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(54) **Title:** SYNERGISTIC COMBINATION OF DICLOFENAC, FAMOTIDINE AND A CARBONATE

(57) **Abstract:** The present invention relates to immediate release fixed dose oral compositions of diclofenac with a gastro protective agent and at least one carbonate and to processes for the preparation thereof. Specifically, the present invention provides an oral immediate release pharmaceutical composition in a single unit dosage form comprising diclofenac or a pharmaceutically acceptable salt thereof, famotidine or a pharmaceutically acceptable salt thereof and a carbonate.

WO 2019/098984 A1

SYNERGISTIC COMBINATION OF DICLOFENAC, FAMOTIDINE AND A CARBONATE

TECHNICAL FIELD

The present invention relates to immediate release fixed dose oral compositions of diclofenac with a gastro protective agent and at least one carbonate and to processes for the preparation thereof.

BACKGROUND ART

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) and has been widely prescribed for the treatment of pain and inflammation. However it is well known that it has the potential to cause gastrointestinal (GI) side effects, such as gastric and duodenal ulcers, bleeding and perforation, oesophageal inflammation and strictures, and small bowel and colonic ulcers and strictures.

Laine L. (Semin. Arthritis Rheumatism. 2002;32:25–32) reports that NSAIDs exert their pharmacological action by inhibiting the synthesis of prostaglandins (PGs) by non-selectively blocking cyclooxygenases 1 and 2 (COX-1 and COX-2) or by selectively blocking COX-2. Inhibition of COX-1 is also responsible, in part, for gastrointestinal side effects, which are the most frequent side effects of NSAIDs.

Gwaltney-Brant S.M. reports that non-selective COX inhibitors have other contributors to their gastrointestinal side effects, which are the carboxylic acid group in compounds, such as aspirin, ibuprofen and diclofenac, and the acidic enolic group in oxicams, such as piroxicam(Charlene A.M., editor. Comprehensive Toxicology. 2nd ed. Elsevier; Oxford, UK: 2010. pp. 159–161). These acidic groups cause local irritation upon oral administration, which can lead to the clinically observed gastrointestinal side effects either independently or in tandem with inhibition of the COX-1 enzyme.

In a report, Lanas et al. (2011) have concluded that more than 90% of the treated patients with osteoarthritis are at increased GI risk, with 60% of them at high risk.

Another important issue related to the use of NSAIDS, in particular diclofenac is the time of onset and duration of action. It is desirable to obtain a rapid onset of action and long duration of analgesic effect for an efficient pain management.

Diclofenac is a proven, commonly prescribed NSAID that has analgesic, anti-inflammatory, and antipyretic properties, and has been shown to be effective in treating a variety of acute and chronic pain and inflammatory conditions. However, diclofenac, similar to other NSAIDs, is associated with an increased risk of serious dose-related GI side effects. Besides, diclofenac is associated with low absorption which influences the analgesic and anti-inflammatory activity and accordingly its effectiveness in the treatment of pain and inflammatory conditions.

Vane JR. et al. (Nat N Biol. 1971;231(25):232–5), Ku EC.et al. (Am J Med. 1986;80(4B):18–23), and Patrono C. et al. (J Clin Invest.2001;108(1):7–13) report that diclofenac belongs to a group of NSAIDs that inhibit both COX-1 and COX-2 enzymes. The binding of NSAIDs to COX isozymes inhibits the synthesis of prostanoids (i.e., prostaglandin [PG]-E2, PGD2, PGF2, prostacyclin [PGI2], and thromboxane [TX] A2). Furthermore, Patrono C. et al. (J Clin Invest.2001;108(1):7–13), Smyth EM et al., and Grosser T. et al. (J Clin Invest. 2006;116(1):4–15) report that PGE2 is the dominant prostanoid produced in inflammation, and the inhibition of its synthesis by NSAIDs is believed to be the main mechanism of the potent analgesic and anti-inflammatory properties of these agents.

Since its introduction in 1973, a number of different diclofenac-containing drug products have been developed with the goal of improving efficacy, tolerability, and patient convenience. Long term use of NSAID is very common for the treatment of pain and inflammatory disease. When they are used more than 4 days, especially a week, the toleration of gastrointestinal side effects by the subject is decreased. In prior art, there is some studies to diminish the side effects of NSAIDs. Some of these studies are about the combination of NSAIDs with gastroprotective agents. For example, European patent EP 0814839 B1 relates to a multiple unit tablet wherein a proton pump inhibitor (preferably omeprazole, esomeprazole, lansoprazole or pantoprazole) in the form of individually enteric coated pellets, at least one NSAID (preferably ibuprofen, diclofenac sodium, piroxicam or naproxen) and optionally pharmaceutically acceptable excipients are compressed together, which is a more expensive and cumbersome manufacturing method. EP1411900 B1 mentions also a multilayer tablet comprising PPIs and an NSAID. International patent application WO 2005076987 A2 relates to a pharmaceutical composition comprising at least one proton pump inhibitor (preferably omeprazole), at least one NSAID and at least one buffering agent.

US patent application US 7482377 B2 discloses a unit dose combination of diclofenac and alkali metal bicarbonates for a faster onset of action, although this particular combination does provide

a solution for fast pain relief, it does not address the issue of GI side effects and pain relief over extended periods of time.

In prior art, it is generally reported that there are still considerable side effects with NSAIDs which are especially taken three times or more in a day. Therefore a particular need exists in prior art for a composition of diclofenac giving fast and long duration of pain relief which is more effective and bioavailable without an increase of dosage and also provides no or fewer side effects.

SUMMARY OF THE INVENTION

The aim of this invention is to develop an oral immediate release pharmaceutical composition comprising diclofenac with one or more agents to reduce the occurrence of gastro-intestinal side effects and at the same time providing an efficient pain management.

The present invention provides an oral immediate release pharmaceutical composition comprising diclofenac or a pharmaceutically acceptable salt thereof, an H2 receptor antagonist, or a pharmaceutically acceptable salt thereof and a carbonate. The pharmaceutical composition comprising said three active ingredients provides numerous advantages over either ingredient alone or combinations containing only two of them, including: a significant reduction in the time of onset of action, pain relief over extended periods of time and reduced side effects.

In one embodiment, said oral immediate release pharmaceutical composition of the present invention comprises diclofenac, or a pharmaceutically acceptable salt thereof, an H2 receptor antagonist selected from the group consisting of famotidine, pabutidine, lafutidine, loxtidine, nizatidine, roxatidine, tiotidine, niperotidine and oxmetidine, or pharmaceutically acceptable salts thereof; famotidine being the preferred H2 receptor antagonist, and an alkali metal bicarbonate.

In another embodiment, said an oral immediate release pharmaceutical composition of the present invention comprises diclofenac or a pharmaceutically acceptable salt thereof, famotidine or a pharmaceutically acceptable salt thereof and potassium bicarbonate.

Furthermore, the present invention provides the use of composition of diclofenac, an H2 receptor antagonist and a carbonate for the treatment of inflammation and pain.

The present invention further relates to an oral immediate release pharmaceutical composition comprising a combination of disclofenac, an H2 receptor antagonist and an alkali metal bicarbonate and at least one pharmaceutically acceptable carrier.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an oral immediate release pharmaceutical composition comprising diclofenac or a pharmaceutically acceptable salt thereof, an H2 receptor antagonist or a pharmaceutically acceptable salt thereof and an alkali metal carbonate or bicarbonate.

The combination of an H2 receptor antagonist with diclofenac has the benefit of diminishing the gastro-intestinal side effects associated with diclofenac, and creates a treatment that can be used for longer periods of time due to the decreased side effects. Furthermore, the combination of an H2 receptor antagonist, preferably famotidine with diclofenac, surprisingly increases the permeability and rate of absorption of the diclofenac. In other words, said combination increases Cmax and AUC values of diclofenac and decreases the Tmax.

For the purposes of the present invention Tmax means the amount of time that a drug takes to reach the peak concentration in serum; Cmax is the peak serum concentration of a drug; and AUC (the area under the curve) represents the area under the plasma concentration curve, also called the plasma concentration-time profile, a measure of total systemic exposure to the drug.

The addition of a carbonate to the combination of H2 receptor antagonist and diclofenac has added further synergistic effect, whereby higher plasma levels of diclofenac is obtained in a shorter period of time compared to the combination of H2 receptor antagonist and diclofenac. Furthermore, the Cmax and AUC of diclofenac have increased compared to the combination of two active ingredients, namely famotidine (an H2 receptor antagonist) and diclofenac.

In one embodiment, the present invention provides an oral immediate release pharmaceutical composition in a single unit dosage form comprising diclofenac or a pharmaceutically acceptable salt thereof, famotidine or a pharmaceutically acceptable salt thereof and a carbonate; wherein famotidine is in an amount of 20 to 55% based on the weight of diclofenac.

Accordingly, it has been surprisingly found that the dissolution rate of pharmaceutically active ingredients comprised in the pharmaceutical composition of the present invention is extremely increased while they are used in combination. Especially the addition of carbonate provides rapid dissolution and by extension rapid absorption of diclofenac and famotidine. Increase in absorption influences directly the circulating drug concentration (blood concentration) and result

in a more successful treatment modality. Thus, higher synergistic effect and gastro intestinal protection are obtained when diclofenac and famotidine are combined with a carbonate.

Preferably, dissolution of diclofenac is considerably increased while used in combination with famotidine.

According to one embodiment, the present invention provides An oral immediate release pharmaceutical composition in a single unit dosage form comprising diclofenac or a pharmaceutically acceptable salt thereof, famotidine or a pharmaceutically acceptable salt thereof and a carbonate; wherein famotidine is in an amount of 20 to 55% based on the weight of diclofenac,

- wherein at least 60% of famotidine and 60% of diclofenac are released within 20 minutes when subjected to an in vitro dissolution test according to US Pharmaceopoeia at about 50 rpm in 900 mL of pH from 6.8 to 7.4, preferably pH 7.2 phosphate buffer and at 37.0°C. ± 0.5°C, and/or,
- wherein at least 60% of famotidine and 60 % of diclofenac are released within 20 minutes when subjected to an in vitro dissolution test according to US Pharmaceopoeia at about 50 rpm in 900 mL of pH 4.5 phosphate buffer and at 37.0°C. ± 0.5°C.

In one preferred embodiment, at least 70% of famotidine and at least 70% of diclofenac are released into a solution with a pH of about 4.5 or a pH from 6.8 to 7.4, preferably pH 7.2 within 20 minutes under in vitro assay conditions.

According to one preferred embodiment of the present invention, the pharmaceutical composition is formulated without an enteric or other type of coating that would delay the release of the active ingredients. As an example of an immediate release profile; in one embodiment the unit dosage form is formulated so that famotidine and diclofenac are released rapidly under both neutral pH conditions, e.g. an aqueous solution at about pH 6.8 to about pH 7.4, preferably e.g. pH 7.2. As used herein, “immediate” means that both active ingredients are significantly released into solution within 20 minutes under in vitro assay conditions according to the present invention.

In one embodiment of the present invention, both APIs, diclofenac and famotidine, are significantly released into solution within 20 minutes under in vitro assay conditions, wherein at least about 60% of both diclofenac and famotidine by weight in the unit dosage form is released

within 20 minutes, preferably at least about 70%, more preferably at least about 80%, and most preferably at least about 90%.

The present invention provides an oral immediate release pharmaceutical composition in a single unit dosage form wherein diclofenac and famotidine are significantly released into solution within 20 minutes under in vitro assay conditions; such that at least 60% of the weight of the API in the unit dosage form is released, or preferably at least 65%, or more preferably at least 70% is released under neutral and acidic pH conditions

Diclofenac and famotidine dissolution and release rate from the formulation was measured in vitro using a USP type II dissolution apparatus (paddle) according to US Pharmacopoeia at pH 7.2 and also at pH 4.5 to better simulate the upper gastro-intestinal tract. The human stomach has a pH of about 1.2 to 3 and the transit time of an oral drug product can be from 20 minutes to 240 minutes, the pH of the intestines is about 6 to 7.5 and the transit time is about 1 to 2 hours, accordingly the composition of the present invention provides a highly soluble diclofenac and gastroprotective agent combination throughout the gastro intestinal tract, solving the major issue for the absorption of diclofenac and famotidine.

In one embodiment of the present invention combination comprises potassium or sodium salt of diclofenac, most preferably potassium salt due to the fact that potassium salt is associated with a faster absorption and as a result of this a more rapid onset of pain relief is achieved compared to the sodium salt.

In one embodiment of the present invention combination comprises famotidine, or pharmaceutically acceptable salt thereof as an H2 receptor antagonist.

Famotidine protects the gastric mucosa against irritation, thus it is used in the treatment of gastrointestinal diseases.

In another embodiment of the present invention, the pharmaceutical composition comprises a carbonate wherein the carbonate is selected from the group consisting of sodium carbonate, sodium bicarbonate, calcium carbonate, calcium bicarbonate, magnesium carbonate, ammonium carbonate, ammonium bicarbonate, potassium bicarbonate, potassium carbonate, sodium glycine carbonate, disodium glycine carbonate, arginine carbonate, arginine bicarbonate, lysine carbonate or derivatives thereof. In the preferred embodiment of the present invention, the carbonate is arginine carbonate or arginine bicarbonate, potassium or sodium carbonate, or potassium or sodium bicarbonate, or calcium carbonate or calcium bicarbonate.

In another most preferred embodiment of the present invention the carbonate is analkali metal bicarbonate or amino acid based bicarbonate.

In the most preferred embodiment of the present invention the carbonate is selected from an alkali metal bicarbonate; potassium bicarbonate or sodium bicarbonate or calcium bicarbonate and preferably potassium bicarbonate or sodium bicarbonate and more preferably potassium bicarbonate. Potassium bicarbonate (also known as potassium hydrogen carbonate or potassium acid carbonate) is a colorless, odorless, slightly basic, salty substance used to neutralize acid in the stomach.

The pharmaceutical dosage forms of the present invention may comprise active components in the form of a racemic mixture, or in the form of substantially pure enantiomers or salts thereof.

In one embodiment of the present invention the combination comprises diclofenac, famotidine and an alkali metal bicarbonate. It has now been found that said combination provides the most efficient diclofenac treatment when a fast onset of action and over an extended period of time pain reduction is needed. The reason why this combination can be stated as the most efficient diclofenac treatment is that the results obtained in the current study demonstrate a superior, surprising effect with a Cmax over 1400 ng/ml, a Tmax below 10 minutes and an AUC over 10.000 ng.h/ml.in a 12 hour period. These results clearly demonstrate the synergistic effect between alkali metal bicarbonates, H2 receptor antagonists and diclofenac. Thus the present invention provides a gastroprotective, antiarthritic/analgesic combination with fast and extended period of time pain relief and reduced risk of developing gastrointestinal damage such as ulcers, erosions and hemorrhages. In other words, the present invention is able to provide a longer period of therapeutic effect due to the slow elimination of diclofenac as evidenced by its high AUC value despite its instant release and fast onset of action.

The combination of the present invention is synergistically effective for the treatment of inflammation and pain by reducing gastrointestinal side effects, therefore having a prophylactic effect on the primary side effect of diclofenac administration while increasing diclofenac's Cmax and AUC and decreasing its Tmax. The single unit pharmaceutical dosage forms of the present invention would also allow for relatively safe administration of high doses of diclofenac and long administration duration, which would be especially important for patients who have acute pain attacks in a period shorter than 6 months but also for patients who have pain and inflammation related problems over a long period of time.

In one embodiment of the present invention, the combination comprises between12.5 to 100 mg, preferably 12.5 to 60 mg, more preferably 25 to 55 mg or 25 to 50 mg, most preferably 50 mg of diclofenac or pharmaceutically acceptable salt thereof.

In one embodiment of the present invention, the combination comprises between 10 to 60 mg, preferably 20 to 40 mg or 15 to 30 mg, more preferably 20 mg of famotidine or pharmaceutically acceptable salt thereof.

In one embodiment of the present invention, the combination comprises between 5 to 200 mg, preferably 10 to 120 mg, more preferably 20 to 80 and most preferably 30 to 50 mg of potassium bicarbonate.

Further described is a pharmaceutical unit dosage form, preferably a tablet or capsule, wherein the active ingredients consist of:

a) between 12.5 to 100 mg, preferably 12.5 to 60 mg, more preferably 25 to 50 mg of diclofenac or pharmaceutically acceptable salt thereof,
b) between 10 to 60 mg, preferably 20 to 40 mg or 15 to 30 mg of famotidine or pharmaceutically acceptable salt thereof,
c) between 5 to 200 mg, preferably 10 to 120 mg, more preferably 20 to 80 and most preferably 30 to 50 mg of potassium bicarbonate.

Further described is a pharmaceutical unit dosage form, preferably a tablet or capsule, wherein the active ingredients consist of:

d) 50 mg of diclofenac or pharmaceutically acceptable salt thereof,
e) 20 mg of famotidine or pharmaceutically acceptable salt thereof,
a) 36 mg of potassium bicarbonate.

Oral dosage forms of the present invention may comprise suitable diluents, binders, lubricants, disintegrating agents, surfactants, glidants, sweetening agents, coloring agents and coating agents.

Examples of pharmaceutically acceptable diluents include, but not limited to, magnesium stearate, lactose, microcrystalline cellulose, starch, pre-gelatinized starch, calcium phosphate, calcium sulfate, calcium carbonate, mannitol, sorbitol, xylitol, sucrose, maltose, fructose and dextrose.

Examples of pharmaceutically acceptable binders include, but not limited to, starches, natural sugars, corn, sweeteners, natural and synthetic gums, cellulose derivatives, gelatin, PVP, polyethylene glycol, waxes, sodium alginate, alcohols and water.

Examples of pharmaceutically acceptable lubricants include, but not limited to, metallic stearates, metallic lauryl sulfates, fatty acids, fatty acid esters, fatty alcohols, paraffins, hydrogenated vegetable oils, polyethylene glycols, boric acid, sodium benzoate, sodium acetate, sodium chloride and talk.

Example of pharmaceutically acceptable glidants include, but not limited to, silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate, calcium silicate, magnesium silicate, colloidal silicon dioxide and silicon hydrogel.

Examples of pharmaceutically acceptable disintegrating agents include, but not limited to, starches, cellulose derivatives, PVP, crospovidone, clays, ion-exchange resins, alginic acid and sodium alginate.

Examples of pharmaceutically acceptable surfactants of the present invention include, but not limited to, sulfates, sulfonates, phosphates, carboxylates, primary-secondary-tertiary amines, quaternary ammonium compounds, fatty alcohols, sugar esters of fatty acids, glycerides of fatty acids, polyoxy ethylene glycol alkyl ethers, polisorbates, sorbitan alkyl esters and poloxamers.

In one embodiment of the present invention, pharmaceutical dosage form is an immediate release tablet comprising diclofenac potassium, famotidine and potassium bicarbonate as active compounds; lactose, microcrystalline cellulose, hydroxypropyl cellulose, crospovidone, colloidal silicon dioxide and magnesium stearate as inactive ingredients.

In one embodiment, the pharmaceutical composition of the present invention comprises a metallic stearate, preferably magnesium stearate as lubricant and/or colloidal silicon dioxide as glidant. Thus, content uniformity problem of low dose famotidine and higher dose diclofenac is decreased and flow and process ability of the dosage form is increased. In one embodiment, the metallic stearate, preferably magnesium stearate and/or colloidal silicon dioxide are in an amount of from 3 to 30% by weight of famotidine.

In one embodiment of the present invention, the pharmaceutical composition comprises

a) diclofenac or a pharmaceutically acceptable salt thereof, famotidine and an alkali metal carbonate or bicarbonate as active ingredients, and

b) one or more pharmaceutically acceptable excipients selected from the group consisting of glidants and lubricants wherein said excipient(s) is present in an amount of from 3% to 30% by weight of famotidine, preferably in an amount of from 3% to 20% by weight of famotidine.

In another embodiment of the present invention, the pharmaceutical composition comprises

a) diclofenac or a pharmaceutically acceptable salt thereof, famotidine and an alkali metal carbonate or bicarbonate as active ingredients, and

b) magnesium stearate as a lubricant and colloidal silicon dioxide as a glidant.

It has been also found that an homogenous composition with content uniformity is provided although the large dose difference among the active ingredients. In addition, for an homogenous composition, the present invention provides the method of direct compression. In one embodiment, the composition of the present invention is prepared by direct compression method, wherein the active ingredients and excipients are mixed for at least 5 minutes.

In one embodiment, the present invention is related to a method for preparing said pharmaceutical composition which comprises the following steps:
a) sieving diclofenac, lactose, HPC and potassium bicarbonate together and mixing for at least 5 minutes,
b) adding famotidine and microcrystalline cellulose and mixing for at least 5 minutes,
c) adding crospovidone and mixing at least 5 minutes,
d) sieving colloidal silicon dioxide and microcrystalline cellulose and mixing for at least 5 minutes,
e) compressing and coating tablets.

In one embodiment, the composition of the present invention can be administered in various dosage forms and strength in pharmaceutically effective amount. A unit dosage form containing the combination of present invention may be in the form of a tablet, capsule, pellet, granule, effervescent tablet, tablet in tablet, tablet in capsule or powder, preferably tablet, granule, capsule or powder form.

In another embodiment of the present invention a faster onset of pain relief or faster antipyretic/anti-inflammatory effect beginning less than 20 minutes after oral administration of the combination comprising diclofenac, famotidine and sodium or potassium bicarbonate is obtained due to the increased rate of diclofenac absorption potentiated by famotidine and also

due to the synergistic, pharmacokinetic effect created by alkali metal bicarbonates and famotidine administered together with diclofenac.

In another embodiment of the present invention an oral single unit pharmaceutical dosage form comprises diclofenac, famotidine and potassium or sodium bicarbonate, wherein diclofenac combined with famotidine and alkali metal bicarbonates creates higher than usual blood concentration of diclofenac in the blood stream compared to the oral administration of diclofenac alone.

In another embodiment of the present invention administration of a single unit pharmaceutical dosage form comprises the combination of diclofenac, famotidine and potassium or sodium bicarbonate for use in the treatment of inflammation or pain caused by muscular or skeletal system diseases.

In one embodiment, the composition of the present invention is used for the treatment of osteoarthritis, rheumatoid arthritis, acute musculoskeletal pain, dysmenorrhea, headache, toothache, fever, muscular pain, back pain, shoulder pain, bursitis, tendinitis, epicondylitis ichronic polyarthritis, ankylosing spondilytis, gout attacks, extra-articular rheumatism, post-traumatic and postoperative pain.

In another embodiment of the present invention administration of a single unit pharmaceutical dosage form comprises the combination of diclofenac, famotidine and potassium or sodium bicarbonate to attain fast pain or inflammation relief under 20 minutes after oral administration.

In another embodiment of the present invention administration of a single unit pharmaceutical dosage form comprises the combination of diclofenac, famotidine and potassium or sodium bicarbonate wherein inflammation or pain is caused by chronic polyarthritis, ankylosing spondilytis, osteoarthritis, gout attacks, extra-articular rheumatism, post-traumatic and postoperative pain, rheumatoid arthritis and dysmenorrheal.

In another embodiment of the present invention administration of a single unit pharmaceutical dosage form comprises the combination of diclofenac, famotidine and potassium or sodium bicarbonate to create a fast anti-pyretic effect.

In another embodiment of the present invention administration of a single unit pharmaceutical dosage form comprises the combination of diclofenac, famotidine and potassium or sodium bicarbonate wherein the oral dosage form can be administered between 2 to 4 times a day.

In one embodiment of the present invention an oral pharmaceutical fixed-dose composition is provided which comprises the combination of a) diclofenac b) an H2 receptor antagonist, preferably famotidine or a pharmaceutically acceptable salt thereof, and c) an alkali metal carbonate or bicarbonate, preferably potassium or sodium bicarbonate, and one or more pharmaceutically acceptable excipients.

In another embodiment of the present invention, pharmaceutical composition comprises diclofenac, famotidine and potassium or sodium bicarbonate wherein the Tmax of diclofenac is less than 30 minutes, preferably less than 20 minutes.

In another embodiment of the present invention, pharmaceutical composition comprises diclofenac, famotidine and potassium or sodium bicarbonate wherein the Cmax of diclofenac is between 1200 to 1500 ng/ml, preferably over 1300 ng/ml.

In another embodiment of the present invention, pharmaceutical composition comprises diclofenac, famotidine and potassium or sodium bicarbonate wherein the AUC of diclofenac within 12 hours of administration is between 10,000 to 10,600 ng/ml.h, preferably over 9,500 ng/ml.h.

In another embodiment of the present invention, pharmaceutical composition comprises diclofenac, famotidine and potassium or sodium bicarbonate wherein famotidine and potassium or sodium bicarbonate increases the Cmax of diclofenac by at least 5%.

In another embodiment of the present invention, pharmaceutical composition comprises diclofenac, famotidine and potassium or sodium bicarbonate wherein famotidine and potassium or sodium bicarbonate creates an AUC at least 10% higher than the diclofenac administered alone in a 12 hour period.

In another embodiment of the present invention, pharmaceutical composition comprises diclofenac, famotidine and potassium or sodium bicarbonate wherein famotidine creates a Tmax of less than about 25 minutes for diclofenac.

In another embodiment of the present invention, an oral single unit pharmaceutical dosage form with an instant release profile comprises diclofenac, famotidine and potassium or sodium bicarbonate wherein at least 25% of diclofenac and at least 25% of famotidine is released in the stomach before reaching the intestines.

EXAMPLES

Preparation of the film tablet formulation comprising diclofenac potassium, famotidine and potassium bicarbonate

Diclofenac Potassium / Famotidine 50mg / 20mg Film Tablet	
Direct Compression	
Ingredients	mg/tb.
Diclofenac potassium	50
Potassium bicarbonate	36
Famotidine	20
Lactose granule	28
Microcrystalline cellulose tip 102	67
Hydroxypropyl cellulose	8
Crospovidone	10
Colloidal silicone dioxide	2
Magnessium stearate	2
Weightining of Core Tablet	223
Aquarius™ Preferred HSP BPP316041 Green	7
Weightining of Coated Tablet	230

Manufacturing Directions (Direct compression)

1. Sieve Diclofenac potassium, lactose granule, hydroxypropyl cellulose and potassium bicarbonate together and mix for at least 5 min
2. Add famotidine and microcrystalline cellulose and mix for at least5 min
3. Add crospovidone and mix for at least 5 min
4. Sieve colloidal silicone dioxide and microcrystalline cellulose together and mix for at least 5 min
5. Add magnessium stearate to the mixture and mix for at least 2 minutes.
6. Compress tablets,
7. Coat tablets with coating solution (Preferred HSP BPP316041 Green)

Content Uniformity Test:

The tablets shown in Example were used in this test. The content uniformity of 10 dosage units randomly chosen, were assessed according to the USP requirements for content uniformity.

The amount of active ingredients in each of the 10 tested tablets were assayed by using HPLC wherein the method for the HPLC assay was based on the article "Simultaneous RP-HPLC determination of diclofenac potassium and famotidine in pharmaceutical preparations" (January 2011). The content uniformity assay for 10 tablets for diclofenac potassium was between 99,4% (49.7mg) and 100,72% (50,36mg) The content uniformity assay for famotidine was between 98.5% (19.7mg) and 99,6% (19,92) All of the HPLC results were well within the range of 85% to115% for the APIs in the pharmaceutical composition of the present invention. And furthermore the RSD (relative standard deviation) between the tablets was far less than 6% for both diclofenac and famotidine.

DISSOLUTION STUDY OF DIFFERENT COMBINATIONS OF DICLOFENAC WITH POTASSIUM BICARBONATE AND FAMOTIDINE

The aim of this study was to determine the dissolution profile of fixed dose oral pharmaceutical compositions of diclofenac with famotidine and potassium bicarbonate The dissolution study test is executed in vitro using a USP type II dissolution apparatus (paddle) based on the US Pharmacopoeia at pH 7.2 and also at Ph 4.5 to better simulate the upper gastro-intestinal tract.

Dissolution Apparatus:	Apparatus II (Paddles)
Dissolution Medium:	pH 7.2 & 4.5
Dissolution Medium Volume:	900 mL
Temperature in Vessel:	37.0° C. ± 0.5° C.
Speed:	50 RPM
Sampling Time:	5 min, 10 min, 15 min, 20 min, 30 min, 45 min, 60 min
Sampling Volume:	1 mL analysed by HPLC

The unit dosage form according to the present invention is added to the vessel and dissolution is started. At the sampling times specified above, a portion (e.g., 1ml) of medium is withdrawn and the amount of API in solution is determined using routine analytical methods (e.g., HPLC).

Comparative Example: Film tablet formulation comprising diclofenac potassium and famotidine

Film Tablet	Weight (mg) / unit dose
Diclofenac potassium	50
Famotidine	20
Lactose granule	64

Microcrystalline cellulose	67
Hydroxypropyl Cellulose	8
Crospovidone	10
Colloidal silicon dioxide	2
Magnesium stearate	2
Coating based on copovidone with cellulosic polymers	7

RESULTS

Diclofenac Potassium (DP) (50 mg) and Famotidine (Fam) (20 mg) combination tablet (comparative example) and Diclofenac Potassium (DP) (50 mg), Famotidine (Fam) (20 mg) and potassium bicarbonate (Pb) (36 mg) (example) were released at a higher percentage and dissolved faster when compared with tablet formulation comprising only diclofenac potassium at pH 7.2 as evidenced by Tables 1-2 and Figures 1-2. As seen in Table 2 and Figure 2, the dissolution percentage of diclofenac potassium alone between 5 and 15 minutes is extremely low at pH 4.5 (only 42.71% at 60 min). It is clearly seen that the solubility rates of the composition comprising diclofenac potassium, famotidine and potassium carbonate according to the present invention were surprisingly superior at pH 4.5 when compared with the diclofenac potassium tablets. It is clearly demonstrated the synergy created by the addition of both a carbonate (potassium bicarbonate) and a gastro protective agent (famotidine).

Dissolution and release rate from the formulation was measured in vitro using a USP type II dissolution apparatus (paddle) according to US Pharmacopoeia at pH 7.2 and also at pH 4.5 to better simulate the upper gastro-intestinal tract. The surprising results of the study clearly demonstrate a good dissolution profile throughout a pH from 4.5 to 7.2 which means that the composition of the present invention is released throughout the gastro intestinal tract. It is of special importance that famotidine begins to be significantly released within 30 minutes under in-vitro assay conditions at a pH of about 4.5, as the significant release of famotidine at such low pH conditions means that the absorption of famotidine will begin sooner and the gastro protective affect will begin before the majority of diclofenac is released, so famotidine can induce it's protective effect for the GI side effects of diclofenac before the majority of diclofenac is released.

Table 1. Dissolution Properties of Diclofenac potassium alone and in combination at pH 7.2.

Soluble API % (pH 7.2 Buffer)				
n	**Min**	**Ref DP USP**	**Dic+Fam**	**Dic + Fam + PB**
1	5	10.69	20.74	81.50
2	10	26.03	39.40	80.52
3	15	42.78	69.04	81.74
4	20	59.75	93.16	82.41
5	30	78.67	85.89	80.42
6	45	90.20	81.75	82.31
7	60	90.75	82.44	82.37

Table 2. Dissolution Properties of Diclofenac potassium alone and in combination at pH 4.5.

Soluble API % (pH 4.5)				
n	**Min**	**Ref Dic USP**	**Dic + Fam**	**Dic + Fam + PB**
1	5	0.00	0.93	75.58
2	10	0.58	4.16	72.33
3	15	3.43	7.29	76.65
4	20	11.10	9.23	77.23
5	30	22.47	11.13	79.94
6	45	38.35	12.36	79.52
7	60	42.71	14.60	79.70

Details of the study proving the synergistic effect between diclofenac, famotidine and potassium bicarbonate

Studying the effects of famotidine and potassium bicarbonate on the pharmacokinetics of diclofenac in rats

The primary objective of the test was to compare the pharmacokinetics of diclofenac potassium when used as a single active compound with diclofenac potassium in combination with famotidine and/or potassium bicarbonate. In this experimental study, the aim was to observe how the addition of potassium bicarbonate to diclofenac and famotidine would change the pharmacokinetic properties of diclofenac potassium when diclofenac potassium is given alone or in combination with famotidine and/or potassium bicarbonate.

MATERIALS AND METHODS

Chemicals and Reagents

Diclofenac potassium, famotidine, potassium bicarbonate.

Animals

Male Wistar rats (240-260 g) were used in the study. The rats were maintained in an air-conditioned animals quarter at a temperature of 22 ± 2 °C and a relative humidity of 50 ± 10 %. Food and water were allowed ad libitum. The animals were acclimatized to the facilities for five days, and then fasted with free access to water for 12 h prior to the experiment. All the animals were housed under similar conditions.

Drug Administration

Bioavailability and pharmacokinetics of diclofenac were studied in all the normal state of rats following an oral administration of 1 mg/kg diclofenac potassium, 0.4 mg/kg famotidine and 0.72 mg/kg or 0.36 mg/kg potassium bicarbonate in different occasions. Each rat was further subjected to similar studies after administration of diclofenac potassium and/ or diclofenac in combination with famotidine. A total of 30 rats were used in the study divided into 5 groups, each group was administered; diclofenac alone, or 4 different combinations of diclofenac as outlined below.

Six male and/or female rats per group were lavaged with 1 mg/kg Diclofenac potassium and combinations at a dosing volume of 2 ml/kg. Blood (0.2 ml) was taken from the tail vein prior to administration of test substances (0 h) and after 0.083, 0.167, 0.25, 0.5, 1, 2, 4, 8 and 12h.

Extraction of Blood Samples

Blood samples were collected in tubes containing %5 Na2-EDTA and kept on ice until 50 ul dichloromethane was added and they were centrifuged at 7000 x g for 5 min at 4°C and supernatants were collected for LC/MSMS analysis.

Evaluation of the Results

Table 3 shows the Cmax and Tmax values of diclofenac, diclofenac + famotidine, diclofenac + 0,72mg/kg potassium bicarbonate, diclofenac + famotidine + 0,72 mg/kg potassium bicarbonate and diclofenac + famotidine + 0,36mg/kg potassium bicarbonate. As it can be seen there is an evident increase in the Cmax values of diclofenac when it is used in combination with

famotidine or potassium bicarbonate or famotidine + potassium bicarbonate. The Cmax of diclofenac when used as a single active ingredient is 1.262 mg/ml, whereas it is 1.457 ng/ml when used in combination with famotidine and 0,72mg/kg potassium bicarbonate. Similarly, Tmax values in Table 3 also show that combinations of the present invention provide a faster pain relief compared to the diclofenac alone. Tmax of diclofenac when used as a single active ingredient is 0,25h, whereas it is 0,083h when used in combination with famotidine and potassium bicarbonate. Combinations of diclofenac + famotidine and diclofenac + potassium bicarbonate also provides efficient pain management compared to diclofenac alone but the combinations of three active ingredients provide the most efficient diclofenac treatment in general by reducing the side effects as well.

In addition to Table 3, Table 4 provides 12 hour AUC values of diclofenac. The combination of diclofenac + famotidine + 0,72mg/kg potassium bicarbonate has the highest AUC value, meaning this combination provides a long duration of pain and inflammation relief. Diclofenac + Famotidine + 0,36mg/kg potassium bicarbonate combination also provides similar results whereas AUC of diclofenac alone shows that when diclofenac is taken alone, duration of pain management is much shorter compared to the combinations.

Table 3. Blood Concentrations of Diclofenac Potassium

Time	0.083 h	0.25 h	0.5 h	1 h	2 h	4 h	8 h	12 h
Groups								
Diclofenac-K	1.096 ±0.054	1.262 ±0.048	1.078 ±0.137	0.943 ±0.015	0.600 ±0.159	0.600 ±0.015	0.578 ±0.033	0.486 ±0.092
Dic-K + Fam	1.331 ±0.056	1.289 ±0.041	1.216 ±0.052	0.948 ±0.027	0.851 ±0.037	0.816 ±0.023	0.661 ±0.177	0.584 ±0.045
Dic-K +0,72mg/kg PB(36mg)	1.746 ±0.22	1.453 ±0.182	1.388 ±0.133	0.967 ±0.0181	0.858 ±0.075	0.921 ±0.2185	0.642 ±0.076	0.664 ±0.218
Dİc-K+ Fam + 0,72mg/kg PB(36mg)	1.457 ±0.053	1.359 ±0.099	1.269 ±0.148	1.059 ±0.136	0.875 ±0.079	0.978 ±0.13	0.808 ±0.128	0.695 ±0.129
Dic-K + Fam + 0,36mg/kgPB (18mg)	1.277 ±0.075	1.166 ±0.116	1.06 ±0.291	0.901 ±0.063	1.022 ±0.067	0.918 ±0.021	0.832 ±0.029	0.672 ±0.027

Table 4. Pharmacokinetic Parameters of Diclofenac in blood

Groups	T_{max}	C_{max} (ng/ml)	AUC 12 hours(ng/ml.h)
Diclofenac-K	0.25	1262 ± 0.048	7.5101
Dic-K + Fam	0.083	1331 ± 0.056	9.0834
Dic-K + 0,72mg/kg PB(36mg)	0.083	1746 ± 0.22	9.6551
DİC-K + Fam + 0,72mg/kg PB(36mg)	0.083	1457 ± 0.053	10.5436
Dic-K + Fam + 0,36 mg/kg PB(18mg)	0.083	1277 ± 0.075	10.382

The results of the study prove the superior treatment modality of the present invention with the surprising effect of longer lasting therapeutically effective blood concentrations (AUC) coupled with the diminished gastro intestinal side effects due to the presence of famotidine and carbonate in the combinations.

CLAIMS

1. An oral immediate release pharmaceutical composition in a single unit dosage form comprising diclofenac or a pharmaceutically acceptable salt thereof, famotidine or a pharmaceutically acceptable salt thereof and a carbonate; wherein famotidine is in an amount of 20 to 55% based on the weight of diclofenac,

- wherein at least 60% of famotidine and 60% of diclofenac are released within 20 minutes when subjected to an in vitro dissolution test at about 50 rpm in a solution volume of 900 mL at a pH of 7.2 and at 37.0°C. ± 0.5°C, and/or,
- wherein at least 60% of famotidine and 60 % of diclofenac are released within 20 minutes when subjected to an in vitro dissolution test at about 50 rpm in a solution volume of 900 mL at a pH of 4.5 and at 37.0°C. ± 0.5°C.

2. The pharmaceutical composition according to claim 1, wherein diclofenac is in an amount of from 12.5 to 100 mg.

3. The pharmaceutical composition according to claim 2, wherein diclofenac is in an amount of from 25 to 55 mg.

4. The pharmaceutical composition according to any one of claims 2 to 3, wherein diclofenac is diclofenac sodium or diclofenac potassium.

5. The pharmaceutical composition according to any one of claims 1 to 4, wherein famotidine is in an amount of from 15 to 30 mg.

6. The pharmaceutical composition according to any one of claims 1 to 5, wherein the carbonate is in an amount of from 5 to 200 mg.

7. The pharmaceutical composition according to claim 6, wherein the carbonate is sodium carbonate, sodium bicarbonate, calcium carbonate, calcium bicarbonate, magnesium carbonate, ammonium carbonate, ammonium bicarbonate, potassium carbonate, potassium bicarbonate, sodium glycine carbonate, disodium glycine carbonate, arginine carbonate, arginine bicarbonate, lysine carbonate or derivatives thereof.

8. The pharmaceutical composition according to claim 7, wherein the carbonate is sodium bicarbonate or potassium bicarbonate.

9. The pharmaceutical composition according to any one of the preceding claims, wherein the single unit dosage form is selected from tablet, capsule, granule or powder form.

10. The pharmaceutical composition according to any one of the preceding claims, further comprising one or more excipients selected from the group consisting of diluents, binders, lubricants, glidants, disintegrating agents, surfactants, sweetening agents, coloring agents and coating agents.

11. The pharmaceutical composition according to claim 10, wherein the lubricant is selected from the group consisting of metallic stearates, metallic lauryl sulfates, fatty acids, fatty acid esters, fatty alcohols, paraffins, hydrogenated vegetable oils, polyethylene glycols, boric acid, sodium benzoate, sodium acetate, sodium chloride and talk.

12. The pharmaceutical composition according to claim 10, wherein the lubricant is a metallic stearate.

13. The pharmaceutical composition according to claim 12, wherein the lubricant is magnesium stearate.

14. The pharmaceutical composition according to any one of claims 10 to 13, wherein the glidant is colloidal silicon dioxide.

15. The pharmaceutical composition according to any one of the preceding claims, wherein the glidant or lubricant is present in an amount of from 3 to 30% by weight of famotidine.

16. The pharmaceutical composition according to claim 15, wherein the glidant or the lubricant are present in an amount of from 3 to 20% by weight of famotidine.

17. The pharmaceutical composition according to any preceding claims for use in a method for the treatment of pain and inflammation.

18. The pharmaceutical composition for use according to claim 17, wherein the method is for the treatment of osteoarthritis, rheumatoid arthritis, acute musculoskeletal pain, dysmenorrhea, headache, toothache, fever, muscular pain, back pain, shoulder pain, bursitis, tendinitis, epicondylitis ichronic polyarthritis, ankylosing spondilytis, gout attacks, extra-articular rheumatism, post-traumatic and postoperative pain.

19. The pharmaceutical composition for use according to claims 17 or 18, wherein the pharmaceutical composition is administered 2 to 4 times a day.

Figure 1. Dissolution profile of Diclofenac potassium alone and in combination in pH 4.5.

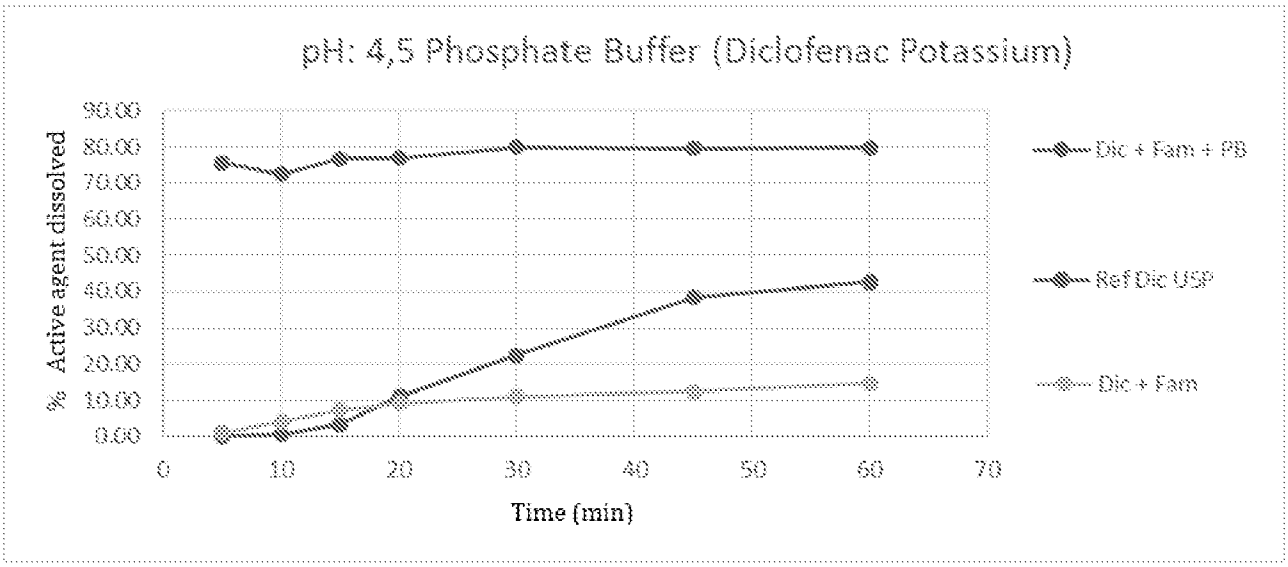
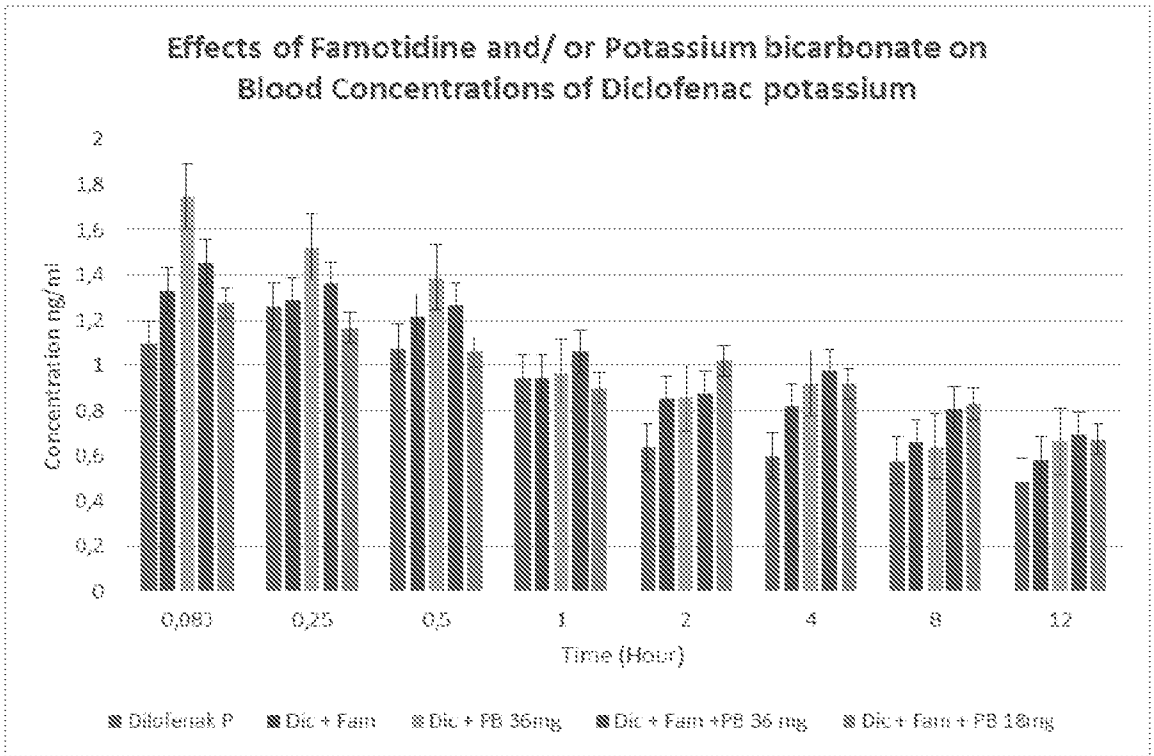


Figure 2



INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2018/050701

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/46 A61K9/20 A61K31/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2005/147671 A1 (REINER ALBERTO [IT] ET AL) 7 July 2005 (2005-07-07) page 1, paragraphs 11, 12 page 5; example 11	1-19
Y	WO 2004/064815 A1 (SMARTRIX TECHNOLOGIES INC [CA]; ZERBE HORST G [CA]; SZABO POMPILIA [CA) 5 August 2004 (2004-08-05) page 20, lines 10-20	1-19
Y	SURYAKUMAR J ET AL: "FAMOTIDINE AFFECTS THE PHARMACOKINETICS OF DICLOFENAC SODIUM", DRUG INVESTIGAT, ADIS INTERNATIONAL, NZ, vol. 4, no. 1, 1 January 1992 (1992-01-01) , pages 66-68, XP008031074, ISSN: 0114-2402 the whole document	1-19

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

☒ See patent family 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
20 March 2019	27/03/2019

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1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2018/050701

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