydrogen phosphate, trisodium phosphate, dipotassium phosphate or L-arginine.

14. A solid preparation according to claim 1 which contains magnesium oxide.

15. A solid preparation according to claim 1 which contains magnesium hydroxide.

16. A solid preparation according to claim 1 which contains magnesium oxide and magnesium hydroxide.

17. A solid preparation according to claim 14 or claim 16, wherein the magnesium oxide is one obtained by calcination at a temperature ranging from about 500°C to about 1000°C and of purity higher than 95%.

18. A solid preparation according to claim 14, wherein the magnesium oxide has a BET specific surface area of about $10m^2/g$ to about $50m^2/g$.

19. A solid preparation according to claim 6, which contains at least one component selected from metal oxides and metal hydroxides at a ratio of 0.1 to 1500 parts by weight relative to 1 part by weight of the benzimidazole

compound.

20. A solid preparation according to claim 6, which contains at least one component selected from metal oxides and metal hydroxides together with a salt of alkali earth metal at a total ratio thereof of 0.1 to 1800 parts by weight relative to 1 part by weight of the benzimidazole compound.

21. A solid preparation according to claim 1, which is a tablet, a granule or a capsule.

22. A solid preparation according to claim 1, wherein a group containing an acid labile active ingredient and a group containing a metal oxide or a metal hydroxide but containing no active ingredient are separately compounded.

23. A solid preparation according to claim 4, wherein (1) a group containing both an active ingredient and at least one component selected from metal oxides, metal hydroxides, carbonates of alkali earth metal and basic additives having high water-solubility and (2) a group not containing an acid labile active ingredient but containing at least one component selected from metal oxides, metal hydroxides, carbonates of alkali earth metal and basic additives having high water-solubility are separately compounded.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 02/08704

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K9/20

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)
IPC 7 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 51050 A (UNIV MISSOURI) 19 July 2001 (2001-07-19) page 31, line 13,14 See examples I-C, I-D, I-E. ---	1-23
X Y	EP 1 004 305 A (EISAI CO LTD) 31 May 2000 (2000-05-31) examples 24-26; table 3 ---	1-9, 19-23 1-23
X	WO 01 28559 A (EISAI) 26 April 2001 (2001-04-26) examples 4,5; table 2 See table 2, examples 4,5: disintegration time claims 1,2 --- -/--	1-3,5-9, 19-22

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

[X] Patent family members are listed in 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
6 December 2002	16/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Veronese, A

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 235 311 B1 (ULLAH ISMAT ET AL) 22 May 2001 (2001-05-22) Example 1: Tablet comprising: Pravastatin, Magnesium Oxide, Magnesium Carbonate. column 1, line 31,32	1-4,9-23
X	WO 97 25066 A (ASTRA AB ;DEPUI HELENE (SE); HALLGREN AGNETA (SE)) 17 July 1997 (1997-07-17) page 23, line 21-30	1-4,9-23
X	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 15, 6 April 2001 (2001-04-06) & JP 2000 355540 A (EISAI CO LTD), 26 December 2000 (2000-12-26) abstract	1,3,5-9
X	TETSURO TABATA ET AL: "STABILIZATION OF A NEW ANTIULCER DRUG (LANSOPRAZOLE) IN THE SOLID DOSAGE FORMS" DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, NEW YORK, NY, US, vol. 18, no. 13, 1992, pages 1437-1447, XP002921226 ISSN: 0363-9045	1,3, 5-10,14, 21
Y	See table 5, magnesium oxide.	1-23

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims 22 and 23 relate to compositions according to claims 1 comprising " a group containing an acid labile ingredient and a group containing a metal oxide or metal hydroxide but containing no active ingredient". No reference to any "group" is made in claim 1. Claims 22 and 23 are therefore considered not clear. Consequently the search has been carried out for the compositions as claimed in claims 1-21 and the ones described in the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/08704

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: –
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/JP 02/08704

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0151050 A	19-07-2001	AU 3276701 A	24-07-2001
		EP 1246622 A1	09-10-2002
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EP 1004305 A	31-05-2000	EP 1004305 A1	31-05-2000
		CN 1275079 T	29-11-2000
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		US 2002039597 A1	04-04-2002
WO 0128559 A	26-04-2001	AU 7950200 A	30-04-2001
		CN 1382049 T	27-11-2002
		EP 1222922 A1	17-07-2002
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(54) **Title:** PHARMACEUTICAL COMPOSITION CONTAINING A NSAID AND A BENZIMIDAZOLE DERIVATIVE

(57) **Abstract:** The present invention provides an oral pharmaceutical dosage form consisting in a combination, in the same dosage form, of an enteric coated or controlled release coated pellets and/or tablets, and an enteric coated tablet of a benzimidazole derivative, both coatings presenting different release characteristics.

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Pharmaceutical Composition containing a NSAID and a benzimidazole derivative

BACKGROUND OF THE INVENTION

Non steroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed and used drugs worldwide. Despite the therapeutic benefits of NSAIDs, their use is commonly limited by an increased risk of gastrointestinal (GI) side effects, mainly upper gastro-intestinal side effects like peptic ulceration and dyspeptic symptoms. Strategies to reduce the gastro-intestinal injurious effects of these drugs with enteric coatings, have had limited success. Although it is clear that the gastro-intestinal side effects of NSAIDs are in part attributable to their ability to inhibit the biosynthesis of gastroprotective prostaglandins, a significant amount of evidence exists that NSAIDs act locally on the mucosa to induce GI ulcers and bleeding by a prostaglandin-independent mechanism.

NSAIDs may be responsible of iatrogenic gastro-intestinal side effects which may lead to discontinuation of the treatment and in some cases necessitate hospital treatment. The term "NSAIDs-induced gastropathy" has been used to describe those adverse effects, which include haemorrhage, erosions and ulcers in the gastro-duodenal mucosa. The pathogenesis of NSAIDs-induced gastropathy is not fully understood, but both local and systemic effects are thought to contribute. Therefore, the galenical improvements consisting in gastro-resistant formulations have been of little influence on the frequence and severity of gastro-intestinal

effects provoked by NSAIDs. A new generation of NSAIDs has been developed, called "cox 2 inhibitors" because they appear to act more specifically on the cyclooxygenase 2 and hence their administration result in a lower incidence of GI side effects. Examples of cox 2 inhibitors are celecoxib and rofecoxib. But now, after several years of marketing of those drugs, they also appear to have significant GI side effects (even if their incidence and/ or their severity is lower than with the old generation of NSAIDs). That means that, at the moment there is no safe and efficient acute or chronic antiinflammatory treatment of inflammation disorders in people with potential GI sensibility or people subjects to ulcers and / or gastritis. The aim of the present invention is to provide such a treatment

The "oxicam" family of NSAIDs is a family of well-known efficient antiinflammatory drugs presenting as all the NSAID a relatively high risk of gastrointestinal side effects. The oxicam family contains, among others, piroxicam, meloxicam and tenoxicam. Administered orally, those molecules are indicated in several musculoskeletal disorders such as ankylosng spondylitis, osteoarthritis and rheumatoid arthritis. They are also prescribed in acute inflammation of soft tissues and in acute gout. The molecules owning to the oxicam family present the advantage to possess a relatively high elimination half-life what allows to administer them once daily. This is an important advantage in terms of posology and compliance of patients

Benzimidazole derivatives also called proton pump inhibitors (PPIs) are widely known pharmacological agents used in the treatment of gastric and

duodenal ulcers and other pathologies of the gastro-intestinal tract. Proton pump inhibitors have been shown to be able to prevent gastric and duodenal erosions in healthy volunteers during treatment with acetylsalicylic acid. Clinical studies have shown that omeprazole heals gastric and duodenal ulcers as fast and effectively in patients on a continuous NSAID treatment as in non NSAID uses (Walon A, Engl. S. Med, 1989;320,69). These results have been the basis for an amendment to the dose recommendation for the use of omeprazole in healing of gastric and duodenal ulcers during continuous NSAID treatment, approved by several European countries. Recent studies confirm that omeprazole significantly reduces the risk of developing gastric ulcers, duodenal ulcers and also dyspeptic symptoms in patients on continuous NSAID treatment. Physicians have already prescribed, in some cases, a therapy comprising a NSAID and proton pump inhibitor but the different active substances are administered separately. It is well known that patient compliance is a main factor in receiving a good result in medical treatments. Therefore, administration of two or even more different tablets to the patient is not convenient or satisfactory to achieve the most optimal results. The benzimidazole derivative is formulated as enteric compositions since it is well known that this class of drugs are very sensitive to the acidic pH of the stomach.

A large amount of patents have been granted about pharmaceutical compositions of benzimidazole derivatives and especially about oral enteric formulations of benzimidazole derivatives and several patents about

compositions of NSAIDs but the combination, in the same pharmaceutical composition, of a NSAID owning to the oxicam family and a benzimidazole derivative has never been described. This combination allows to administer the NSAID molecule very safely in patients in need of such treatment by very significantly decreasing the possibility of GI side effect. One particular advantage of the present invention is to minimize the possibility of drug-drug interaction once they are released in vivo. Another advantage of the invention is that a once a day administration of said composition is enough to maintain the activity for 24 hours, what is of considerable importance in terms of patient's compliance and comfort.

A further advantage of the composition of the invention is that a well predetermined amount of NSAID owning to the oxicam family is administered to the patient with a well predetermined amount of benimidazole derivative.

US patent 6,365,184 describes a combination of a proton pump inhibitor with a NSAID under the form of a multiple unit tablet dosage form. In this invention, the PPI is preferably under the form of compressible enteric coated beads.

The present invention provides an oral pharmaceutical dosage form consisting in a capsule containing a non steroidal antiinflammatory drug (NSAID) owning to the family of oxicam derivatives or a salt thereof under the form of coated pellets or alternatively coated tablets, and an enteric

coated tablet of a benzimidazole derivative, said pharmaceutical composition being suitable for a once a day administration

SUMMARY OF THE INVENTION

The present invention provides an oral pharmaceutical dosage form consisting in a pharmaceutically acceptable capsule containing a non steroidal antiinflammatory drug (NSAID) owning to the family of oxicam derivatives or a salt thereof under the form of enteric coated or controlled released composition, advantageously enteric coated or controlled release pellets or alternatively one or more coated or controlled release tablets, and an enteric coated tablet of a benzimidazole derivative, both coatings presenting different release characteristics in order to minimize the possible interaction between both classes of drugs.

The said pharmaceutical composition being suitable for a once a day administration.

DETAILED DESCRIPTION OF THE INVENTION

As explained before, it has been found out that a pharmaceutical composition combining in a single dosage form a NSAID from the oxicam family or salts thereof and a benzimidazole derivative or salts thereof, is a new, advantageous and innovative method of treatment of inflammatory disorders, especially in patients presenting an history of gastro-intestinal

pathologies line gastritis, GI ulcers, etc,... The oxicam compound is thus advantageously selected from the group consisting of pharmaceutically acceptable oxicam derivatives, pharmaceutically acceptable salts of oxicam derivatives and mixtures thereof. Preferred oxicam compounds are meloxicam, piroxicam, tenoxicam, salts thereof, and mixtures thereof. The benzimidazole compound is advantageously selected from the group consisting of pharmaceutically acceptable benzimidazole derivatives, pharmaceutically acceptable salts of benzimidazole derivatives, and mixtures thereof. Preferred benzimidazole compounds are omeprazole, lansoprazole, rabeprazole, pantoprazole, pharmaceutically acceptable salts thereof, and mixtures thereof (omeprazole, pharmaceutically acceptable salts thereof and mixtures thereof being more preferred).

When developing a combination of drugs, a particular attention should be paid to the chemical and physical compatibility between active ingredients and/or between each active ingredient and the excipients used.

Oxicam derivatives are usually poorly water soluble molecules. Piroxicam is a white to slightly yellow crystalline powder. It shows polymorphism. Practically insoluble in water, slightly soluble in dehydrated alcohol. Piroxicam is well absorbed from the gastro-intestinal tract. Piroxicam has a long elimination half-life of approximately 50 hours. Enterohepatic recycling occur. Meloxicam is well absorbed after oral administration and is 99% bound to plasma proteins. Meloxicam has a plasma elimination

half-life of about 20 hours. The marketed oral compositions of oxicam available on the market until today are immediate release forms (uncoated)

Benzimidazole compounds also called proton pump inhibitors (because their mechanism of action is to inhibit the so-called proton pump) are very effective drugs for the treatment of gastric and duodenal ulcers, gastroesophageal reflux diseases and Helicobacter pylori eradication, including the gastro-duodenal pathologies due to NSAID use. The main benzimidazole derivatives used are omeprazole, lansoprazole, rabeprazole and pantoprazole. All the benzimidazole compounds have the common properties of presenting very poor stability. They are sensitive to heat, moisture and light, and in aqueous solution or suspension, their stability decreases with decreasing pH. The formulation of benzimidazole must be protected from gastric fluids since it is rapidly chemically degraded at acidic pH. Different oral compositions of benzimidazole compounds have been patented including our previous patent (WO 02/32425) describing a stable oral formulation containing a benzimidazole derivative.

The main challenge(s) when combining two or more molecules in the same pharmaceutical form is (i) to guarantee the chemico-physical compatibility between the different active ingredients and/or between the active ingredients and the excipients used; and (ii) to insure the therapeutical compatibility between active ingredients regarding their pharmacokinetic and/or pharmaceutical properties in order that the posology of the

combined composition allows to obtain safe and efficient plasma levels of both pharmacological agents.

The metabolism of PPI is mainly due to cytochromes P450 2C19 system while the oxicams are mainly metabolized by P450 2C9 system. There are consequently no significant direct pharmacokinetic interactions described between those 2 family of drugs. But another kind of interaction may occur between two drugs, which can result in significant alteration of the bioavailability of the drugs. This interaction results from the physico-chemical properties of drugs.

Oxicam derivatives present the properties of possessing a pH dependent solubility profile with a lower solubility at low pH than at higher pH. This is particularly true for Meloxicam, which presents a solubility in water at 25°C of 0.037 mg/ 100 ml at pH = 2, of 2.7 mg/ 100 ml at pH = 6, and of 155 mg/ 100 ml at pH = 8. This means that to obtain a good bioavailability of an oxicam derivative, often a pH modifyer agent is added to the composition in order to confer a neutral to alkaline pH to the composition. For instance, the marketed form of meloxicam (Mobic®, Boehringer Ingelheim) present a pH in water of 7.2 due to the presence in the tablet of sodium citrate, an alkaline excipient

On the other hand, oxicam derivatives are acidic molecules. For instance, pKa values for meloxicam are 4.35 and 1.29 respectively.

Those two properties of oxicams are particularly important since they may result in an interaction between the oxicam composition and the benzimidazole composition when they are administered simultaneously.

Indeed, as today the oxicams are available on the market in immediate release uncoated forms (tablets or capsules) and benzimidazoles derivatives are available in enteric coated forms, when both classes of molecules will be administered simultaneously, the oxicam derivative will be released in first position in stomach and the beginning of intestine while the benzimidazole derivative will be released only after the passage of the pylori (i.e. after the stomach) because of the presence of the enteric coating.

Two kinds of interactions may actually occur from this. First, an interaction due to the fact that oxicam composition is released first, so releasing the alkaline excipients contained in the oxicam composition which present a pH between 6 to 9, may locally attack the enteric coating of the benzimidazole derivative, so provoking holes in the coating and then releasing the benzimidazole in the stomach where it is unstable and degrades very rapidly. This will result in a loss of bioavailability of oxicam derivative due to an early release and degradation of the benzimidazole derivative in the stomach. On the other hand, oxicams which are acidic molecule may also possibly provoke a direct degradation of benzimidazole compound by direct chemical contact in the gastro-intestinal tract.

The present invention provides a solution to avoid this potential interaction between meloxicam and benzimidazole derivatives.

The invention consists in avoiding, at the same time or at the same site, important release of both drugs. A possible aspect of this invention is to provide an oxicam composition form which is coated with an enteric release coating having a dissolution pH of at least 0.5 pH unit, advantageously comprised between 0.5 and 5 pH unit preferably comprised between 0.5 and 3 pH unit (such as about 0.5, about 1, about 1.5, advantageously about 0.5 to about 1), superior to the enteric coating of the benzimidazole derivative, in order that when taken simultaneously, the oxicam derivative will be released after the benzimidazole derivative (due to its higher pH soluble coating), so avoiding possible interactions between meloxicam or alkaline excipients contained in the meloxicam composition and the benzimidazole derivatives.

As the dissolution pH of enteric coating formulations of benzimidazole derivatives is usually 5 to 5.5, it is proposed that the dissolution pH of the meloxicam formulation is from 5.5 to 8, preferably between 6 to 7. Suitable enteric polymer for obtaining release at those pH are for example, but not limited to, acrylic derivatives such as EUDRAGIT® L30D-55 (pH 5.5), EUDRAGIT® L100 (pH 6), EUDRAGIT® S100 (pH 7-8) or mixtures thereof.

Other suitable polymers are cellulose polymers such as cellulose acetophtalate (pH 6), hypromellose phtalate (pH = 5.5, HP50®, SHINETSU).

The tablet containing the benzimidazole derivative or salt thereof is advantageously provided with at least two coating layers, preferably two different coating layers, such as a precoating and an outer enteric coating.

The tablet containing the benzimidazole derivative or salt thereof is preferably free of oxicam derivative.

According to an embodiment, the composition of the invention is adapted (for example the control release coating or the enteric coating is adapted) so that the benzimidazole derivative starts to be released before the release of oxicam derivative. Advantageously the peak of release of benzimidaole derivative is reached before the peak of release of oxicam derivative, preferably before reaching a level of release of oxicam derivative corresponding to less than 50% of the peak of release of oxicam.

According to another embodiment, the composition of the invntion is adapted (for example the control release coating or the enteric coating is adapted) so that the release peak of oxicam derivative is retarded with respect to the release peak of benzimidazole derivative. For a human , the time between the two peaks is comprised for example between 5 minutes

and 6 hours, advantageously between 15 minutes and 3 hours, for example 20 minutes, 30 minutes, 45 minutes, 1 hour, 90 minutes, 120 minutes.

The presence of a coating also prevents from contact between both kinds of drugs within the final composition (capsule) so further guarantying the absence of chemical interaction between both kinds of drugs within the pharmaceutical composition, and hence making their compatibility more sure.

Alternatively, the oxicam derivative (composition, pellets, beads or tablets) may be coated with a controlled release coating in order to release the drug slowly all along the gastro-intestinal tract. In this manner, high concentrations of the oxicam derivative are never in contact with high concentration of the benzimidazole derivative. The controlled release of the oxicam derivative can be obtained by using well-known polymers films like acrylic (polyacrylate dispersions,...) or cellullosic (ethylcellulose,...) sustained release polymer.

The oxicam derivative can also have the form of a controlled release matrix.

The capsule used in the composition of the invention is advantageously a hard gelatin capsule, an hypromellose capsule, a starch capsule or any other pharmaceutically acceptable capsule.

The oxicam derivative is present in said capsule for example as enteric coated pellets or alternatively as controlled release pellets and/or as an one or more enteric coated tablets or alternatively as on or more controlled

release tablets, said oxicam derivative containing pellets or tablets being preferably free of benzimidazole derivative.

Advantageously, the weight ratio between the pharmaceutically acceptable oxicam derivative or salt thereof and the pharmaceutically acceptable benzimidazole derivative is between 0.2 (w/w) and 5 (w/w), most preferably between 0.5 and 2.

The composition of the invention comprises advantageously only two different pharmaceutically active agents, namely one pharmaceutically acceptable oxicam derivative and one pharmaceutically acceptable benzimidasole derivative. Preferably at least three layers or barriers separate the oxicam derivative from the benzimidazole.

In case of pellets, the pellets of the oxicam derivative or salt thereof have advantageously a diameter comprised between 0.2 and 3 mm, preferably between 0.5 and 2 mm, and most preferably between 0.7 and 1.6 mm

The pellets containing the oxicam derivative or salt thereof are preferably manufactured by the process of extrusion – spheronisation

The enteric coated tablets containing the benzimidazole derivative or salt thereof is advantageously manufactured by direct compression, coated with a pre-coating and subsequently coated with an enteric coating

The enteric coated tablets containing the benzimidazole derivative or salt thereof contains preferably at least one pharmaceutically acceptable lipophilic antioxidant, advantageously selected from the group consisting of ascorbyl palmitate, butylhydroxyanisole, butylhydroxyanisole, propylgallate and mixtures thereof.

According to a specific preferred embodiment of a composition, the oxicam derivative is selected from the group consisting of meloxicam, pharmaceutically acceptable salts thereof, and mixtures thereof, while the benzimidazole derivative is selected from the group consisting of omeprazole, pharmaceutically acceptable salts thereof, and mixtures thereof.

According to a specific preferred embodiment of a composition, the oxicam derivative is selected from the group consisting of piroxicam, pharmaceutically acceptable salts thereof, and mixtures thereof, while the benzimidazole derivative is selected from the group consisting of omeprazole, pharmaceutically acceptable salts thereof, and mixtures thereof.

The amount of the benzimidazole (determined as base for salts thereof) per capsule is advantageously between 5 and 80 mg, preferably between 5 and 40 mg

The amount of the oxicam derivative per capsule is between 5 and 40 mg, preferably between 5 and 25 mg.

The composition is preferably suitable for a once a day administration to patients in need in such a treatment.

The invention relates also to a manufacturing process suitable to obtain a composition of the invention. In said process, (a) an enteric coated tablet containing at least one pharmaceutically acceptable benzimidazole derivative or salt thereof and (b) an enteric or controlled release composition containing a nonsteroidal antiinflammatory drug from the

family of oxicams or pharmaceutically acceptable salt thereof, both coatings presenting different release characteristics in order to minimize the possible interaction between both classes of drugs , said pharmaceutical composition being suitable for a once a day administration, and the tablet (a) and the composition (b) being filled together in a capsule. Alternatively, the tablet (a) and the composition (b) can be administered or released separately, but simultaneously orally absorbed.

The invention relates also to an oral pharmaceutical composition or kit comprising (a) a first enteric coated tablet containing at least one pharmaceutically acceptable benzimidazole derivative or salt thereof and (b) a second enteric coated composition containing a nonsteroidal antiinflammatory drug from the family of oxicams and pharmaceutically acceptable salts thereof, the coating dissolution of the first enteric coated tablet (a) being at least 0.5 pH unit, advantageously between 0.5 pH unit and 3 pH unit (such as about 0.5 pH unit, 1 pH unit and 1.5 pH unit) lower than the coating dissolution of the second enteric coated composition (b), and the first enteric coated tablet (a) and the second enteric coated tablet (b) being in a form for being administered or released separately

The invention further relates to the use of a composition of the invention for a once a day administration to patients in need in such a treatment.

Different examples of formulations corresponding to the present invention are given hereinbelow together with examples of manufacturing process to obtain the composition of the invention.

Examples

Example 1

A) meloxicam enteric coated pellets

30 g of meloxicam sodium, 200 g of microcrystalline cellulose (Avicel pH 101, FMC), 25 g of sucroester (Crodesta, Gattefosse, France) and 10 g of Povidone (Plasdone K25, BASF, Germany) are introduced in a planetary mixer. The powders are mixed together for 10 minutes at speed 1. 200 g of demineralized water are then added, under mixing, to the powder blend in order to obtain granulates presenting adequate plastic properties. The granulates obtained are extruded through a 1.2 mm sieve of the extruder (Fuji-paudal, Japan). The extrudates obtained are then spheronized at 800 and 1000 rpm for 60 seconds in order to obtain pellets. The pellets obtained are dried in an oven at 60°C for 16 hours. The dried pellets are sieved between 0.7 and 1.4 mm.

500 g of the sieved pellets are introduced in a fluidized bed coater (Strea-1, Aeromatic, Germany). The enteric coating solution is obtained by dispersing 40 g hypromellose phthalate (HP55® , Shin-etsu) which has a

dissolution pH of 5.5, 24 g of talc, 10 g of glycerol triacetate in a mixture alcohol 96 % - water 85/15 (w/w).

The enteric coating is applied on the uncoated pellets with the following parameters :

Flow rate : 10 g/min

T° input air : 38°C

T° output air : 28-30°C

T° product : 25°C

10 % of coating, expressed as percentage of dry residue applied on the pellets, were sprayed on the pellets. The coated pellets were dried at 40°c for 16 hours and then sieved between 0.8 and 1.6 mm.

B) enteric coated omeprazole tablet

100 g of Omeprazole, 10 g of ascorbyl palmitate, 765 g of lactose monohydrate, 250 g of cellulose microcrystalline, 85 g of crospovidone and 10 g of magnesium stearate, are blended together for 10 minutes at speed in a planetary mixer. The powder is then compressed directly to obtain tablets using round biconvex stamps of 6.5 mm of diameter.

The tablets obtained are then coated with a precoating solution in order to avoid direct contact between the benzimidazole derivative and the enteric polymer, which could result in a degradation of omeprazole.

The tablets will then be coated using (i) a pre-coating layer or insulating coating destined to avoid contact between omeprazole and the enteric coating polymer and (ii) an enteric coating layer

The precoating solution is obtained by dissolving 15 g of povidone in absolute alcohol (100 g ethanol anhydrous). The coating process is preferably performed on a pan-coating machine (GS Pellegrini or Accela-Cota) but can alternatively be performed on fluidized bed apparatuses (Aeromatic or Glatt).

The enteric coating layer is then applied on the precoated tablets using a GS-Pellegrini pan coater.

The enteric coating solution is obtained by dispersing 40 g hypromellose phthalate (HP50® , Shin-etsu) which has a dissolution pH of 5.0, 24 g of talc, 10 g of glycerol triacetate and 10 g of red iron oxide in a mixture alcohol 96 % - water 85/15 (w/w).

Coating parameters :

Pre-coating and coating:

- T° input air: 45°C
- T° out put air : 30-32°C
- T° product: 25-28°C
- Flow rate: +/- 35-40 g/min

The enteric coated tablets are then dried in an oven at 25°C for 16 hours.

Manufacturing of the final capsules

The final pharmaceutical form of the present invention is a pharmaceutically acceptable capsule (hard gelatin capsule, Hypromellose capsule, starch capsule, polyethyleneglycol). The filling of the capsule with the tablet(s) of omeprazole and enteric pellets of meloxicam has been made manually in this case given the small size of the batch. Nevertheless, some industrial capsule filling machines like the Futura (Mg2, Italy) or the KFM (Haro Hofliger, Germany) are able to perform such a filling of one or more tablets together with pellets in a reliable way.

In the present example, capsules were filled with one enteric coated tablet containing 10 mg of omeprazole and a weight of enteric pellets corresponding to 7.5 mg meloxicam (with 10 % of enteric coating).

- The results of the gastro-resistance dissolution test of omeprazole enteric tablets performed on this composition is given hereinbelow :

Gastro-resistance test on omeprazole tablets

The gastro-resistance on omeprazole tablets has been assessed by putting the 6 capsules containing the enteric tablet of omeprazole and the enteric coated pellets of meloxicam in a disintegration apparatus (European Pharmacopoeia 4th edition). The disintegration test is designed to control the enteric resistance of the tablet coating over time. It is performed according to the monograph "Gastro-resistant tablet" of the 4 th edition of the European Pharmacopoeia. No signs of either disintegration (apart from fragments of coating) or cracks that would allow the escape of the contents after 2 hours in HCl 0.1 M medium.

All six tablets have disintegrated within 60 minutes in pH 6.8 buffer medium.

Those results confirm (i) the efficacy of the enteric coating of the tablets and (ii) the adequate dissolution profile of omeprazole once the pH is increased.

Example 2 : combination in a hard gelatin capsule of piroxicam pellets / lansoprazole coated tablets

table 1 :uncoated piroxicam pellets

Ingredients	Amount
piroxicam	20 mg
Avicel PH 101	200 mg
Sucroester	20 mg
PVP	10 mg

The manufacturing process of piroxicam pellets was similar as this described in example 1 for meloxicam. In this case the pellets of piroxicam were not enteric coated but controlled release coated. The controlled release coating used was a polyacrylate dispersion at 30% (EUDRAGIT NE30D®) together with other excipients : talc, polysorbate 80, hypromellose, magnesium stearate. 12 % (w/w) of coating was applied on the pellets.

Table 2 : Formulation of uncoated Lansoprazole tablets

Ingredient	Amount
Lansoprazole	30.0 g
Povidone (PVP K29/32)	25 g
Mannitol	300 g
Ascorbyl Palmitate	1 g
Sodium Starch Glycolate	20 g
Stearate Mg	6 g

The precoating and the enteric coating applied on lansoprazole tablets have the same compostion as the coatings described in example 1 for omeprazole enteric coated tablets.

The final pharmaceutical form of the present invention is a pharmaceutically acceptable capsule (hard gelatin capsule, Hypromellose capsule, starch capsule, polyethyleneglycol).

In the present example, size 0 hard gelatin capsules were filled with one enteric coated tablet containing 30 mg of lansoprazole and 20 mg of controlled release pellets of piroxicam.

Example 3 : <u>combination in a HPMC capsule of meloxicam enteric tablets / omeprazole enteric coated tablets</u>

Table 3 : enteric coated tablets of meloxicam :

Ingredient	Amount
meloxicam	15.0 g
Povidone (PVP K29/32)	10 g
cellulose microcrystalline (Avicel PH102)	50 g
lactose monohydrate	100 g
Crospovidone	3 g
calcium diphosphate	20 g
Stearate Mg	2 g

The ingredients of table were mixed together on al planetary mixer and the tablets were manufactured by direct compression on spheric punches of diameter 6.5 mm in order to obtain 15 mg of meloxicam / tablet. Those tablets were then coated using an enteric coating cotaining EUDRAGIT S100® (which has a dissolution pH of about 7), triethylcitrate, ammonium and water .

10 % (expressed as dry residue deposited on the tablets) of coating were applied on the meloxicam tablets.

The enteric coated omeprazole tablets were the same as described in example 1 (with a dissolution pH of 5.0).

One enteric coated tablet of meloxicam and one enteric coated tablet of omeprazole were then filled in a HPMC capsule to obtain the final pharmaceutical composition.

Alternatively, enteric coated meloxicam pellets are filled in a capsule and the enteric coated tablet of benzimidazole derivative remains as a tablet and both drugs are administered separately but simalteneously, without significant interaction.

CLAIMS

1. An oral pharmaceutical dosage form consisting in a combination, in the same dosage form, of a Non Steroidal AntiInflammatory Drug (NSAID) of the oxicam family and a benzimidazole derivative, said dosage form containing a non steroidal antiinflammatory drug (NSAID) owning to the family of oxicam derivatives or a salt thereof under the form of enteric coated composition, advantageously enteric coated or controlled release coated pellets or alternatively one or more coated or controlled release coated tablets, and an enteric coated tablet of a benzimidazole derivative, both coatings presenting different release characteristics.
2. An oral pharmaceutical composition of claim 1, in the form of a capsule comprising (a) a first enteric coated tablet containing at least one pharmaceutically acceptable benzimidazole derivative or salt thereof and (b) a second enteric coated composition containing a nonsteroidal antiinflammatory drug from the family of oxicams and pharmaceutically acceptable salts thereof, the coating dissolution of the first enteric coated tablet being at least 0.5 pH unit, advantageously between 0.5 and 4 pH unit, preferably between 0.5 and 3 pH unit, lower than the coating dissolution of the second enteric coated tablet.

3. An oral pharmaceutical composition of claim 2, in the form of a capsule comprising (a) an enteric coated tablet containing at least one pharmaceutically acceptable benzimidazole derivative or salt thereof and (b) a controlled release composition containing a nonsteroidal antiinflammatory drug from the family of oxicams and pharmaceutically acceptable salts thereof
4. The composition of any one of the claims 1 to 3 wherein the capsule is a hard gelatin capsule, an hypromellose capsule, a starch capsule or any other pharmaceutically acceptable capsule.
5. The composition of any one of the claims 1 to 3, wherein the oxicam derivative is present in said capsule as enteric coated pellets
6. The composition of any one of the claims 1 to 3, wherein the oxicam derivative is present in the capsule as an enteric coated tablet
7. The composition of any one of the claims 1 to 3, wherein the oxicam derivative is present in said capsule as controlled release pellets
8. The composition of any one of the claims 1 to 3, wherein the oxicam derivative is present in the capsule as controlled release tablet
9. The composition of any one of the claims 1 to 3, wherein the weight ratio between the pharmaceutically acceptable oxicam derivative or salt thereof and the pharmaceutically acceptable benzimidazole

derivative is between 0.2 (w/w) and 5 (w/w), most preferably between 0.5 and 2.

10. The composition of any one of the claims 1 to 3, wherein the benzimidazole derivative is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, pantoprazole, pharmaceutically acceptable salts thereof and mixtures thereof.

11. The composition of any one of the claims 1 to 3, wherein the oxicam derivative is selected from the group consisting of meloxicam, piroxicam, tenoxicam and mixtures thereof.

12. The composition of any one of the claims 1 to 3, wherein the weight ratio between the oxicam derivative or salt thereof and the benzimidazole derivative or salt thereof is between 0.2 (w/w) and 5 (w/w), most preferably between 0.5 and 2.

13. The composition of claim 5 or 7, wherein the pellets of the oxicam derivative or salt thereof have a diameter comprised between 0.2 and 3 mm, preferably between 0.5 and 2 mm, and most preferably between 0.7 and 1.6 mm

14. The composition of claim 5 or 7, wherein the pellets containing the oxicam derivative or salt thereof are manufactured by the process of extrusion – spheronisation

15. The composition of claim 6 or 8 , wherein the tablets containing the benzimidazole derivative or salt thereof is manufactured by direct compression, coated with a pre-coating and subsequently coated with an enteric coating

16. The composition of any one of the claims 1 to 3 wherein the tablets containing the benzimidazole derivative or salt thereof contains at least one pharmaceutically acceptable lipophilic antioxidant, advantageously selected from the group consisting of ascorbyl palmitate, butylhydroxyanisole, butylhydroxyanisole, propylgallate and mixtures thereof.

17. The composition of any one of the claims 1 to 3 wherein the benzimidazole derivative is selected from the group consisting of omeprazole, pharmaceutically acceptable salts thereof, and mixtures thereof.

18. The composition of any one of the claims 1 to 3 wherein the oxicam derivative is selected from the group consisting of meloxicam, pharmaceutically acceptable salts thereof, and mixtures thereof, while the benzimidazole derivative is selected from the group consisting of omeprazole, pharmaceutically acceptable salts thereof, and mixtures thereof.

19. The composition of any one of the claims 1 to 3 wherein the oxicam derivative is selected from the group consisting of piroxicam, pharmaceutically acceptable salts thereof, and mixtures thereof, while the benzimidazole derivative is selected from the group consisting of omeprazole, pharmaceutically acceptable salts thereof, and mixtures thereof.

20. The composition of any one of the claims 1 to 3 wherein the amount of the benzimidazole derivative (calculated as base) per capsule is between 5 and 80 mg, preferably between 5 and 40 mg

21. The composition of any one of the claims 1 to 3 wherein the amount of the oxicam derivative (calculated as base) per capsule is between 5 and 40 mg, preferably between 7 and 25 mg

22. The composition of any one of the claims 1 to 3 wherein said composition is suitable for a once a day administration to patients in need in such a treatment.

23. The composition of any one of the claims 1 to 3, wherein the enteric coated tablet containing at least one pharmaceutically benzimidazole derivative is provided with at lest two coatings, preferably two different coatings.

24. A manufacturing process suitable to obtain the composition as described in any one of the claims 1 to 3, in which (a) an enteric coated tablet containing at least one pharmaceutically acceptable benzimidazole derivative or salt thereof and (b) a nonsteroidal antiinflammatory drug from the family of oxicams or pharmaceutically acceptable salt thereof are placed in a capsule.

25. The manufacturing process of claim 23, in which the composition as one or more characteristics mentioned in anyone of the claims 4 to 23.

26. The use of a composition of any one of the claims 1 to 3 for a once a day administration to a patient in need in such a treatment.

27. An oral pharmaceutical composition or kit comprising (a) a first enteric coated tablet containing at least one pharmaceutically acceptable benzimidazole derivative or salt thereof and (b) a second enteric coated composition containing a nonsteroidal antiinflammatory drug from the family of oxicams and pharmaceutically acceptable salts thereof, the coating dissolution of the first enteric coated tablet (a) being at least 0.5 pH unit lower than the coating dissolution of the second enteric coated composition (b), and the first enteric coated tablet (a) and the second enteric coated tablet (b) being in a form for being administered or released separately.

28. An oral pharmaceutical composition in the form of a capsule comprising (a) a first enteric coated tablet containing at least one pharmaceutically acceptable benzimidazole derivative or salt thereof and (b) a second controlled release composition containing a nonsteroidal antiinflammatory drug from the family of oxicams and pharmaceutically acceptable salts thereof, and the first enteric coated tablet (a) and the second controlled release composition (b) being administered or released separately.

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(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING A NSAID AND A BENZIMIDAZOLE DERIVATIVE

(57) Abstract: The present invention provides an oral pharmaceutical dosage form consisting in a combination, in the same dosage form, of an enteric coated or controlled release coated pellets and/or tablets, and an enteric coated tablet of a benzimidazole derivative, both coatings presenting different release characteristics.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/48 A61K9/32 A61K31/5415 A61K31/542 A61K31/4439

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)
IPC 7 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, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/25064 A (ASTRA AB ;DEPUI HELENE (SE); LUNDBERG PER JOHAN (SE)) 17 July 1997 (1997-07-17) cited in the application page 3, paragraph 4 page 4, paragraph 2 page 6, last paragraph - page 7, paragraph 1 page 9, line 11 - page 13, line 14 page 15, paragraph 3 page 16, paragraph 3 - paragraph 4 page 17, last paragraph - page 18, paragraph 1; claims 1,3,6,8,9,15,18,29; examples 5,8	1-28

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

[X] Patent family members are listed in 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
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Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANDERSSON T ET AL: "Lack of drug-drug interaction between three different non-steroidal anti-inflammatory drugs and omeprazole" EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, vol. 54, no. 5, July 1998 (1998-07), pages 399-404, XP002292866 ISSN: 0031-6970 abstract page 400, paragraph 4 page 401, left-hand column, last paragraph - right-hand column, paragraph 1; figure 1; table 1 page 402, right-hand column, last paragraph - page 403, left-hand column, paragraph 1	27
A	WO 02/32425 A (GALEPHAR M F ;SERENO ANTONIO (BE); BAUDIER PHILIPPE (BE); VANDERBI) 25 April 2002 (2002-04-25) cited in the application page 9, line 9 - page 10, last line ; claims 1-7,14-18	1-28
T	WO 2004/060372 A (TAP PHARMACEUTICAL PRODUCTS IN) 22 July 2004 (2004-07-22) page 1, line 31 - page 2, line 29 examples claims	1-28

2

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/BE2004/000003

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 26 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No
PCT/BE2004/000003

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 2004060372 A1	22-07-2004

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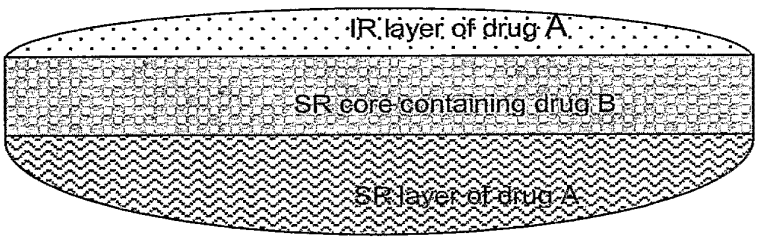
(54) Title: ORAL DOSAGE FORMULATION



(57) Abstract: A multi-layer oral dosage form, preferably a tablet, comprising a matrix core comprising a therapeutically effective amount of a first drug (NSAID), wherein the matrix core allows sustained release of the first drug; a first layer, which is in contact with the matrix core, comprising a first portion of a pharmaceutically effective amount of a second drug (H_2-blocker antagonist) , wherein the first layer allows sustained release of the second drug; and a second layer, which is in contact with said matrix core, comprising a second portion of the second drug, wherein the second layer allows immediate release of the second drug. Methods for preparing the multi-layer dosage form are also disclosed.

WO 2004/064815 A1

TITLE OF THE INVENTION

ORAL DOSAGE FORMULATION

FIELD OF THE INVENTION

The present invention relates to oral dosage formulations. More particularly, the present invention relates oral dosage formulations comprising a non-steroidal anti-inflammatory drug (NSAID) and an H_2-receptor antagonist.

BACKGROUND OF THE INVENTION

In recent years an increased interest in multi-layered tablets as controlled-release systems has been observed. Multi-layered tablets have some obvious advantages over conventional tablets, and are commonly used to avoid chemical incompatibilities between formulation components. These chemically incompatible formulation components, often biologically active ingredients (drugs), can be incorporated into one tablet by physically separating them into distinct layers. In the context of drug delivery systems, multi-layered tablets allow for the modification of release profiles, by combining layers with different release profiles, *i.e.* by combining slow-release with immediate-release layers.

Conte *et al.* (1) have proposed a controlled-release tablet called Geomatrix®, which is based on the multi-layered tablet concept. Functionally, the product represents a swellable matrix. The swelling of the drug-containing layer causes an increase of the surface area and therefore an increase in the amount of drug released per unit of time. Meanwhile, the outer cover layers control the diffusion of the drug from the drug containing layer. Other examples of products involving the

multiple-layered tablet concept were published by Qiu *et al.* (2), Yang *et al.* (3), Abraham *et al.* (4), Nangia *et al.* (5), and Chidambaram *et al.* (6).

Complex multi-layered tablets are tablets having differently shaped layers. The shape of the outer layers depends on the shape of the tablet core (Zerbe and Krumme (7)). The concept of complex multi-layered tablets to achieve zero-order release from matrix-based systems, was first introduced by Cremer (US Patent 5,853,760) and by Cremer and Asmussen (8).

NSAIDs comprise a class of drugs having long been recognized as being of high therapeutic value in the treatment of inflammatory conditions. Despite their therapeutic benefits, the use of NSAIDs is frequently limited by an increased risk of gastrointestinal side-effects such as peptic ulceration and dyspeptic symptoms.

Attempts at modifying the NSAID structure in order to prevent such side-effects have been moderately successful at best. A more promising alternative to the problem of NSAID associated gastrointestinal side-effects, more particularly in patients with a need for continuous NSAID treatment, is to combine the NSAID with an anti-ulcer drug such as for example prostaglandin analogues, H_2-receptor antagonists such as for example omeprazole or sucralefate, or proton pump inhibitors. Yet another suggested alternative involves the administration of NSAIDs following the ingestion of food or milk.

The NSAID sodium diclofenac has been used for decades for the symptomatic treatment of osteoarthritis and rheumatoid arthritis. Famotidine, an H_2-receptor antagonist, has proven to be useful for the treatment of gastric and duodenal ulcers as well as for the relief of heartburn. Famotidine has also been shown to reduce the frequency of

gastric and duodenal ulcers associated with non-selective NSAIDs such as diclofenac, ibuprofen, naproxen, and ketoprofen (Taha *et al.*, New England Journal of Medicine, 1996; 334:1435-1437).

The frequency of gastric and duodenal ulcers associated with COX-2 inhibitors and non-selective NSAIDs in patients suffering from osteoarthritis and rheumatoid arthritis, as well as in a subset of these patients additionally taking low dosages of aspirin, has also been investigated. Commercially available COX-2 inhibitors such as Celebrex®, Vioxx® and Bextra®, have been shown to produce a lower frequency of gastroduodenal ulcers than non-selective NSAIDs. However, low dosages of aspirin administered with COX-2 inhibitors substantially increase the frequency of upper GI ulceration. This seems to indicate that COX-2 inhibitors do not offer sufficient protection against ulcers induced by low-dosages of aspirin, which in turn has important implications since a large portion of patients suffering from osteoarthritis and rheumatoid arthritis also ingest low dosages of aspirin.

Gimet *et al.* (US Patent 5,601,843) teach pharmaceutical compositions, more specifically a core/mantle tablet, comprising a core consisting of an NSAID which is either diclofenac or piroxicam, and a coating incorporating a prostaglandin such as misoprostol. Misoprostol, even though effectively preventing NSAID-induced gastroduodenal ulceration, is associated with a high incidence of adverse effects such as abdominal pain, diarrhea, nausea and flatulence.

Ouali *et al.* (US Patent 6,287,600) disclose pharmaceutical compositions for oral administration consisting of a bi-layer tablet comprising an NSAID and a prostaglandin, wherein the NSAID is enterically coated.

Woolfe *at al.* (US Patent 6,387,410) teach oral pharmaceutical compositions, more specifically multi-layer tablets comprising a mixture of a delayed release formulation of an NSAID and a mixture comprising a prostaglandin, wherein the NSAID formulation is in the form of coated beads or granules providing programmed release according to the position in the gastrointestinal tract.

Saslawski *et al.* (US Patent 6,372,255) teach multi-layer tablets for the instant and then prolonged release of active substances. The tablets comprise a first layer containing an active substance in the form of a granule which disintegrates immediately upon contact with an aqueous medium such as a physiological medium, and a second layer composed of an inert matrix wherein is dispersed a second active substance, and wherein the matrix allows for the prolonged release of the second active ingredient.

Depui *et al.* (US Patent 6,365,184) disclose an oral pharmaceutical dosage form comprising an NSAID (diclofenac) and an acid susceptible proton pump inhibitor (omeprazole). The proton pump inhibitor is generally in the form of an enterically coated pellet capable of compression into tablets together with the NSAID. The enteric coating layer has mechanical properties such that the acid resistance of the enterically coated pellets is not significantly affected by the compression of the pellets with the other components during tableting.

There thus remains a need to develop an improved oral dosage form comprising an extended-release NSAID and an H_2-receptor antagonist for the treatment of osteoarthritis in patients at an elevated risk for developing gastrointestinal side effects.

The present invention seeks to meet these and other needs.

The present invention refers to a number of documents, the content of which is herein incorporated by reference in their entirety.

SUMMARY OF THE INVENTION

The present invention relates to a novel oral dosage form, preferably a tablet, more preferably a fixed-dose multi-layer tablet comprising two or more drug combinations, as well as to methods of making the multi-layer tablet. Most preferably, the present invention relates to fixed-dose combination tablets comprising an NSAID and an H_2-receptor antagonist. Still most preferably, the present invention relates to an improved fixed-dose multi-layer tablet comprising an extended-release NSAID as well as an H_2-receptor antagonist, useful for the treatment of osteoarthritis in patients who are at an elevated risk for developing gastrointestinal side effects, more specifically NSAID-induced gastric and duodenal ulcers. Yet even more preferably, the present invention relates to an improved fixed-dose multi-layer tablet comprising an extended-release NSAID as well as an H_2-receptor antagonist, useful for the treatment of osteoarthritis in patients who are at an elevated risk for developing gastrointestinal side effects, more specifically NSAID-induced gastric and duodenal ulcers, and who are also taking low doses of aspirin for the prevention of myocardial infarction.

In a preferred embodiment, the present invention relates to a multi-layer oral dosage form comprising a matrix core comprising a therapeutically effective amount of a first drug, wherein the matrix core allows sustained release of the first drug; a first layer, which is

in contact with the matrix core, comprising a first portion of a pharmaceutically effective amount of a second drug and optionally an additional amount of the first drug, wherein the first layer allows sustained release of the first and second drug; and a second layer, which is in contact with the matrix core, comprising a second portion of the second drug, wherein the second layer allows immediate release of the second drug.

The present invention may also relate to a multi-layer oral dosage form comprising a matrix core comprising a therapeutically effective amount of a first drug, wherein the matrix core allows sustained release of the first drug; a first layer, which is in contact with the matrix core, comprising a first portion of a pharmaceutically effective amount of a second drug, wherein the first layer allows sustained release of the second drug; and a second layer, which is in contact with the matrix core, comprising a second portion of the second drug, wherein the second layer allows immediate release of the second drug.

The present invention may also relates to a method for preparing a multi-layer oral dosage form comprising:

(a) preparing a sustained release matrix core comprising a therapeutically effective amount of a first drug or pharmaceutically acceptable salts thereof;

(b) preparing a sustained release blend comprising a first portion of a pharmaceutically effective amount of a second drug or pharmaceutically acceptable salts thereof;

(c) preparing an immediate release blend comprising a second portion of the second drug or pharmaceutically acceptable salts thereof; and

(d) combining, by compressing, the matrix core of step (a), the sustained release blend of step (b) and the immediate release blend of step (c).

The present invention may also relate to new oral pharmaceutical compositions for use in the treatment and prophylaxis of gastrointestinal disorders associated with the use of Non Steroidal Anti-Inflammatory Drugs (NSAIDs).

The present invention may also relate to pharmaceutical compositions comprising a combination of a non-steroidal anti-inflammatory drug and an H_2-receptor antagonist as well as to methods of preparing such compositions.

In related embodiments, the present invention relates to an improved fixed-dose pharmaceutical formulation comprising an extended-release NSAID and an H_2-receptor antagonist, wherein a first portion of the H_2-receptor antagonist is released following an immediate release profile and wherein a second portion is released following an extended release profile.

The present invention may also relate to a method for reducing the undesirable gastrointestinal side effects associated with the oral administration of NSAIDs, comprising administering a fixed-dose multi-layer tablet containing an NSAID and an H_2-receptor antagonist to a patient in need thereof.

In a further preferred embodiment, the present invention relates to a fixed-dose multi-layer tablet comprising an extended release NSAID and an H_2-receptor antagonist, wherein the NSAID is diclofenac and wherein the H_2-receptor antagonist is famotidine.

In another preferred embodiment, the present invention relates to a method for treating or preventing osteoarthritis in patients at an elevated risk for developing gastrointestinal side effects, more specifically NSAID induced gastric and duodenal ulcers, comprising administering an effective amount of a fixed-dose multi-layer tablet comprising an extended release NSAID and an H_2-receptor antagonist, wherein the NSAID is diclofenac and wherein the H_2-receptor antagonist is famotidine.

In yet another preferred embodiment, the present invention relates to a method for treating or preventing osteoarthritis in patients at an elevated risk for developing gastrointestinal side effects, more specifically NSAID induced gastric and duodenal ulcers, and who are also taking low doses of aspirin for the prevention of myocardial infarction, comprising administering an effective amount of a fixed-dose multi-layer tablet comprising an extended release NSAID and an H_2-receptor antagonist, wherein the NSAID is diclofenac and wherein the H_2-receptor antagonist is famotidine.

Further scope and applicability will become apparent from the detailed description given hereinafter. It should be understood however, that this detailed description, while indicating preferred embodiments of the invention, is given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a multi-layered dosage form comprising: an immediate release layer (IR) comprising X mg of drug A, a

sustained release layer (SR) comprising Y mg of drug A, as well as a sustained release core comprising Z mg of drug B;

Figure 2 shows a combined *in-vitro* dissolution profile of an immediate release (IR) and a sustained release (SR) layer containing famotidine (drug A), obtained in SGF (Simulated Gastric Fluid) at 100 rpm and 37°C;

Figure 3 shows an *in vitro* dissolution profile for a sustained release (SR) core comprising diclofenac (drug B), obtained in SIF (Simulated Intestinal Fluid);

Figure 4 shows *in vitro* dissolution profiles obtained simultaneously from a multi-layer tablet comprising famotidine (drug A), subdivided into immediate and sustained release layers, and diclofenac (drug B), present in a sustained release core, obtained in SIF (Simulated Intestinal Fluid) at 100 rpm; and

Figure 5 shows an *in vitro* dissolution profile for a sustained release (SR) core comprising aspirin as well as for a sustained release (SR) core comprising aspirin and which is integrated in a multi-layer tablet obtained in SIF (Simulated Intestinal Fluid) at 100 rpm.

DETAILED DESCRIPTION OF THE INVENTION

The terms "active agent", "active ingredient", "drug" and "pharmaceutically active agent" are used interchangeably herein, and are meant to refer to a compound which, when administered to a human or an animal induces, a pharmacological effect.

As used herein, the term "effective amount" or "therapeutically effective amount" is well known in the art. It is meant to describe a non-toxic but sufficient amount of the agent capable of providing

a desired therapeutic effect. An appropriate "effective amount" in any individual case may be determined by one of ordinary skill in the art using only routine experimentation.

As used herein, the term "erosion" is given the general meaning as commonly accepted in the pharmaceutical arts. The term "erosion" is generally accepted in the pharmaceutical arts as being a process in which solid masses are cleared away.

As used herein, the term "prodrug" refers to an inactive form of a drug, that exerts its effects after metabolic processes within the body convert it to a usable or active form. The usable or active form is generally the active form of the drug prior to conversion into a prodrug.

As used herein, the term "oral dosage formulation" refers to a pharmaceutical composition comprising a therapeutically effective amount of the active agent optionally in addition with pharmaceutically acceptable excipients, which may be orally administered. For oral administration, the formulation may take the form of tablets, caplets, lozenges or capsules, formulated in a conventional manner.

The pathogenesis of NSAID-induced gastroduodenal mucosal injury encompasses topical injury as well as systemic mechanisms. Topical mucosal injury is believed to be mediated by the inherent acidic properties of aspirin as well as many other NSAIDs. Systemic effects are thought to be largely the result of the inhibition of endogenous prostaglandin synthesis.

Pharmaceutical formulations wherein an NSAID such as for example diclofenac is combined with an H_2-receptor antagonist, such as for example famotidine, are useful in helping and/or preventing

NSAID-induced ulcers in patients suffering from osteoarthritis and rheumatoid arthritis, in addition to helping to prevent aspirin induced ulceration.

In a broad sense, the present invention relates to novel oral pharmaceutical compositions comprising an NSAID and an H_2-receptor antagonist, capable of addressing both topical or systemic mechanisms of NSAID-induced gastroduodenal mucosal injury.

Preferably, the present invention is embodied in an improved fixed-dose combination tablet comprising an sustained release NSAID and an H_2-receptor antagonist, wherein a first portion of the H_2-receptor antagonist is released in the gastroduodenal lumen following an immediate release profile, followed by the concomitant release of a second portion of the H_2-receptor antagonist and the NSAID. The second portion of the H_2-receptor antagonist and the NSAID are released following sustained (extended) release profiles. The immediately released portion of the H_2-receptor antagonist addresses any possible topical ulcerogenic effects, whereas the sustained portion addresses any systemic ulcerogenic effects of the NSAID.

In one particular embodiment, the present invention relates to an improved fixed-dose multi-layer tablet comprising a sustained release NSAID and an H_2-receptor antagonist, wherein the NSAID is diclofenac and wherein the H_2-receptor antagonist is famotidine.

Other non-limiting examples of NSAIDs that can be incorporated into the multi-layer tablets as defined herein comprise ibuprofen, naproxen, flurbiprofen, alminoprofen, and tiaprofenic acid. Other non-limiting examples of H_2-blocker antagonists that can be incorporated

into the multi-layer tablets as defined herein comprise ranitidine, nizatidine, cimetidine, and roxatidine.

The multi-layer tablet is preferably prepared by first producing the NSAID containing core (in the form of a layer structure), followed by at least partially coating it with an erodable layer comprising a first portion of the H_2-receptor antagonist, providing for a sustained release layer of the antagonist. An immediate release layer comprising a second portion of the H_2-receptor antagonist is then applied.

Diclofenac is an NSAID having acidic properties. The design of sustained release formulations comprising one or more drugs having acidic properties represents an important technological challenge. The low pH environment commonly encountered in the stomach suppresses the ionization of acidic drugs, thus considerably reducing the solubility of these drugs in gastric juices. A pH increase, as is observed in the intestines, results in a solubility increase and a faster release rate. The fixed-dose multi-layer pharmaceutical formulations of the present invention ensure essentially constant blood plasma levels of acidic drugs, such as for example diclofenac, throughout the digestive tract.

Famotidine's primary pharmacological function is the inhibition of gastric secretion. Famotidine was shown to inhibit basal and nocturnal gastric secretion, as well as food and pentagastrin stimulated secretion, one hour following oral administration. The maximum effect is dose dependent, and was observed within one to three hours following oral administration. Doses of 20 mg and 40 mg effectively inhibit gastric secretion over periods ranging from 10 to 12 hours. The nocturnal intra-gastric pH was raised to mean values of 5.0 and 6.4 following nocturnal doses of 20 mg and 40 mg respectively. The basal daytime inter-digestive pH, at three and eight hours following the administration after breakfast of

20 or 40 mg of famotidine, was raised to about 5 (Physician's Desk Reference, 2001).

A fixed-dose multi-layer tablet as described herein and comprising a combination of an NSAID and an H_2-receptor antagonist, wherein the NSAID is formulated such as to be released following a sustained release profile, and wherein the H_2-receptor antagonist is formulated such that a first portion is released following an immediate release profile and wherein a second portion is released following a sustained release profile, provides for better patient compliance and increased efficiency of the NSAID. The fixed dose pharmaceutical compositions of the present invention are so formulated that a first portion of the H_2-receptor antagonist is released, followed by the concomitant release of the NSAID and a second portion of the H_2-receptor antagonist. The suppression of gastric secretion by the H_2-receptor antagonist significantly reduces the rate of occurrence of ulceration, in addition to increasing the intra-gastric pH which favorably effects the solubility and absorbance of the NSAID.

Tablet design

The pharmaceutical compositions of the present invention are multi-layered solid fixed-dosage forms, more preferably multi-layered fixed-dose combination tablets. The compositions can be administered once-daily or twice-daily, depending on the dosage of the active components. Both dosage forms provide for sufficient plasma levels for the treatment of osteoarthritis, while at the same time preventing gastrointestinal side effects, more specifically the formation of NSAID induced gastric and duodenal ulcers. This is of particular benefit to patients also taking low dosages of aspirin as a preventive measure against

myocardial infarction. The H_2-receptor antagonist is released following two distinct release profiles; a first portion being released following an immediate release profile and a second portion being released following an extended release profile.

Several systems capable of providing for the controlled release of pharmaceutical agents, such as diffusion systems (including reservoir devices and inert polymeric matrices), erodable systems (based on the inherent dissolution of the drug itself), and osmotic systems (drug containing core coated with a semi-permeable membrane having a small orifice) have been investigated and published (9-14).

The controlled release of a drug from a pharmaceutical dosage form can also be achieved by more than one mechanism. For example, for the same pharmaceutical dosage form, the drug release can occur for example by simultaneous swelling and diffusion, simultaneous diffusion and erosion, and simultaneous swelling, diffusion and erosion.

In the case of matrix systems, the rate of drug release is largely dependant on the properties of the composition used to make the matrix, on the physical properties and concentration of the active as well as on the geometry of the matrix. Tablet diameter and surface area of the tablet are additional factors influencing the rate of drug release.

The fixed-dose multi-layer tablets of the present invention are useful for the treatment of osteoarthritis in patients who are at an elevated risk for developing gastrointestinal side effects, more specifically NSAID-induced gastric and duodenal ulcers. The fixed-dose combination tablets include a pharmaceutical formulation comprising at least two active ingredients, more preferably two active ingredients (Figure

1). The first active ingredient is an H_2-blocker antagonist, divided into a first portion formulated as an immediate release layer, and a second portion formulated as a sustained release layer.

The pharmaceutical formulation providing the immediate release layer is conceived to rapidly disintegrate, and will preferably contain from about 5 to about 25% of the H_2-receptor antagonist. Moreover, the pharmaceutical formulation providing the immediate release layer is comprised of a dry mixture of the drug (H_2-blocker antagonist) and pharmaceutically acceptable excipients such as for example polysaccharides and their derivatives, cross-linked polymers, soluble salts, disintegrants and other excipients well known by a person skilled in the art. Additives such as colorants, fillers, anti-tacking and anti-static agents may also be incorporated into the formulation. Non-limiting examples of such additives are magnesium stearate and talc.

The pharmaceutical formulation providing the sustained release layer will preferably contain from about 75 to about 95% of the H_2-receptor antagonist. The H_2-receptor antagonist present in the sustained release layer may be directly mixed with pharmaceutically acceptable excipients or it may be first coated with hydrophilic or hydrophobic agents, which are specifically chosen to regulate the rate of release of the antagonist. The sustained release layer may be further comprised of polymeric materials, which are slowly water-soluble and/or slowly gel-forming when exposed to an aqueous medium. Non-limiting examples of such polymeric materials are cellulose derivatives and modified starches. The sustained release layer is then applied to an NSAID containing core. The thickness of the sustained release layer can be varied, depending on the specific requirements.

The sustained release layer has a direct impact on the rate of release of the NSAID from the core, and provides for a sustained release of the H_2 receptor antagonist. In one particular embodiment, an erodable mass of solids can be incorporated into the sustained release layer in order to adjust the release of the NSAID from the core. It is understood that an increased amount of erodable mass incorporated into the sustained release layer will result in an increase in the amount of NSAID released from the core. In another embodiment, the sustained release layer is formulated to provide an essentially stable layer from which the H_2 receptor antagonist diffuses at a sustained rate, while simultaneously providing for a sustained release of the NSAID from the core.

Matrix-forming excipients are commonly used to ensure a sustained release of pharmaceutically active agents. Such materials form a hydrophilic / hydrophobic matrix, providing for the sustained release of the active following both diffusion and erosion mechanisms. Hydrophilic drugs are predominantly released from the matrix following diffusion mechanisms. Surface area fluctuations play an important role in those cases where erosion is the leading factor in controlling the rate of drug release.

An erodable mass is commonly generated by specific grades of polymers and combinations thereof optionally in association with various fillers. Non limiting examples of polymers include polysaccharides, polylactides, polyglycolides, polyethylenes and polypropylenes, metacrylates, polyvinylchlorides and polyvinyl chlorides and polyvinyl pyrolidones.

As mentioned previously, the fixed-dose combination tablets include a pharmaceutical formulation comprising at least two active

ingredients, more preferably two active ingredients (Figure 1), the H_2-blocker antagonist being the first active ingredient. The second active ingredient is an NSAID. The NSAID is formulated as a separate sustained release layer, more specifically the core of the multi-layer fixed-dose combination tablet as described herein. The sustained release core will preferably contain from about 50 to about 100% of the recommended daily dose of the NSAID. The NSAID containing sustained release core is prepared in accordance with known techniques in the art. The core composition comprises an easily flowable homogeneous mixture that is compressed under a pressure ranging from about 3 to about 15 kN. The sustained release core represents a non-erodable structure from which the NSAID diffuses at a sustained rate into the surrounding media.

The NSAID comprising core formulation is commonly generated by combinations of specific polymers, optionally in association with adjuvants. Non-limiting examples of polymers that can be used in the NSAID comprising core formulation are Insoluble cellulose-based materials, polyvinyl acetates, polyvinyl alcohols, polyethylene oxides, metacrylates and non-crosslinked polyvinylpyrolidone. Non-limiting examples of adjuvants are sucrose, lactose, colloidal silica and magnesium stearate. The ratio of polymer to active agent (NSAID) in the core formulation varies with the type of active ingredient.

Multi-layer tablets possess numerous advantages in comparison to conventional dosage forms. Chemically incompatible components can be incorporated into a multi-layer tablet by integrating them into separate layers. Moreover, a different active ingredient can be incorporated into one or more of the distinct layers of the multi-layer tablet, thereby offering the possibility of designing each layer so as to obtain a

desired release profile for each active ingredient, thus maximizing both their individual and combined therapeutic effect.

Tablets may be designed to have pulsatile, immediate onset, delayed onset or any other suitable predetermined release profile. The different layers of the fixed-dose multi-layer tablet as described herein may comprise different active agents, different amounts of active agent and/or different forms of active agent. Moreover, the various layers of the fixed-dose multi-layer tablet as described herein, may comprise different amounts of one or more polymers as well as different kinds of additional pharmaceutical excipients, thus providing for additional control of the release of the active agents from the tablet.

As the fixed-dose multi-layer tablet passes through the digestive tract, it releases varying amounts of active or active agents depending on its location in the digestive tract (*i.e.* stomach, versus small intestine versus colon). A predetermined release scheme can thus be rationally designed for the active or active agents comprised in the fixed-dose multi-layer tablet, based on the formulation of the different layers. It may be desirable that a first active agent be released in the upper digestive tract (*e.g.*, stomach or small intestine) while a second active agent is released in the lower digestive tract. Alternatively, it may be desirable that a portion of a first active ingredient be released in the upper digestive tract (*e.g.*, stomach or small intestine) while a second portion of the first active agent and the second active agent be released in the lower digestive tract.

The pharmaceutical compositions of the present invention comprise a combination of famotidine and diclofenac, wherein a first portion of famotidine is released in the upper digestive tract while a second portion is released in the lower digestive tract together with diclofenac. The first portion of released famotidine is essentially provided

by the immediate release layer of the fixed-dose multi-layer tablet, whereas the second portion is essentially provided by the sustained release layer of the multi-layer tablet. However, it is to be noted that small amounts of famotidine may be released from the sustained release layer as part of the first portion.

Active components having different water solubilities, requiring different dosages, and having different absorption profiles, can be formulated into a multi-layered tablet. A multi-layer (two or more layers) combination tablet as described herein allows for the controlled release of the active agent(s). Furthermore, the multi-layer combination tablet as described herein, provides for the combination of famotidine and diclofenac in such a way that the bioavailability is essentially similar to that of a separate administration of each active. A suitable ratio of the two active ingredients (diclofenac and famotidine) into a single dosage form, provides many important advantages from a therapeutic perspective.

Diclofenac is released from the core by diffusion, displaying a Fickian release profile. However, when the core is covered with erodable layers, the controlled erosion of these outer layers results in a steady increase of the surface area available for the release of the drug, thus providing a linear drug release.

Diclofenac is present in the multi-layer fixed-dose combination tablet as described herein, in a therapeutically effective amount. Preferably, the combination tablet is administered in unit dosage form. Preferably, the multi-layer fixed-dose combination tablet as described herein will comprise from about 50 to about 150 mg of diclofenac, and more preferably about 75 mg.

The active agents of the present composition, i.e., both the NSAID (diclofenac) and the H_2-blocker antagonist (famotidine) may be administered in the form of a pharmaceutically acceptable salt, ester, amide, prodrug or analog, or as a combination thereof. Salts, esters, amides, prodrugs and analogs of the active agents may be prepared using standard procedures known to those skilled in the art of synthetic organic chemistry (March, J., "*Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*", 4th Edition (John Wiley & Sons, New York, 1992).

It is to be understood that the present invention is not to be limited to fixed dose combination tablets comprising an NSAID such as diclofenac, and an H_2-receptor antagonist such as famotidine. Other non-limiting examples comprise ibuprofen / famotidine; aspirin / famotidine; morphine / diclofenac; pioglitazone / metformin; ACE-I / statin; and ACE-I / β-blocker.

In a preferred embodiment of the present invention, the potential for gastric erosion is reduced by ensuring that a sufficient amount of famotidine is released before the release of diclofenac. The immediate release of famotidine helps raise the pH of the gastric fluid, which in turn aids in the dissolution of diclofenac.

EXAMPLES

Example 1: Formulation of an immediate release layer, comprising famotidine.

The immediate release layer contains from about 5 to about 30% of the H_2 receptor antagonist famotidine, homogeneously mixed with a disintegrant, in a ratio ranging from about 1:10 to about 2:8.

A 100 mg layer containing 10% of the total amount of famotidine in addition to microcrystalline cellulose (Avicel PH 102 grade, Dow Chemical) was prepared. The bulk drug was sieved prior to use and dry-mixed with the polymer. The compression was performed in a Korch EK 0 tableting machine using a round die (diameter 10.0 mm).

Example 2: Formulation of a sustained release layer, comprising famotidine.

The sustained release layer containing famotidine possesses narrowly defined erosive properties and, at the same time, maintains good bonding to the core. The erosion rate of the core-covering layer has to be adjusted to match the intended release rate of famotidine, while providing the required continuous increase in exposed surface area for the release of diclofenac from the core, over the duration of time of the dosage.

An erodable layer can be typically manufactured by dry blending a mixture comprising from about 5 to about 40% of famotidine, from about 5% to about 50% of a hydrophilic polymer, from about 5% to about 50% of a hydrophobic polymer, and less then about 2% of a lubricant (magnesium stearate).

In a preferred embodiment, a portion of the famotidine is formulated as a sustained release layer. More preferably, the sustained release layer will comprise from about 15 to about 80% of the total amount of famotidine formulated in the multi-layer combination tablet. An erodable sustained release layer weighing about 150 mg, comprises about 30% hydroxypropylmethyl cellulose (Methocel K100), about 20% ethyl cellulose (Ethocel EC-20™), about 5-30% lactose, and about 1% of a lubricant. The mixture was compressed in a Korch EK 0 tableting machine, using a round die (diameter of 10.0 mm).

In another preferred embodiment, the erodable layer weighing about 100 mg comprises from about 15 to about 80% of the total amount of famotidine formulated in the multi-layer tablet, about 40% hydroxypropylmethyl cellulose (Methocel K100), from about 5 to about 15 % ethyl cellulose (Aqualon N 100), from about 10 to about 30% lactose monohydrate, and about 1% of a lubricant. Compositions having enhanced compressibility and flow characteristics are obtained using dry/wet granulation.

The immediate release layer (Example 1) and the sustained release layer (Example 2), following respective pre-compression, were combined and compressed into a tablet following multi-layer technology using a rotary press. In one embodiment, the rotary press may contain the pre-compressed immediate release layer, to which is added the pre-compressed sustained release layer.

In vitro dissolution tests were conducted with tablets based on the formulations of Examples 1 and 2, using Apparatus II and the method detailed in USP 25. The stirrer paddle speed of the apparatus was 100 rpm, and the temperature of the medium was maintained at 37 °C. The dissolution was observed at pH 1 (in simulated gastric fluid - SGF). Aliquot

samples were assayed for famotidine by UV spectrophotometric measurements and the test results are shown in Figure 2.

Example 3: Preparation of a SR core containing diclofenac

The sustained release matrix comprising diclofenac is preferably provided as a non-erodable core made in accordance with the following steps:

a) intimately blending a pharmaceutically acceptable salt of diclofenac (from about 10 to about 40% by weight) with ethylcellulose (from about 5 to about 30% by weight; preferably EC-22, Aqualon) and a channeling agent, preferably lactose monohydrate (from about 25 to about 70% by weight) in a planetary or high shear mixer;

b) adding to the homogeneous blend from step (a), a solution of ethylcellulose (about 10% or less of ethylcellulose dissolved in ethanol) and monitoring the granulation process in order to obtain a uniform and complete distribution of the granulation liquid in the powder blend.

The release properties of the drug (diclofenac) from the core are dependent on the ratio of soluble to insoluble components, their particle sizes, the level of compaction, and the remaining porosity of the system. In addition to the physicochemical properties of the powder materials, the homogeneity of the blend and the distribution of the binders throughout the mix are essential. Consequently, the processing conditions selected for the granulation process determine the porosity of the granules and, eventually, the compression parameters of the final tablet. Throughout the process, the viscosity, the mixer speed and the chopper speed are parameters that are constantly monitored.

c) passing the composition through a 1.70 mm mesh;

d) drying the wet granules at about 50-60°C;

e) size reducing the dried granules in a mill (preferably a Hammer mill) to obtain a granule size of less than 850 microns;

f) homogeneously blending the milled granules with a flowing agent such as silicone dioxide (less than about 4%) in a blender;

g) dry blending the mixture with a lubricant such as magnesium stearate (about or less than 2%); and

h) compressing the composition under a force ranging from about 3 kN to about 15 kN.

The non-erodable core could also be obtained by dry granulation followed by direct compression using blends comprising diclofenac (from about 25 to about 45% by weight), physical mixtures of polyvinyl acetate and polyvinyl pyrolidone (from about 20 to about 60% by weight), polyethylene oxides (from about 2 to about 10% by weight), silicon dioxide (from about 1 to about 3% by weight) and magnesium stearate (less then about 3% by weight).

SR formulations for a 200 mg core comprising diclofenac were prepared using various diclofenac / polymer ratios (physical mixtures of polyvinyl acetate and polyvinyl pyrrolidone) (*i.e.* 1:1, 1:1.5 and 1:2). A more preferred diclofenac / polymer ratio is 1:2. A dry-mixture of powders was passed through a 30 mesh screen and extra glidands and lubricants were added in a proportion of about 1% by weight (relative to the total core weight) for each excipient.

The mixture was compressed at a compression force of about 10 kN in a Korch EK 0 tableting machine having a round die (diameter of 9.8 mm). The influence of the compression force on the

mechanical properties of the core, on the interlayer binding as well as on the *in vitro* dissolution profiles was studied. It was found that varying degrees of core hardness do not affect the dissolution of the drug in an aqueous medium. However, a very high compression force could induce weak interlayer binding. Figure 3 illustrates a release profile of diclofenac (diclofenac / polymer ratio is 1:1) in SIF medium.

Example 4: Preparation of a SR core containing Aspirin (80mg)

The sustained release matrix comprising aspirin is preferably provided as a non-erodable core made in accordance with the steps as previously described for diclofenac (Example 3).

The non-erodable core could also be obtained by direct compression using blends comprising aspirin (from about 25 to about 50% by weight), physical mixtures of polyvinyl acetate and polyvinyl pyrolidone (from about 20 to about 60% by weight), and magnesium stearate (less then about 2%).

SR formulations for a 270 mg core comprising aspirin were prepared using various drug aspirin / polymer ratios (physical mixtures of polyvinyl acetate and polyvinyl pyrrolidone) (*i.e.* 1:1, 1:1.5 and 1:2). A more preferred aspirin / polymer ratio is 1:2. A dry-mixture of granulated and regular powders was obtained and extra glidants and lubricants were added in a proportion of about 1% by weight (relative to the total core weight) for each excipient.

The mixture was compressed at a compression force of about 10 KN in a Korch EK 0 tableting machine having a round die (diameter of 7.0 mm.). The influence of the compression force on the mechanical properties of the core, on the interlayer binding as well as on

the *in vitro* dissolution profiles was studied. It was found that varying degrees of core hardness do not affect the dissolution of the drug in an aqueous medium. Figure 5 illustrates a release profile of aspirin from a SR matrix-core, as well as from a tablet comprising famotidine IR+SR layers in SIF medium.

Example 5: Manufacture of a multi-layer fixed-dose combination tablet.

Using multi-layer technology, diclofenac (drug B) was compressed in a SR core. The core was then transferred into a rotary press containing either the IR or SR blend comprising famotidine (drug A). In one embodiment, the rotary press may contain the pre-compressed famotidine comprising IR layer, to which is added the diclofenac comprising core. Subsequent a first compression, the famotidine comprising SR layer is added followed by a final compression at a force of about 25 kN. This allows for a three-layer tablet to be independently processed using wet or dry granulated materials, as needed to enhance flow or compressibility.

Example 6: Manufacture of a multi-layer tablet.

Using multi-layer technology, aspirin (drug B) was compressed in a SR core The core was then transferred into a rotary press, containing either the IR or SR blend comprising famotidine (drug A). In one embodiment, the rotary press may contain the famotidine comprising IR layer, to which is added the diclofenac comprising core. Subsequent a first compression, the famotidine comprising SR layer is added followed by a final compression at a force of about 25 kN. This allows for a three-layer tablet to be independently processed using wet or dry granulated materials, as needed to enhance flow or compressibility.

GENERAL PROCEDURES

Dry granulation, fluidization, wet granulation, and extrusion are some of the methods commonly used for preparing the materials to be included in a solid dosage form.

Dry granulation procedures may be utilized where one of the components of the formulation, either the drug or the diluent, has insufficient cohesive or flow properties to be tabletted. The method includes mixing the ingredients, slugging the ingredients, dry screening, lubricating and finally compressing the ingredients.

An active agent can be pelletized or granulated using any suitable method known in the art. Pelletization or granulation is commonly defined as a size-enlargement process in which small particles are gathered into larger, permanent aggregates, in which the original particles can still be identified. Prior to granulation, a binder can be added to the active agent in order to improve the granulation process. Solvents and binders are typically added to a formulation to provide larger aggregates of granules. The temperature during granulation is generally not exceeding the melting point of any one of the components of the formulation. Typically, the mixture is granulated at a temperature ranging from about 35°C to about 65°C over a period ranging from about 10 to about 30 minutes. The granules are then typically air dried for a suitable duration of time (*e.g.* one or more hours). Preferably, the active agents are granulated using high shear mixer granulation or fluid-bed granulation. Both of these granulation processes provide enlarged granules or pellets, but differ in the apparatus used. In high shear mixing, blending and wet massing is accomplished by high mechanical agitation using an impeller and a chopper.

Fluidized bed granulation is a process in which granules are produced by spraying a binder solution onto a fluidized powder bed. The binder solution can be sprayed, for example, from a spray gun positioned in any suitable manner (*e.g.*, top or bottom). The spray position and the rate of spraying may depend on the nature of the active agent and the binder used, and can be readily determined by those skilled in the art.

Optionally, granulated active agents can be milled. The mesh size of the screen can be selected depending on the size of the active agent granule or pellet desired. Typically, the mesh size can range from about mesh 20 to about mesh 100. The milling process aids in providing relatively uniform active agent granules.

Typically, the mean size of the active agent granule or pellet can range from about 50 μm to about 3 mm; preferably from about 100 μm to about 2 mm; or more preferably from about 300 μm to about 1 mm.

The bulk density or the tap density of the active agent granules or pellets ranges from about 0.1 g/ml to about 1.5 g/ml, preferably from about 0.3 g/ml to about 0.8 g/ml, or more preferably from about 0.4 g/ml to about 0.6 g/ml. The bulk density is measured based on the USP method.

Direct compression involves directly compressing the powdered material(s) to be included in the solid dosage form, without modifying the physical nature of the material itself.

COMPRESSION INTO TABLETS

Tableting can be accomplished using a tablet press. The tablet is formed by applying pressure on the lower and upper punches. Typical compression pressures range from about 6 kN to about 30 kN and will vary based on the desired size and hardness of the tablet. Preferably, the compression pressure is adjusted depending on the formulation characteristics and on the interlayer binding. Strong interlayer binding, more specifically between cover layers and the core matrix layer, is mandatory in order to ensure an erosion-controlled linear release of the drug from the core matrix. The physicochemical properties of the formulations are important factors influencing interlayer binding, as are the surface roughness and the hardness of the core. These properties and characteristics have a direct impact on the susceptibility to further compression The pre-compression force is therefore an essential parameter. If the compaction of the core granules exceeds a certain range, a tightly packed, "closed" core surface is formed. In such a tightly packed core, no penetration of particles of the cover layer into the core layer will occur during the main compression, which is essential for the formation of a strong bond between the two layers.

MATERIALS

One or more binders may be present in the pharmaceutical formulations in addition to, or in lieu of the fillers, in an amount ranging from about 0 to about 35%, and preferably from about 0.5 to about 30% by weight of the composition. Non-limiting examples of such binders, suitable for use herein, include polymeric materials (from natural or synthetic sources), sugars, salts, as well as wax binders such as carnauba wax, paraffin, spermaceti, or microcrystalline wax.

The polymeric material is a member selected from the group consisting of chitosan, modified starches, zein, maltodextrin, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, polyacrylic acid, metacrylate copolymers, polyvinyl acetate, polyvinylacetate phthalate, polyvinyl alcohol, polyethylene oxide, polyethylene glycol, polyvinyl pyrrolidone, polylactic acid, polyglycolic acid, polylactic/glycolic acid, polydimethyl silicone, polyhydroxyethyl metacrylate, polyethylene/vinyl acetate, polyethylene/vinyl alcohol, and mixtures thereof.

The pharmaceutical compositions as described herein are in the form of a tablet, and will include one or more tableting lubricants in an amount ranging from about 0.2 to about 8% and preferably from about 0.5 to about 2% by weight of the composition. Non-limiting examples of such lubricants are magnesium stearate, stearic acid, palmitic acid, calcium stearate, and the like. Other conventional ingredients, which may optionally be present, include preservatives, stabilizers, anti-adherents and silica flow conditioners or glidants such as silicon dioxide.

If so-desired, the fixed-dose combination tablets of the present invention may include appropriate amounts of other pharmaceutically acceptable excipients such as vehicles (*e.g.*, lactose, mannitol, potato starch, wheat starch, rice starch, corn starch, and crystalline cellulose), binders (*e.g.*, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, and arabic gum), swelling agents (*e.g.*, carboxymethylcellulose and carboxymethylcellulose calcium), lubricants (*e.g.*, stearic acid, calcium stearate, magnesium stearate, talc, calcium hydrogen phosphate, and anhydrous calcium hydrogen

phosphate), fluidizers (*e.g.*, hydrous silica, light anhydrous silicic acid), colorants (*e.g.*, red iron oxide), surfactants (*e.g.*, sodium lauryl sulfate, sucrose fatty acid ester), coating agents.

The pharmaceutical compositions of the present invention may further comprise a disintegrant. Disintegrants are agents that aid in the disintegration of the tablets and include, but are not limited to, starch, clays, microcrystalline cellulose, sodium starch glycolate, and cross-linked polymers, preferably, crospovidone. The amount of each excipient can be readily determined by routine experimentation.

The tablets of the present invention may further comprise a coating - a light protective layer that may account for about 0 to about 15% by weight of the tablet composition. The coating layer, which is applied over the entire tablet, may comprise any conventional coating formulations and will include one or more film-formers or binders, such as a hydrophilic polymer like hydroxypropylmethylcellulose, and/or a hydrophobic polymer like ethyl cellulose, cellulose acetate, and one or more plasticizers, such as triethyl citrate, diethyl phthalate, propylene glycol, glycerin, butyl phthalate, castor oil and the like.

The film formers are applied from a solvent system containing one or more solvents including water, alcohols such as ethyl alcohol or isopropyl alcohol, ketones such as acetone, or ethylmethyl ketone, chlorinated hydrocarbons such as methylene chloride, and dichloroethane. Where a color is employed, the color will be applied together with the film former, plasticizer and solvent composition.

Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified

without departing from the spirit and nature of the subject invention as defined in the appended claims.

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CLAIMS

1. A multi-layer oral dosage form, preferably a tablet, comprising:

(a) a matrix core comprising a therapeutically effective amount of a first drug, wherein the matrix core allows sustained release of the first drug;

(b) a first layer, which is in contact with said matrix core, comprising a first portion of a pharmaceutically effective amount of a second drug and optionally an additional amount of the first drug, wherein the first layer allows sustained release of the first and second drug; and

(c) a second layer, which is also in contact with said matrix core, comprising a second portion of the second drug, wherein the second layer allows immediate release of the second drug.

2. A multi-layer oral dosage form, preferably a tablet, comprising:

(a) a matrix core comprising a therapeutically effective amount of a first drug, wherein the matrix core allows sustained release of the first drug;

(b) a first layer, which is in contact with said matrix core, comprising a first portion of a pharmaceutically effective amount of a second drug, wherein the first layer allows sustained release of the second drug; and

(c) a second layer, which is also in contact with said matrix core, comprising a second portion of the second drug, wherein the second layer allows immediate release of the second drug.

3. The multi-layer oral dosage form as defined in claims 1 and 2, wherein said matrix core further comprises insoluble polymers and adjuvants.

4. The multi-layer oral dosage form as defined in claim 3, wherein said polymers are selected from the group consisting of insoluble cellulosic materials, polyvinyl acetates, polyvinyl alcohols, polyethylene oxides, metacrylates, and non-crosslinked polyvinylpyrolidone.

5. The multi-layer oral dosage form as defined in claim 3, wherein said adjuvants comprise sugars, colloidal silica, calcium diphosphate, talc and magnesium stearate.

6. The multi-layer oral dosage form as defined in claim 3, wherein said first layer further comprises water-soluble and/or gel forming polymeric materials.

7. The multi-layer oral dosage form as defined in claim 3, wherein said second layer further comprises pharmaceutically acceptable excipients selected from the group consisting of cellulose derivatives, cross-linked polymers, sugars, soluble salts, colorants, fillers, disintegrants, anti-tacking agents and anti-static agents.

8. The multi-layer oral dosage form as defined in claim 6, wherein said first layer comprises from about 15 to about 95% of the second drug.

9. The multi-layer oral dosage form as defined in claim 7, wherein said second layer comprises from about 5 to about 85% of the second drug.

10. The multi-layer oral dosage form as defined in any one of claims 1 to 9, wherein said first drug is an NSAID.

11. The multi-layer oral dosage form as defined in claim 10, wherein said NSAID consists essentially of diclofenac.

12. The multi-layer oral dosage form as defined in claim 11, comprising from about 50 to about 150 mg of diclofenac.

13. The multi-layer oral dosage form as defined in claim 12, comprising about 75 mg of diclofenac.

14. The multi-layer oral dosage form as defined in claim 10, wherein said NSAID consists essentially of aspirin.

15. The multi-layer oral dosage form as defined in claim 12, comprising from about 50 to about 150 mg of aspirin.

16. The multi-layer oral dosage form as defined in claim 12, comprising about 80 mg of aspirin.

17. The multi-layer oral dosage form as defined in any one of claims 1 to 16, wherein said second drug is an H_2-receptor antagonist.

18. The multi-layer oral dosage form as defined in claim 17, wherein said H_2-receptor antagonist consists essentially of famotidine.

19. The multi-layer oral dosage form as defined in claim 18, comprising from about 20 to about 60 mg of famotidine.

20. The multi-layer oral dosage form as defined in claim 19, comprising about 40 mg of famotidine.

21. The multi-layer oral dosage form as defined in claims 1 and 2, further comprising a coating.

22. The multi-layer oral dosage form as defined in claim 21, wherein the coating is a light protective coating.

23. The multi-layer oral dosage form as defined in claim 22, wherein the light protective coating comprises film-formers, plasticizers and pigments.

24. The multi-layer oral dosage form as defined in claim 23, wherein said film formers comprise hydrophilic polymers.

25. The multi-layer oral dosage form as defined in claim 24, wherein said hydrophilic polymers comprise hydroxypropylmethyl cellulose.

26. The multi-layer oral dosage form as defined in claim 23, wherein said plasticizers are selected from the group consisting

of triethyl citrate, diethyl phthalate, propylene glycol, glycerin, butyl phthalate, and castor oil.

27. The multi-layer oral dosage as defined in any one of claims 1 to 26, wherein the dosage form is a tablet.

28. A method for treating and preventing osteoarthritis in patients susceptible to developing NSAID induced gastric and duodenal ulcers comprising administering a multi-layer oral dosage form as defined in claim 1.

29. A method for treating and preventing osteoarthritis in patients susceptible to developing NSAID induced gastric and duodenal ulcers comprising administering a multi-layer oral dosage form as defined in claim 2.

30. A method for preparing a multi-layer oral dosage form according to claim 2, comprising:

(a) preparing a sustained release matrix core comprising a therapeutically effective amount of a first drug or pharmaceutically acceptable salts thereof;

(b) preparing a sustained release blend comprising a first portion of a pharmaceutically effective amount of a second drug or pharmaceutically acceptable salts thereof;

(c) preparing an immediate release blend comprising a second portion of the second drug or pharmaceutically acceptable salts thereof; and

(d) combining, by compressing, the matrix core of step (a), the sustained release blend of step (b) and the immediate release blend of step (c).

31. The method as defined in claim 30, wherein the matrix core further comprises insoluble polymers and adjuvants.

32. The method as defined in claim 31, wherein said polymers are selected from the group consisting of insoluble cellulosic materials, polyvinyl acetates, polyvinyl alcohols, polyethylene oxides, methacrylates, and non-crosslinked polyvinylpyrolidone.

33. The method as defined in claim 31, wherein said adjuvants comprise sugars, colloidal silica, calcium diphosphate, talc and magnesium stearate.

34. The method as defined in claim 30, wherein said sustained release blend further comprises water-soluble and/or gel forming polymeric materials.

35. The method as defined in claim 30, wherein said immediate release blend further comprises pharmaceutically acceptable excipients selected from the group consisting of cellulose derivatives, cross-linked polymers, sugars, soluble salts, colorants, fillers, disintegrants, anti-tacking agents and anti-static agents.

36. A method as defined in claim 34, wherein said sustained release blend comprises from about 15 to about 95% of the second drug.

37. A method as defined in claim 35, wherein said immediate release blend comprises from about 5 to about 85% of the second drug.

38. A method as defined in any one of claims 30 to 37, wherein said first drug is an NSAID.

39. A method as defined in claim 38, wherein said NSAID consists essentially of diclofenac.

40. A method as defined in claim 39, comprising from about 50 to about 150 mg of diclofenac.

41. A method as defined in claim 40, comprising about 75 mg of diclofenac.

42. A method as defined in claim 38, wherein said NSAID consists essentially of aspirin.

43. A method as defined in claim 42, comprising from about 50 to about 150 mg of aspirin.

44. A method as defined in claim 43, comprising about 80 mg of aspirin.

45. A method as defined in any one of claims 30 to 37, wherein said second drug is an H_2-receptor antagonist.

46. A method as defined in claim 45, wherein said H_2-receptor antagonist consists essentially of famotidine.

47. A method as defined in claim 46, comprising from about 20 to about 60 mg of famotidine.

48. A method as defined in claim 47, comprising about 40 mg of famotidine.

49. The method as defined in claim 30, further comprising the step of coating the multi-layer tablet with a protective coating.

50. The method as defined in claim 49, wherein the protective coating is a light protective coating.

51. The method as defined in claim 50, wherein the light protective coating comprises film formers, plasticizers and pigments.

52. The method as defined claim 51, wherein the film formers comprise hydrophilic polymers.

53. The method as defined in claim 52, wherein the hydrophilic polymers comprise hydroxypropylmethyl cellulose.

54. The method as defined in claim 51, wherein the plasticizers are selected from the group consisting of triethyl citrate, diethyl phthalate, propylene glycol, glycerin, butyl phthalate, and castor oil.

55. A multi-layer oral dosage form comprising:

(a) a matrix core comprising from about 50 to about 150 mg of diclofenac;

(b) a sustained release layer, which is in contact with said matrix core, comprising from about 10 to about 40 mg of famotidine; and

(c) an immediate release layer, which is in contact with said matrix core, comprising from about 5 to about 20 mg of famotidine.

56. The multi-layer oral dosage form as defined in claim 55, wherein said matrix core comprises about 75 mg of diclofenac.

57. The multi-layer oral dosage form as defined in claim 56, wherein said sustained release layer comprises about 30 mg of famotidine.

58. The multi-layer oral dosage form as defined in claim 57, wherein said immediate release layer comprises about 10 mg of famotidine.

59. The multi-layer oral dosage form as defined in any one of claims 55 to 58, wherein the oral dosage form is a tablet.

60. A multi-layer oral dosage form comprising:

(a) a matrix core comprising from about 50 to about 150 mg of aspirin;

(b) a sustained release layer, which is in contact with said matrix core, comprising from about 10 to about 40 mg of famotidine; and

(c) an immediate release layer, which is also in contact with said matrix core, comprising from about 5 to about 20 mg of famotidine.

61. The multi-layer oral dosage form as defined in claim 60, wherein said matrix core comprises about 80 mg of aspirin.

62. The multi-layer oral dosage form as defined in claim 59, wherein said sustained release layer comprises about 30 mg of famotidine.

63. The multi-layer oral dosage form as defined in claim 59, wherein said immediate release layer comprises about 10 mg of famotidine.

64. The multi-layer oral dosage form as defined in any one of claims 60 to 63, wherein the oral dosage form is a tablet.

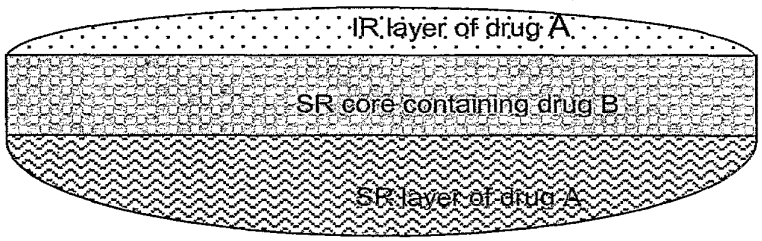
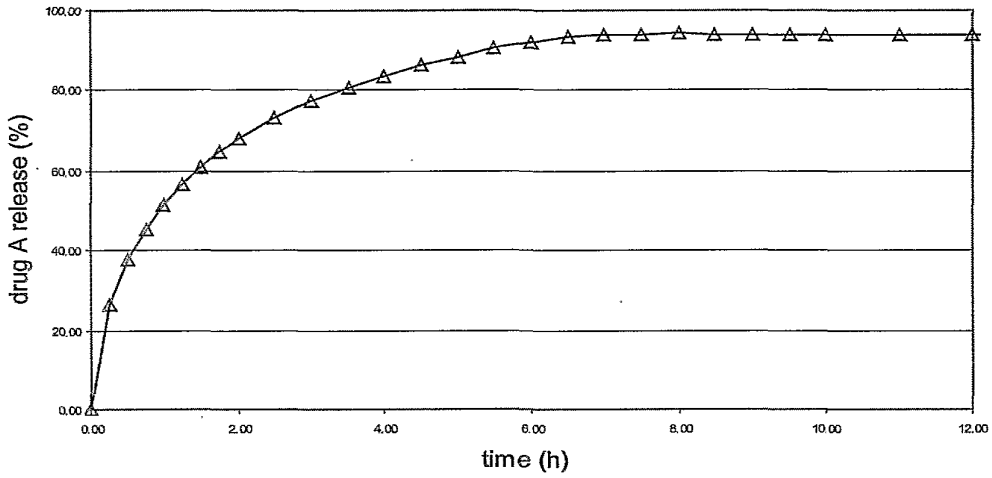


Figure 1


100.00
80.00
60.00
40.00
20.00
0.00
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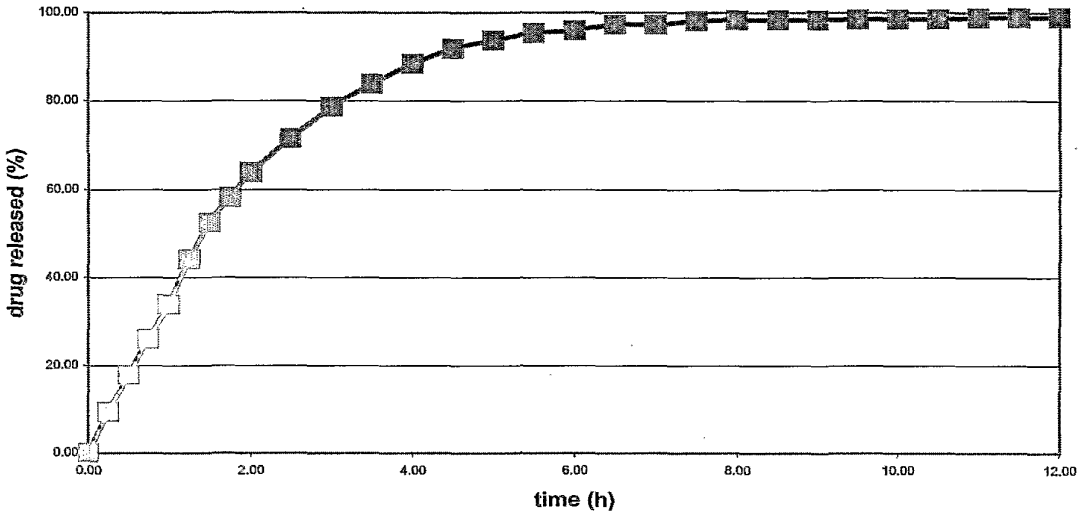
0.00
2.00
4.00
6.00
8.00
10.00
12.00
time (h)

Figure 2


100.00
80.00
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40.00
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drug released (%)
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2.00
4.00
6.00
8.00
10.00
12.00
time (h)

Figure 3

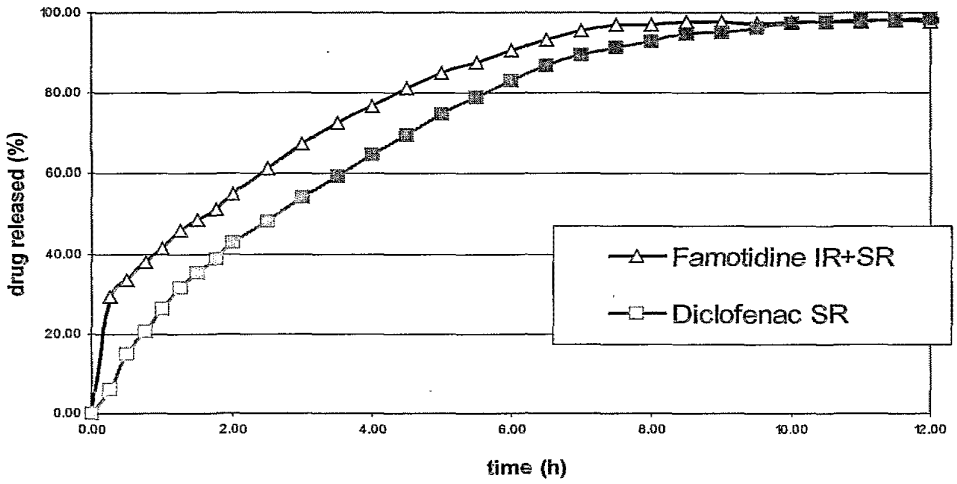
100.00
80.00
60.00
40.00
20.00
0.00
drug released (%)
0.00
2.00
4.00
6.00
8.00
10.00
12.00
time (h)
Famotidine IR+SR
Diclofenac SR

Figure 4

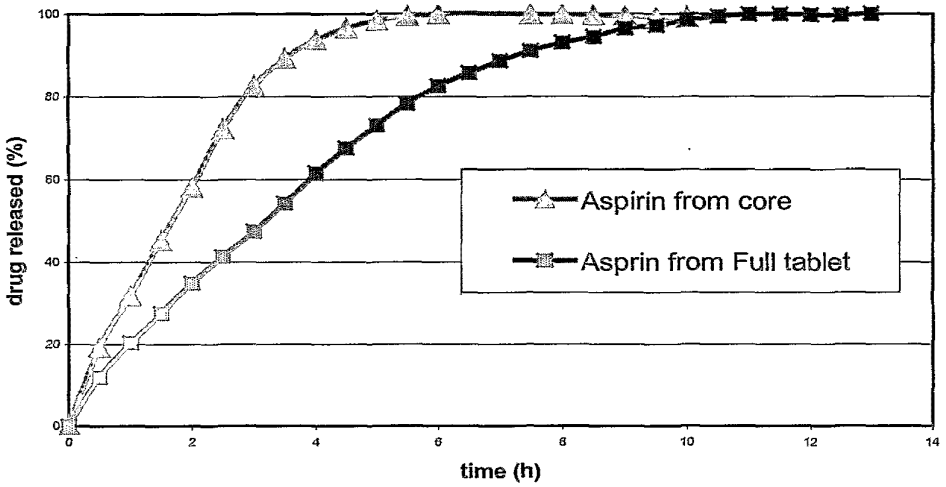
100
80
60
40
20
0
drug released (%)
0
2
4
6
8
10
12
14
time (h)
Aspirin from core
Asprin from Full tablet

Figure 5

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA2004/000073

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/24 A61K45/06

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)
IPC 7 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, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/098352 A (POZEN INC) 12 December 2002 (2002-12-12) page 3, line 30 - page 6, line 13 examples claims page 11, line 16 - line 21	1-64
A	WO 02/066002 A (GLAXO WELLCOME SA ; IBANEZ MATILDE FERNANDEZ (ES); SANZ EMILIO GARRIZ) 29 August 2002 (2002-08-29) page 2, line 1 - line 20 examples claims	1-64
A	US 4 946 685 A (EDGREN DAVID E ET AL) 7 August 1990 (1990-08-07) claims 5,6; figure 3; examples 28,30	1-64

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☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 May 2004	07/06/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Epskamp, S

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
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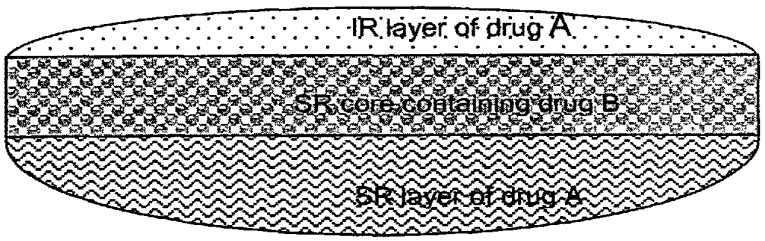
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ORAL DOSAGE FORMULATION



(57) Abstract: A multi-layer oral dosage form, preferably a tablet, comprising a matrix core comprising a therapeutically effective amount of a first drug (NSAID), wherein the matrix core allows sustained release of the first drug; a first layer, which is in contact with the matrix core, comprising a first portion of a pharmaceutically effective amount of a second drug (H_2-blocker antagonist) , wherein the first layer allows sustained release of the second drug; and a second layer, which is in contact with said matrix core, comprising a second portion of the second drug, wherein the second layer allows immediate release of the second drug. Methods for preparing the multi-layer dosage form are also disclosed.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA2004/000073

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/24 A61K45/06

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)
IPC 7 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, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/098352 A (POZEN INC) 12 December 2002 (2002-12-12) page 3, line 30 - page 6, line 13 examples claims page 11, line 16 - line 21	1-64
A	WO 02/066002 A (GLAXO WELLCOME SA ; IBANEZ MATILDE FERNANDEZ (ES); SANZ EMILIO GARRIZ) 29 August 2002 (2002-08-29) page 2, line 1 - line 20 examples claims	1-64
A	US 4 946 685 A (EDGREN DAVID E ET AL) 7 August 1990 (1990-08-07) claims 5,6; figure 3; examples 28,30	1-64

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

[X] Patent family members are listed in 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
27 May 2004	02.07.04

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

nation on patent family members

International Application No
PCT/CA2004/000073

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 02098352	A	12-12-2002	CA	2449098 A1	12-12-2002
			EP	1411900 A2	28-04-2004
			WO	02098352 A2	12-12-2002
			US	2003069255 A1	10-04-2003
WO 02066002	A	29-08-2002	WO	02066002 A2	29-08-2002
			EP	1363604 A2	26-11-2003
US 4946685	A	07-08-1990	CA	1336070 C	27-06-1995
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			DE	3811114 A1	10-11-1988
			ES	2006394 A6	16-04-1989
			FR	2613224 A1	07-10-1988
			GB	2203338 A ,B	19-10-1988
			GR	88100214 A ,B	31-01-1989
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			JP	2916147 B2	05-07-1999
			JP	63258808 A	26-10-1988
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			LU	87189 A1	17-11-1988
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			SE	503611 C2	15-07-1996
			SE	8801240 A	07-10-1988
			ZA	8802034 A	15-09-1988

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2004/000073

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 28 and 29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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60/539,981 30 January 2004 (30.01.2004) US

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(74) Agents: **GRIEFF, Edward, D.** et al.; Wilmer Cutler Pickering Hale and Dorr LLP, 1455 Pennsylvania Avenue, N.W., Washington, DC 20004 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITIONS AND METHODS USING PROTON PUMP INHIBITORS

(57) Abstract: The invention provides methods for treating and preventing cystic fibrosis, radiation therapy-induced emesis, chronic ear infections, bruxism, motion, sickness, tooth decay due to emesis and other disorders by administering to a patient a therapeutically effective amount of at least one proton pump inhibitor. In other embodiments, the proton pump inhibitor can be administered with one or more cystic fibrosis drugs, motion sickness drugs, antibiotics, NSAIDs, and migraine drugs.

WO 2005/074536 A2

Compositions and Methods Using Proton Pump Inhibitors

Related Application

This application claims priority to US Application No. 60/539,981 filed January 30, 2004.

Field of the Invention

The invention provides safe and effective methods for treating and preventing gastrointestinal disorders by administering at least one proton pump inhibitor. In one embodiment, the proton pump inhibitor is rabeprazole, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof.

Background of the Invention

Peptic ulcers are localized erosions of the mucous membrane of the duodenum and/or stomach, which expose the underlying layers of the gut wall to the acid secretions of the stomach and to the proteolytic enzyme pepsin. Peptic ulceration is a common disease of the gastrointestinal tract and it is estimated that about 10 to 20% of the adult male population will experience peptic ulceration at some time in their lives. ACIPHEX® (Eisai, Inc., Teaneck, NJ), a proton pump inhibitor, is highly successful in treating peptic ulcers. ACIPHEX® is described in U.S. Patent No. 5,045,552, the disclosure of which is incorporated by reference herein in its entirety. There is a need in the art for new and improved treatments for peptic ulcers and other gastrointestinal disorders. The invention is directed to these, as well as other, important ends.

Summary of the Invention

The invention provides methods for treating and preventing gastrointestinal disorders, exercise-induced gastroesophageal reflux disease, cystic fibrosis, radiation therapy-induced emesis, chronic ear infections, bruxism, motion sickness, tooth decay due to emesis, and other disorders by administering to a patient a therapeutically effective amount of at least one proton pump inhibitor. The invention is described in more detail below.

Detailed Description of the Invention

"Patients" includes animals, preferably mammals, more preferably humans. "Patients" include infants, children and adults, and includes males and females.

The invention provides methods for treating and/or preventing gastrointestinal

(GI) disorders in a patient in need thereof by administering at least one proton pump inhibitor and one or more nonsteroidal antiinflammatory drugs (NSAIDs).

In one embodiment the invention provides methods for treating GI disorders induced or caused by NSAIDS in a patient in need thereof by administering at least one proton pump inhibitor and one or more nonsteroidal antiinflammatory drugs (NSAIDs).

In other embodiments of each of these methods, the patient can be administered at least two proton pump inhibitors, where the first proton pump inhibitor is rabeprazole, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof and where the second proton pump inhibitor is omeprazole, lansoprazole, esomeprazole, pantoprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, RO 18-5362, IY 81149, 3-butyl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline. The gastrointestinal disorders induced or caused by NSAIDs can be any gastrointestinal disorder known in the art, such as those described herein. In one embodiment, the gastrointestinal disorder is a peptic ulcer or gastrointestinal bleeding. The at least one proton pump inhibitor and at least one NSAID can be administered separately or in the form of a composition.

The term "treating" includes eliminating the gastrointestinal disorder or future re-occurrence thereof, or reducing the severity, duration, and/or symptoms of the gastrointestinal disorder (e.g., compared to an untreated gastrointestinal disorder).

The gastrointestinal disorder can be any known in the art. Exemplary gastrointestinal disorders include *H. pylori* infections, ulcers, erosive esophagitis, gastroesophageal reflux disease (GERD), erosive gastroesophageal reflux disease, gastritis, symptomatic GERD, pregnancy-induced GERD, hypersecretory conditions (e.g., Zollinger-Ellison syndrome, idopathic gastric acid hypersecretion), gastrointestinal motility disorders, Barrett's esophagus, dyspepsia, dysphagia, irritable bowel syndrome, inflammatory bowel disease, infectious enteritis, diarrhea, gastroparesis, collagenous colitis, lymphocytic colitis, short bowel syndrome, bleeding associated with short bowel syndrome, gastrointestinal bleeding, hiatal hernia, emesis, abdominal pain, and the like. "Ulcers" include peptic ulcers, bleeding peptic ulcers, stress ulcers, stomal ulcers, refractory ulcers, esophageal ulcers, fungal-induced ulcers, viral-induced ulcers, and the like. "Peptic ulcers" include gastric ulcers and duodenal ulcers. The ulcers can be associated with *H. pylori*. Inflammatory bowel disease

includes Crohn's disease and ulcerative colitis. Infectious enteritis can be caused, for example, by *Campylobacter* species, *Shigella* species, *Yersinia* species (e.g., *Yersinia enterocolitica*), *Cryptosporidium* species, *Giardia* species (e.g., *Giardia lamblia*), *Salmonella* species, *Pseudomonas* species (e.g., *Pseudomonas aeruginosa*), and the like.

Any NSAID can be used in the compositions and methods of the invention. NSAIDs include COX-1 and/or COX-2 inhibitors. Exemplary COX-2 inhibitors include celecoxib, rofecoxib, valdecoxib, and the like. Exemplary NSAIDs include celecoxib, rofecoxib, valdecoxib, ibuprofen, acetaminophen, aspirin, naproxen, acetaminophen/aspirin/caffeine, ketorolac, ketoprofen, diflunisal, salsalate, salicylate, salicylamide, thiosalicylate, trisalicylate, mesalamine, sulfasalazine, methylsalicylate, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, dipyrone, azapropazone, phenacetin, indomethacin, sulindac, mefenamic, meclofenamic, flufenamic, tolfenamic, etofenamic, tolmetin, naproxen, flurbiprofen, fenoprofen, fenbufen, pirprofen, oxaprozin, indoprofen, tiaprofenic acid, piroxicam, ampiroxicam, tenoxicam, tolmetin, meloxicam, tenidap, diclofenac, diclofenac/misoprostol, sulindac, etodolac, nabumentone, and the like.

In one embodiment, the invention provides methods for treating and preventing gastrointestinal disorders by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor and celecoxib. In one embodiment, the proton pump inhibitor is rabeprazole, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof.

In another embodiment, the invention provides methods for treating and preventing gastrointestinal disorders by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor and rofecoxib. In one embodiment, the proton pump inhibitor is rabeprazole, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof.

In another embodiment, the invention provides methods for treating and preventing gastrointestinal disorders induced or caused by NSAIDs by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor and valdecoxib. In one embodiment, the proton pump inhibitor is rabeprazole, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof.

In another embodiment, the invention provides methods for treating and preventing gastrointestinal disorders induced or caused by NSAIDs by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor and diclofenac. In one embodiment, the proton pump inhibitor is rabeprazole, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof.

The invention provides methods for treating and/or preventing exercise-induced GERD in a patient in need thereof by administering a therapeutically effective amount of at least one proton pump inhibitor. It has been discovered that exercise, such as vigorous or jarring exercises, can cause GERD. In this embodiment of the invention, a patient can be administered at least one proton pump inhibitor before, during and/or after exercise to prevent or treat GERD caused by exercising.

The invention provides methods for treating cystic fibrosis by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor and at least one cystic fibrosis drug. Cystic fibrosis is a disorder of the cells that line the lungs, small intestines, sweat glands and pancreas, where mucus contributes to the destruction of lung tissue. Symptoms of cystic fibrosis include excessive appetite, poor weight gain, diarrhea, persistent cough, and other digestive disorders. The proton pump inhibitor is administered to improve the pH of the gastrointestinal environment by reducing the gastric acid output. The patient can be an adult or a child.

Cystic fibrosis drugs include, for example, bronchodilators, mucolytics, anti-inflammatives, antibiotics, vitamins, pancreatic enzymes, stool softeners, GI drugs, antihistamines, and nasal sprays. Exemplary cystic fibrosis drugs include albuterol, theophylline, ipratropium, guaifenesin, dnase, n-acetylcysteine, triamcinolone, flunisolide, fluticasone, beclomethasone, prednisone, methylprednisone, ibuprofen, montelukast, cromolyn, ciprofloxacin, co-trimoxazole, tobramycin, cephalexin, colistin, dicloxacillin, azithromycin, vitamins, pancrelipase, docusate, casanthranol and docusate, omeprazole, ranitidine, loratadine, cetirizine, fexofenadine, and the like.

The invention provides methods for treating and preventing radiation therapy-induced emesis by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. The proton pump inhibitor can be administered before, during and/or after radiation therapy. Radiation therapy-induced

emesis is an acute event appearing from 30 minutes to 4 hours following irradiation. Emetogenic risk is high for total body irradiation, upper abdomen and hemibody irradiation, moderate for thorax and pelvic irradiation, and low for radiotherapy to the head and neck, brain, skin and extremities. Radiation therapy-induced emesis results from a complex interaction between various neurotransmitters and receptors in the CNS and gastrointestinal tract.

The invention provides methods for treating and/or preventing chronic ear infections by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor and, optionally, at least one antibiotic. A chronic ear infection may be the result of an acute ear infection that does not clear completely, or the result of recurrent ear infections. Acute otitis media (acute middle ear infection), most common in children, occurs when there is bacterial or viral infection of the fluid of the middle ear, causing the production of pus or excess fluid. This may be accompanied by bleeding in the middle ear. Inflammation of the ear (sterile or serous otitis) may occur when there is a collection of fluid in the ear that is not infected. This may be caused by overproduction of fluid by the structures in the middle ear or by blockage of the drainage system (the eustachian tube). Pressure from fluids associated with ear infection may cause the eardrum to rupture. A ruptured eardrum can also result in ear infection by allowing bacteria or viruses direct entry to the middle ear. Ear infections are often associated with respiratory infections or with blocked sinuses or eustachian tubes caused by allergies or enlarged adenoids. A chronic ear infection may spread into the mastoid bone (mastoiditis), or pressure from fluid build-up may rupture the eardrum or damage the bones of the middle ear. A chronic ear infection may be more destructive than an acute ear infection because its effects are prolonged or repeated, and it may cause permanent damage to the ear. Ear infections are more common in children because their eustachian tubes are shorter, narrower, and more horizontal than in adults. In one embodiment, the patient is an adult. In another embodiment, the patient is a child.

Any antibiotic can be used in the compositions and methods of the invention. Exemplary antibiotics include amoxicillin, amoxicillin and clavulanate potassium, cefpodoxime proxetil, ceftriaxone, cefuroxime, trimethoprim/sulfamethoxazole, and the like.

In other embodiments, the invention provides methods for preventing gastroesophageal reflux during and/or after surgery by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor prior to the administration of anesthesia.

In other embodiments, the invention provides methods for treating and preventing bruxism by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. Bruxism, commonly known as tooth grinding, is the clenching together of the bottom and upper jaw accompanied by the grinding of the lower set of teeth with the upper set.

In other embodiment, the invention provides methods for treating and/or preventing motion sickness by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. In another embodiment, the invention provides methods for preventing and treating motion sickness by administering a therapeutically effective amount of at least one proton pump inhibitor and at least one motion sickness drug. The proton pump inhibitor and motion sickness drug can be administered separately or in the form of a composition. Motion sickness applies to seasickness, carsickness, airsickness or sickness caused by anything else such as a swing or fairground amusements.Exemplary motion sickness drugs include scopolamine, promethazine, dimenhydrinate, diphenhydramine, cyclizine, buclizine, and meclizine, and the like.

In another embodiment, the invention provides methods for preventing and treating migraines by administering a therapeutically effective amount of at least one proton pump inhibitor and at least one non-steroidal antiinflammatory drugs (NSAIDs).

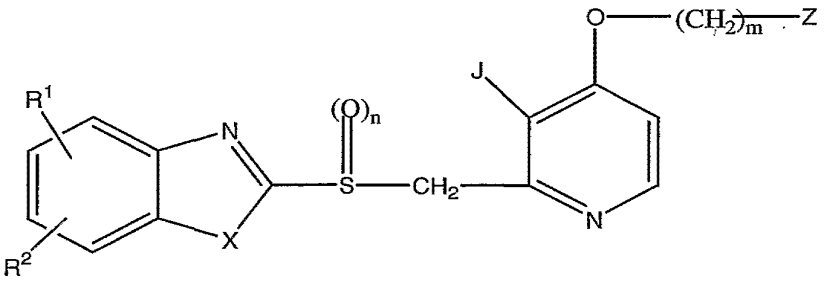
The migraines can be classic migraines, common migraines, complicated migraines, and/or cluster headaches. In other embodiments, the migraines can be menstrual migraines, premenstrual migraines, ophthalmic migraines, and/or ophthalmoplegic migraines. In other embodiments, the migraines can be fulgurating migraines, Harris' migraines, and/or hemiplegic migraines. In still other embodiments, the migraines can be abdominal migraines.

In another embodiment, the invention provides methods for preventing and treating tooth decay caused due to emesis by administering a therapeutically effective amount of at least one proton pump inhibitor. The excessive reflux experienced by

patients with GERD overwhelms their intrinsic mucosal defense mechanisms, resulting in many symptoms. The most common symptom of GERD is heartburn. Besides the discomfort of heartburn, reflux results in symptoms of esophageal inflammation, such as odynophagia (pain on swallowing) and dysphagia (difficult swallowing). The acid reflux may also cause oral symptoms such as tooth enamel decay, gingivitis, halitosis, and waterbrash and throat symptoms such as soreness, laryngitis, hoarseness, and a globus sensation; and earache. The effects of GERD on the mouth and salivary glands result in symptoms of waterbrush, gingivitis, and tooth decay. Waterbrash is the spontaneous appearance of high volumes of saliva in the mouth, and is caused by a vagally mediated reflex initiated by acid in the esophagus. Gingivitis and tooth decay are caused by contact with acidic refluxate.

Any proton pump inhibitor can be used in the compositions and methods described herein. Exemplary proton pump inhibitors include rabeprazole, omeprazole, lansoprazole, esomeprazole, pantoprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, RO 18-5362, IY 81149, 3-butyl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline, and the like.

In one embodiment, the proton pump inhibitors are compounds of formula (I), pharmaceutically acceptable salts thereof, and/or stereoisomers thereof:



(I)

wherein R^1 and R^2 are each independently a hydrogen atom, a halogen atom, a lower alkyl, lower alkoxy, halogenated lower alkyl, lower alkoxycarbonyl or carboxyl group;

X is -O-, -S- or =N-R^3, wherein R^3 is a hydrogen atom or a lower alkyl, phenyl, benzyl or lower alkoxycarbonyl group; and

Z is:

1. $-O(CH_2)_p-O-R^4$

wherein p is an integer of 1 to 3 and R^4 is hydrogen atom or a lower

alkyl, aryl or aralkyl group,

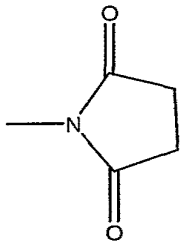
2. $-O-(CH_2)_q-R^5$

wherein q is an integer of 1 to 3 and R^5 is a halogen atom or an alkoxycarbonyl, aryl or heteroaryl group,

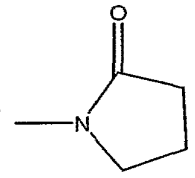
3. $-O-(CH_2)_r-O-(CH_2)_s-O-R^6$

wherein r and s are each independently an integer of 1 to 5 and R^6 is a hydrogen atom or a lower alkyl group,

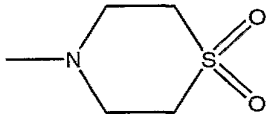
4.



5.

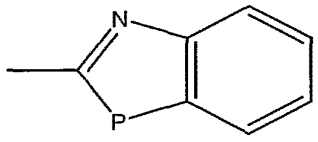


6.

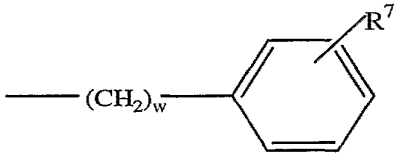


7. $-S(O)_t-A$

wherein t is an integer of 0 to 2, and A is a lower alkyl, alkoxycarbonylmethyl, pyridyl, furyl,



or



wherein B is -NH-, -O- or -S-, and w is an integer of 0 or 1;

8. $-N(R^8)-CH_2-C_6H_5$

wherein R^8 is an acetoxy or lower alkyl group;

9. $-OR^9$

wherein R^9 is a hydrogen atom, a lower alkyl or aryl group;

n is an integer of 0 to 2; m is an integer of 2 to 10, and J and K are each independently a hydrogen atom or a lower alkyl group, with the proviso that when Z is a group falling under the above category (9), then R^9 is a lower alkyl group and m stands for an integer of 3 to 10, and pharmaceutically acceptable salts thereof.

The same definitions for R^1, R^2, X, n, J, K, Z and m are used throughout the specification that follows and in the appended claims.

Also disclosed are pharmaceutical compositions containing one or more of these compounds as the active ingredient(s) in a pharmaceutically acceptable carrier, adjuvant or vehicle.

In the definition of the compounds of formula (I), the lower alkyl group defined with respect to R^1, R^2, R^3, R^4, R^6, R^7, R^8, A, J and K can be a straight-chain or branched alkyl group having 1 to 6 carbon atoms. Examples include methyl, ethyl, n-propyl, n-butyl, isopropyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 1-ethylpropyl, isoamyl and n-hexyl groups, among which methyl and ethyl groups are most preferred.

The lower alkoxy group and the lower alkoxy moiety of the lower alkoxycarbonyl group defined above with respect to R^1 and R^2 can be an alkoxy group derived form the above lower alkyl group. Methoxy and ethoxy groups are most preferred.

The halogen atom defined above includes chlorine, bromine, iodine or fluorine. The aryl group defined above with respect to R^4 and R^5 can be phenyl, tolyl, xylyl, napthyl or the like, which can be substituted with a lower alkoxy or hydroxyl group, a halogen atom or the like.

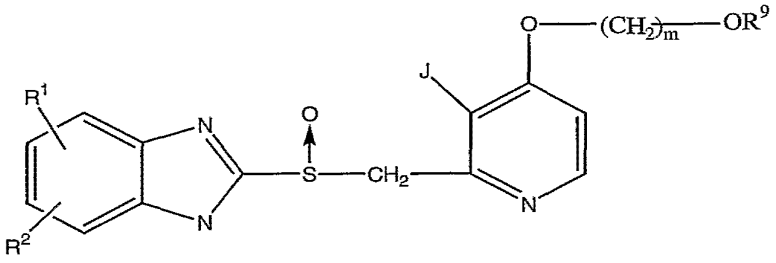
Examples of the arylalkyl defined above with respect to R^4 include benzyl and phenethyl groups.

Examples of the heteroaryl group defined above with respect to R^5 include pyridyl and furyl groups.

In the definition of Z in formula (I), groups 1, 2, 3, 4, 5 and 9 are preferred; and group 9 is the most preferred. As for R^1 and R^2, hydrogens for both and then a combination of a lower alkyl (e.g., methyl) for R^1 and hydrogen for R^2 are preferred. X is preferably $=NR^3$, where R^3 is hydrogen. A preferred value for n is 1. The preferred substituents for J and K are both hydrogen or where J is lower alkyl (e.g., methyl), and

K is hydrogen, or when J is hydrogen and K is lower alkyl (e.g., methyl). Thus, J or K are independently preferably hydrogen or methyl, most preferably J is methyl and K is hydrogen.

In another embodiment, the compounds of formula (I) are compounds of formula (A), pharmaceutically acceptable salts thereof, and/or stereoisomers thereof:



(A)

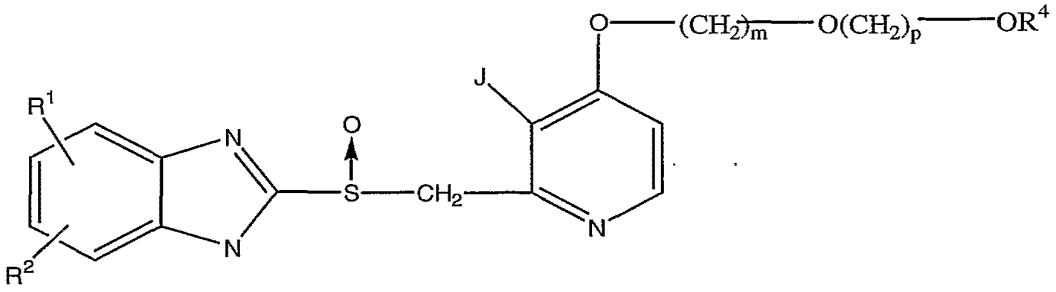
wherein R^1, R^2, J, m and R^9 have the same meanings as defined above.

In formula (A), the preferred R^1 and R^2 substituents are both hydrogen, or R^1 is 5-lower alkoxy, 5- lower alkyl or 5-halogenated lower alkyl and R^2 is hydrogen. The preferred substituent for J is hydrogen or methyl; the preferred value for m is in the range of 3 to 10, the most preferred being 3; and the preferred R^9 substituent is lower alkyl (e.g., methyl), or aryl. Among these possibilities for the compounds of formula (A), the preferred combination is when R^1 and R^2 are both hydrogen, J is methyl, m is 3 and R^9 is methyl.

Another group of preferred compounds in formula (A) are combinations of the above substituents where both R^1 and R^2 are hydrogen, J is hydrogen, m is 3 and R^9 is methyl.

Another group of preferred compounds falling within formula (A) is when both R^1 and R^2 are hydrogen, J is methyl, m is 2 and R^9 is benzyl.

In another embodiment, the compounds of formula (I) are compounds of formula (B), pharmaceutically acceptable salts thereof, and/or stereoisomers thereof:

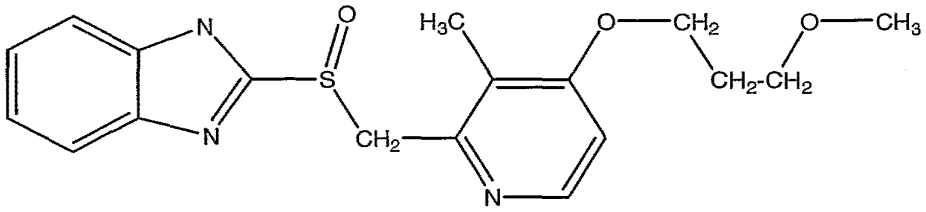


(B)

wherein R^1, R^2, J, p, m and R^4 have the same meanings as given above.

In formula (B), the preferred substituents for R^1 and R^2 are both hydrogen; or when R^1 is 5-lower alkoxy, 5-lower alkyl or 5- halogenated lower alkyl, R^2 is hydrogen. The preferred value of m is 2 or 3; the preferred value for p is 2 or 3; and the preferred substituent for R^4 is methyl or benzyl. Of the above possibilities for formula (B), the most preferred combination is where R^1 is 5- methyl, R^2 is hydrogen, J is methyl, m is 2, p is 2 and R^4 is methyl.

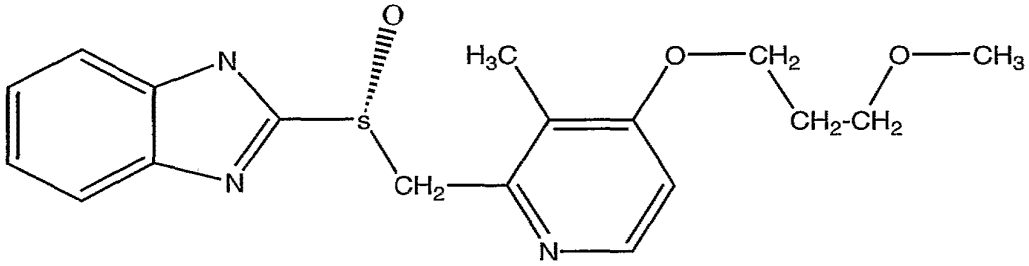
In another embodiment, the compound of formula I is a compound of formula (C), a pharmaceutically acceptable salt thereof, and/or a stereoisomer thereof:



(C).

Preferably, the compound of formula (C) is a sodium salt, which is known as rabeprazole sodium or ACIPHEX® (Eisai Inc., Teaneck, NJ).

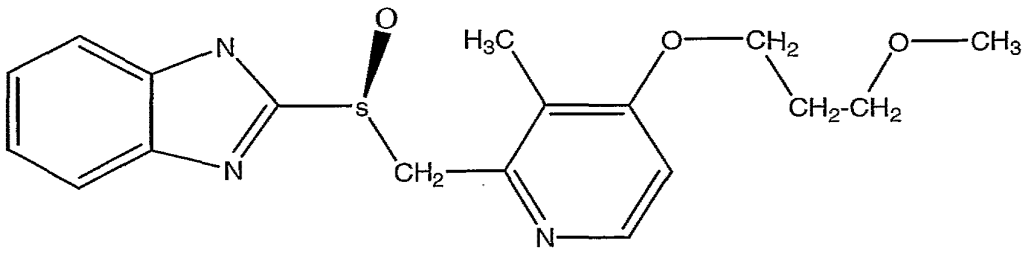
Although the compounds of the invention can be present as a hydrate or as a stereoisomer, the hydrates and stereoisomers are included within the scope of the invention. For example, the compound of formula (C) can be a compound of formula (D) or a pharmaceutically acceptable salt thereof (e.g., a sodium salt):



(D)

The compound of formula (D) is R (+) rabeprazole.

Alternatively, the compound of formula (C) can be a compound of formula (E) or a pharmaceutically acceptable salt thereof (e.g., a sodium salt):



(E)

The compound of formula (E) is S (-) rabeprazole.

The compounds of the invention can be administered as any pharmaceutically acceptable salt known in the art. Pharmaceutically acceptable salts are known in the art and include those of inorganic acids, such as hydrochloride, sulfate, hydrobromide, sulfate, and phosphate; those of organic acids, such as formate, acetate, maleate, tartrate, trifluoroacetate, methanesulfonate, benzenesulfonate and toluenesulfonate, and those of amino acids such as arginine, aspartic acid and glutamic acid. When certain substituents are selected, the compounds of the invention can form, for example, alkali metal salts, such as sodium or potassium salts; alkaline earth metal salts, such as calcium or magnesium salts; organic amine salts, such as a salt with trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine or N,N'-dibenzylethylenediamine. One skilled in the art will recognize that the compounds of the invention can be made in the form of any of these or of any other pharmaceutically acceptable salt. For example, compounds represented by formula (I), wherein X is $=N-R^3$ and R^3 is a hydrogen atom, or compounds represented by formula (I), wherein Z is a group falling under the category 7 and B is a group of -NH-, can be present as a metal salt, such as sodium, potassium, magnesium or calcium.

The proton pump inhibitors are commercially available or can be prepared by processes known in the art. Rabeprazole sodium is commercially available as ACIPHEX® from Eisai Inc., Teaneck, NJ, and is described, for example, in U.S. Patent No. 5,045,552, the disclosure of which is incorporated by reference herein in its entirety. Methods for preparing R (+) rabeprazole are described in WO 99/55157, the disclosure of which is incorporated by reference herein in its entirety. Methods for preparing S (-) rabeprazole are described in WO 99/55158, the disclosure of which is incorporated by reference herein in its entirety.

A therapeutically effective dosage regimen for treating the diseases described

herein with the proton pump inhibitors and/or antibiotics is selected in accordance with a variety of factors, including the age, weight, sex, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular proton pump inhibitor and/or antibiotics, whether a drug delivery system is used and whether the proton pump inhibitor and/or antibiotics is administered as part of a drug combination.

When administered separately, the proton pump inhibitors and/or other drugs described herein (e.g., NSAIDs, antibiotics, motion sickness drugs, cystic fibrosis drugs) can be administered about the same time as part of an overall treatment regimen, i.e., as a combination therapy or drug cocktail. "About the same time" includes administering the proton pump inhibitor and/or other drugs described herein (e.g., NSAIDs, antibiotics, motion sickness drugs, cystic fibrosis drugs) at the same time, at different times on the same day, or on different days, as long as they are administered as part of an overall treatment regimen.

The proton pump inhibitors can be administered in amounts of about 0.01 to about 200 mg per day, preferably about 0.05 to about 50 mg per day, more preferably about 0.1 to about 40 mg per day, still more preferably about 10 to about 30 mg per day, still more preferably about 10 to about 20 mg per day. The compounds and/or compositions can be administered once a day or in divided doses, for example from 2 to 4 times a day, preferably once per day. One skilled in the art will recognize that when the compounds and/or compositions of the invention are administered to infants or children, the dose can be smaller than the dose administered to adults, and that the dose can be dependent upon the size and weight of the patient.

In preferred embodiments of the methods described herein, rabeprazole sodium, which is commercially available as ACIPHEX® (Eisai Inc., Teaneck, NJ), is administered as a tablet containing 10 or 20 milligrams rabeprazole sodium. The tablets can be administered one to about four times a day. In preferred embodiments, one 20 milligram ACIPHEX® tablet is administered once a day for the methods described herein. One skilled in the art will appreciate that when rabeprazole sodium is administered to infants or children, the dose can be smaller than the dose that is administered to adults.

The proton pump inhibitors and/or antibiotics can be administered orally, topically, parenterally, by inhalation (nasal, oral, aural), or rectally in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrathecal, intrasternal injection, or infusion techniques. Preferably, the proton pump inhibitors are orally administered as tablets.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents, suspending agents (e.g., methylcellulose, Polysorbate 80, hydroxyethylcellulose, acacia, powdered tragacanth, sodium carboxymethylcellulose, polyoxytehylene sorbitan monolaurate and the like), pH modifiers, buffers, solubilizing agents (e.g., polyoxyethylene hydrogenated castor oil, Polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, Macrogol, an ethyl ester of castor oil fatty acid, and the like), preservatives and/or stabilizers. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be used are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally used as a solvent or suspending medium. For this purpose any bland fixed oil can be used including synthetic mono- or diglycerides, in addition, fatty acids such as oleic acid find use in the preparation of injectables. The preparations can be lyophilized by methods known in the art.

Solid dosage forms for oral administration can include capsules, tablets, sublingual tablets, powders, granules, gels, effervescent tablets, effervescent wafers, effervescent capsules, and effervescent powders; most preferably tablets. The solid dosage form can be a solid microencapsulated dosage, such as a microencapsulated powder, microencapsulated granules or a microencapsulated gel. A solid dosage form for oral administration can be prepared by mixing an active principle with filler and, if necessary, binder, disintegrating agent, lubricant, coloring agent, corrigent or the like and converting the obtained mixture into a tablet, coated tablet, granule, powder or capsule. Examples of the filler include lactose, corn starch, sucrose, glucose, sorbitol, crystalline cellulose and silicon dioxide, while those of the binder include polyvinyl

alcohol, polyvinyl ether, ethylcellulose, methylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylstarch and polyvinylpyrrolidone. Examples of the disintegrating agent include starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin and pectin, while those of the lubricant include magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils. The coloring agent can be any one which is permitted to be added to drugs. Examples of the corrigent include cacao powder, mentha herb, aromatic powder, mentha oil, borneol and powdered cinnamon bark. The tablets and granules can be, if necessary, coated with sugar, gelatin or the like. Preferably, the tablets have an enteric coating.

The proton pump inhibitor can be formulated or admixed with, for example, an acid (e.g., citric acid) and a bicarbonate (e.g., sodium bicarbonate) to form an effervescent tablet, capsule, wafer or powder. After addition of the effervescent tablet, capsule, wafer or powder to a liquid (e.g., water, juice) a bicarbonate solution of the proton pump inhibitor is formed.

In other embodiments, the solid dosage form can be packaged as granules or a powder in a pharmaceutically acceptable carrier, where the granules or powder are removed from the packaging and sprinkled on food or mixed with a liquid, such as water or juice. In this embodiment, the active compound can be mixed with flavoring or sweetening agents. The packaging material can be plastic, polyester films, nylon films, polyolefin films, shrink packing films, coated paper, or any material that prevents water or moisture from reaching the granules and/or powder.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, and syrups containing inert diluents commonly used in the art, such as water. The liquid dosage form can be a microencapsulated liquid, including microencapsulated emulsions, microencapsulated solutions, microencapsulated suspensions and microencapsulated syrups. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

In another embodiment, the invention provides compositions comprising at least one proton pump inhibitor and at least one cyclodextrin or a cyclodextrin derivative. The compositions can be in the form of a sachet, granules, micro-pellets, or beads.

Cyclodextrin derivatives are described, for example, in U.S. Patent No. 3,459,731, EP-A-149,197, EP-A-197,571, U.S. Patent No. 4,535,152 or WO 90/12035. Cyclodextrin derivatives include alpha-cyclodextrins, beta-cyclodextrins, and gamma-cyclodextrins. The cyclodextrins can be ethers and/or mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6} alkyl (e.g., methyl, ethyl or isopropyl); hydroxy C_{1-6} alkyl (e.g., hydroxyethyl, hydroxypropyl or hydroxybutyl); carboxy C_{1-6} alkyl (e.g., carboxymethyl or carboxyethyl); C_{1-6} alkyl-carbonyl (e.g., acetyl); C_{1-6} alkyloxycarbonyl C_{1-6} alkyl or carboxy C_{1-6} alkyl-oxy C_{1-6} alkyl (e.g., carboxymethoxypropyl or carboxyethoxypropyl); C_{1-6} alkylcarbonyloxy C_{1-6} alkyl (e.g., 2-acetyloxypropyl). In one embodiment, complexants and/or solubilizers for the proton pump inhibitors are beta-cyclodextrin; 2,6-dimethyl-beta-cyclodextrin, 2-hydroxyethyl-beta-cyclodextrin, 2-hydroxyethyl-gamma-cyclodextrin, 2-hydroxypropyl-gamma-cyclodextrin and (2-carboxy-methoxy)propyl-beta-cyclodextrin. and in particular 2-hydroxypropyl-beta-cyclodextrin. In another embodiment, the cyclodextrin is beta-cyclodextrin.

For administration by aural, oral or nasal inhalation, the compounds and compositions can be delivered from an insufflator, a nebulizer or a pressured pack or other convenient mode of delivering an aerosol spray. Pressurized packs can include a suitable propellant. Alternatively, for administration by aural, oral or nasal inhalation, the compounds and compositions can be administered in the form of a dry powder composition or in the form of a liquid spray.

Suppositories for rectal administration can be prepared by mixing one or more compounds or compositions with suitable nonirritating excipients, such as cocoa butter and/or polyethylene glycols, that are solid at room temperature and that melt at body temperature. Alternatively, enemas can be used to for rectal administration of the active compounds.

For topical administration to the epidermis, the proton pump inhibitors can be formulated as ointments, creams or lotions, or as the active ingredient of a transdermal patch. The compounds and compositions can also be administered via iontophoresis or osmotic pump. Ointments, creams and lotions can be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Alternatively, ointments, creams and lotions can be formulated with an aqueous or oily base and can

also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, and/or coloring agents. As creams or lotions, the proton pump inhibitors can be mixed to form a smooth, homogeneous cream or lotion with, for example, one or more of a preservative (e.g., benzyl alcohol 1% or 2% (wt/wt)), emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water, sorbitol solution. Such topically administrable compositions can contain polyethylene glycol 400. To form ointments, the proton pump inhibitors can be mixed with one or more of a preservative (e.g., benzyl alcohol 2% (wt/wt)), petrolatum, emulsifying wax, and Tenox (II) (e.g., butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g., gauze, can be impregnated with the transdermally administrable compositions for topical application.

The proton pump inhibitors can also be topically applied using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the proton pump inhibitors and laminated to an impermeable backing. For example, the proton pump inhibitors can be administered in the form of a transdermal patch, such as a sustained-release transdermal patch. Transdermal patches can include any conventional form such as, for example, an adhesive matrix, a polymeric matrix, a reservoir patch, a matrix- or monolithic-type laminated structure, and are generally comprised of one or more backing layers, adhesives, penetration enhancers, and/or rate-controlling membranes. Transdermal patches generally have a release liner, which is removed to expose the adhesive/active ingredient(s) prior to application. Transdermal patches are described in, for example, U.S. Patent Nos. 5,262,165, 5,948,433, 6,010,715 and 6,071,531, the disclosures of which are incorporated by reference herein in their entirety.

The proton pump inhibitors can also be topically applied using a transdermal system, such as inotophoresis system. Iontophoresis system is a transdermal delivery system in which a substance bearing a charge (e.g., a proton pump inhibitor) is propelled through the skin by a low electrical current. This method can be used to drive a drug across the skin barrier, as is done with pilocarpine to stimulate sweating in the sweat chloride test for cystic fibrosis. Iontophoresis is an effective and painless method of delivering medication to a localized tissue area, in an infant, by applying electrical current to a solution of the medication. The application of a positive current will drive