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(54) **Title:** COMBINED IMMEDIATE RELEASE FORMULATIONS OF NSAIDS

(57) **Abstract:** The present invention is related to a pharmaceutical formulation which comprises NSAID having antiinflammatory, analgesic and antipyretic effect together with an H2 receptor antagonist used for preventing and minimizing the gastrointestinal side effects of NSAID. According to another aspect, the present invention relates to the fact, that the pharmaceutical formulation comprising NSAID as the first drug substance and H2 receptor antagonist as second active substance is a novel solid oral multilayer tablet



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DESCRIPTION

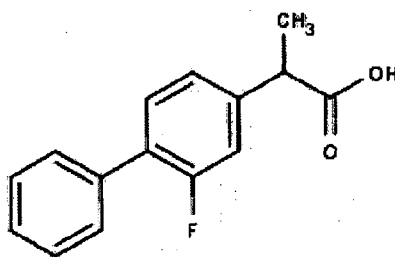
COMBINED IMMEDIATE RELEASE FORMULATIONS OF NSAIDs

5 **Technical Field:**

The present invention is related to a pharmaceutical formulation which comprises NSAID having antiinflammatory, analgesic and antipyretic effect together with an H2 receptor antagonist used for preventing and minimizing the gastrointestinal side effects of NSAID.

10 **Background of the Invention:**

Flurbiprofen (Formula 1) is a propionic acid derivative, also known as NSAID (non-steroidal anti-inflammatory drug), having analgesic, anti-inflammatory and antipyretic activities.



Formula - 1

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Flurbiprofen is used to alleviate the pain in musculoskeletal system and joint disorders such as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis; in soft tissue injuries such as sprains and strains; and for postoperative pain, as well as pains including migraine headache and for painful and difficult menstruation.

20

At the same time, flurbiprofen is used as a pastil for the symptomatic healing of sore throat. Besides tablet and pastil, additionally gel, capsule and solution forms are also among the dosage forms of flurbiprofen.

25

The most commonly used flurbiprofen film tablet releases flurbiprofen immediately and it is immediately absorbed in such a way that its bioavailability reaches to 96%. The most important reason for formulating the flurbiprofen in this way is to have a molecule, which have antiinflammatory, analgesic and antipyretic effect, acting quickly. Therefore, the initiation

of release when the flurbiprofen reaches to the gastrointestinal system is important in terms of drug's effect.

5 The absorption of the flurbiprofen mostly takes place in the gastrointestinal system, in the duodenal part of the stomach and the small intestine. Therefore, the initiation of the release when the flurbiprofen reaches the gastrointestinal system is important in terms of drug's effect.

10 Besides the wide usage area, the flurbiprofen also has a wide range of side effects. These side effects are mostly seen in the gastrointestinal system and the most frequent one affects the stomach mucosa. These side effects can be observed as gastric erosion, peptic ulcer, major upper gastrointestinal system bleedings, alterations in the intestine permeability and inflammation.

15 These side effects are caused by the fact that flurbiprofen inhibits cyclooxygenase enzyme activity and prostaglandin synthesis, thereby damaging gastrointestinal mucosa due to increased gastric acid level. In fact, the mechanism of effect of flurbiprofen in the treatment is realized by the inhibition of prostaglandin and cyclooxygenase enzymes present in the tissues. However, when the same enzymes present also in the gastrointestinal mucosa cells
20 are inhibited, the side effects listed above are observed.

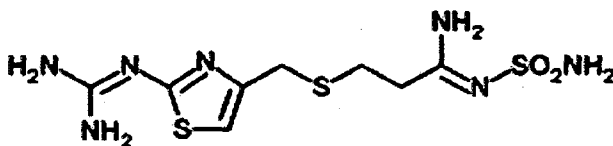
In order to prevent or minimize the side effects emerged as a result of the increase in the acid level caused by NSAID molecules such as flurbiprofen, a lot of studies have been executed in prior art.

25 For example, in order to minimize gastric damage, flurbiprofen is enteric coated (Hashmat D., Shoab H., Mehmood Z. (2008) AAPS PharmaSci Tech 9(1): 116-121) or formulated such that controlled release thereof will be performed (EP0234670).

30 Moreover, the researchers have combined NSAID molecules with acid inhibitors, in addition to formulation studies performed, in order to prevent or treat gastrointestinal damage. Acid level of gastric fluid is balanced, with acid inhibitors in this combination.

35 Patents numbered US5204118 and US5417980 of prior art combine NSAID molecules with proton pump inhibitors, so as to balance gastric acid. Since the researches on this combination have been carried out for many years, NSAID molecules have been combined with many molecules balancing gastric acid so far.

The most important ones among these molecules may be listed as proton pump inhibitors, H2 receptor antagonists and prostaglandin analogues. Among the H2 receptor antagonists, it is known that the molecule called famotidine (Formula 2) is used in the treatment of gastric and duodenal ulcer.



Formula 2

In order to effectively administer the studied NSAID - acid inhibitor combinations to the human body, various studies for multilayer tablet formulations have also been carried out. One of the primary reasons for this situation is to lessen or prevent incompatibility of the substances to be formulated with one another. Moreover, another important reason is that the formulations of two active substances with different release properties can be provided in the same form. The patent numbered EP1411900 relates to a multilayer tablet comprising NSAID and acid inhibitors. Here, NSAIDs are present in the inner core and released after the acid inhibitors present in the outer layer.

When a drug substance is combined with another drug substance in order to minimize or prevent the side effects of the drug substance, these two drug substances must be released, dissolved and absorbed harmoniously. For the efficiency of the formulation, an easy disintegration of both drug substances at a desired time is an important factor.

In order to minimize or prevent the side effects of flurbiprofen; it is very important for the molecule, in which the molecule is used in combination with the H2 receptor antagonists, to release both drug substances at the desired time and desired efficiency. Under normal circumstances, the release and consequently, the absorption of the formulations of prior art which are combined with H2 receptor antagonists to minimize the side effects of flurbiprofen which is released quickly, may be realized very late, as these formulations are formulated in a way to perform a delayed release. In this case, the bioavailability of the flurbiprofen is negatively affected.

Due to the intermolecular incompatibility in these formulations, the suitable formulation with which the desired effect will be actualized can not be obtained. Besides that, the dissolution profile of flurbiprofen whose release in gastrointestinal system, where it is expected to be

released and absorbed, is not achieved will be negatively affected from this situation. Besides them, side effects of it will arise due to the increase in its impurity.

Eventually, there is still a need today for the pharmaceutical formulations in which deficient
5 dissolution profile and bioavailability as a result of delayed release are not observed and likewise, which are formulated in such a way that they will be released effectively with the H2 receptor antagonist while the side effects of flurbiprofen molecule, which is formulated for being used together with the H2 receptor antagonists, are diminished.

10 **Description of the Figures**

Figure 1 shows an oral solid multilayer tablet formulation which comprises i) a first layer (a) comprising the first drug substance, ii) a second layer (c) comprising the second drug substance and iii) a barrier layer (b) separating these two layers.

15 **Detailed Description of the Invention**

The present invention is related to a pharmaceutical formulation which comprises NSAID having antiinflammatory, analgesic and antipyretic effect together with an H2 receptor antagonist used for preventing and minimizing the gastrointestinal side effects of NSAID. Here, H2 receptor antagonist increases acid level of gastric fluid by inhibiting acid secretion,
20 thereby preventing or minimizing such diseases as gastric erosion, peptic ulcer, major upper gastrointestinal system bleedings, alteration the intestine permeability and inflammation, all of which are caused by NSAID.

According to another aspect, the present invention relates to the fact that the pharmaceutical
25 formulation comprising NSAID as first active substance and H2 receptor antagonist as second active substance is a novel solid oral dosage form and the solid oral dosage form is preferably in the form of a tablet or more preferably in the form of multilayer tablet.

The present invention is related to a multilayer tablet formulation which comprises i) a first
30 layer comprising NSAID, ii) a second layer comprising the H2 receptor antagonist molecule and iii) a barrier layer separating these two molecules from each other.

The present invention relates to a multilayer tablet formulation comprising NSAID with anti-inflammatory, analgesic, and antipyretic activities; wherein NSAIDs are selected from the
35 group including aspirin, acetaminophen, ibuprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin, etodolac, indomethacin, ketolorac, lornoxicam, nabumetone, or diclofenac; the said NSAID being preferably flurbiprofen.

The present invention relates to a multilayer tablet formulation comprising a H₂ receptor antagonist increasing gastric acid level; wherein H₂ receptor antagonists are selected from cimetidine, ranitidine, ebrotidine, pabutidine, lafutidine, loxidine, or famotidine; the said H₂ receptor antagonist being preferably famotidine.

From a different viewpoint, the present invention is related to the multilayer tablet formulation which comprises flurbiprofen as NSAID and famotidine as H₂ receptor antagonist.

The present invention may comprise flurbiprofen and famotidine molecules in the multilayer tablet formulation thereof as pharmaceutically acceptable salts, enantiomers, racemates, polymorphs, esters and/or hydrates thereof.

The present invention is related to an oral solid multilayer tablet formulation comprising i) a first layer comprising flurbiprofen molecule as the first drug substance, ii) a second layer comprising famotidine as the second drug substance and iii) a barrier layer separating these two layers from each other, characterized in that; these 3 layers are lined up as a sandwich (Figure 1).

Here, the barrier layer is present in the middle in such a way that it separates the flurbiprofen and famotidine layers and the flurbiprofen and famotidine layers are present at the outer part of the barrier layer. By the virtue of the barrier layer present in the middle part, interaction between the flurbiprofen and famotidine molecules is prevented.

According to another aspect, the present invention relates to formulating the solid oral multilayer tablet, which comprises flurbiprofen as the first drug substance and famotidine as the second drug substance, in a way to release both drug substances rapidly, wherein, this tablet comprises

- i) an immediate release layer comprising flurbiprofen and pharmaceutically acceptable excipient,
- ii) an immediate release layer comprising famotidine and pharmaceutically acceptable excipient, and
- iii) a barrier layer provided between these two layers.

None of the layers of the multilayer tablet according to the present invention are formulated in such a way to alter the release profiles of flurbiprofen or famotidine molecules. Thus, the multilayer tablet according to the present invention has two layers comprising the flurbiprofen

and famotidine molecules separately and it is characterized in releasing these molecules together and rapidly.

5 Thus, as the release is initiated when the flurbiprofen reaches to the gastrointestinal system by way of the multilayer tablet, in which flurbiprofen and famotidine molecules can be released immediately, its dissolution profile and bioavailability are not affected and the possible gastrointestinal side effects are rapidly minimized or prevented with the immediate release of famotidine.

10 Additionally, as it is formulated according to the present invention, famotidine increases the pH of stomach as it inhibits the acid secretion, which is also the reason for its effect on gastrointestinal side effects when the famotidine molecule is released immediately. Thus, with the increasing stomach pH, the flurbiprofen which initiates being released when it enters the stomach resolves better and its dissolution profile increases.

15 The multilayer tablet according to the present invention is formulated in such a way that it increases the pH of the stomach and the dissolution profile of the flurbiprofen consequently thanks to the release profile of famotidine.

20 According to the present invention, pharmaceutically acceptable excipients which are present in the immediate release layers comprising famotidine and flurbiprofen, can be selected from the group including, but not limited to, binding agents, disintegrants, glidants, lubricants, plasticizers, surface active agents, preservatives and mixtures thereof.

25 Suitable binders may include, but not limited to polymetacrylate, polyvinylpyrrolidone (povidon), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), carboxy methyl cellulose (CMC), methyl cellulose (MC), hydroxy ethyl cellulose, sodium carboxy methyl cellulose (NaCMC), carboxymethyl cellulose calcium, ethyl cellulose, polyethylene oxide, gelatin, starch, pregelatinized starch, xanthan gum, guar gum, alginate, carrageenan, 30 pectin, carbomer, cellulose acetate phthalate, hydroxy propyl starch, polaxomer, poly ethylene glycol or mixtures thereof.

Suitable disintegrants of the invention, may include, but not limited to, microcrystalline cellulose, croscarmellose sodium, xylitol, polyplasdone (1-ethenylpyrrolidin-2-one), 35 crospovidone, low-substituted hydroxypropyl cellulose (L-HPC) and sodium starch glycolate or mixtures thereof.

Suitable glidants of the invention may include but not limited to silicon dioxide, magnesium trisilicate, starch, talc, colloidal silicon dioxide or silicon hydrogel or mixtures thereof.

5 Suitable lubricants of the invention may include but not limited to magnesium stearate, sodium stearyl fumarate, polyethylene glycol, stearic acid, metal stearates, boric acid, sodium chloride benzoate and acetate, sodium or magnesium lauryl sulfate or mixtures thereof.

10 Suitable plasticizers of the invention may comprise but not limited to triethyl citrate, triacetin, citric acid esters, phthalic acid esters dibutyl sebacate, cetyl alcohol, polyethylene glycol, polysorbate or mixtures thereof.

15 Suitable surfactants of the invention, may include but not limited to dioctyl sulfosuccinate, polysorbates and polyoxyethylene alkyl esters and ethers thereof, glyceryl monolaurate saponins, sorbitan laurate, sodium lauryl sulfate, magnesium lauryl sulfate or mixtures thereof.

20 Suitable preservatives of the invention may include but not limited to methyl paraben, propyl paraben and salts thereof (e.g. sodium or potassium salts), sodium benzoate, citric acid, benzoic acid, butylated hydroxytoluene and butylated hydroxyanisole or mixtures thereof.

25 On the other hand, the immediate release layer according to the present invention which contains famotidin, comprises colloidal silicone dioxide as excipient. Thus, the uniformity of the famotidine molecule, which inhibits the acid secretion and consequently increases the pH of the stomach, is provided in the tablet and the release profile is improved when the tablet is dissolved.

30 The immediate release layer comprising famotidine according to the present invention comprises colloidal silicone dioxide and microcrystalline cellulose as excipients.

According to the present invention, colloidal silicone dioxide in the immediate release layer comprising famotidine is present in an amount of about 0.1 to 10 % and preferably 0.1 to 2 % by weight of the layer.

35 According to the present invention, microcrystalline cellulose in the immediate release layer comprising famotidine is preferably microcrystalline cellulose pH 101 and it is present in an amount of about 60 to 80 % and preferably 65 to 75 % by weight of the layer.

In the immediate release layer containing famotidine according to the present invention, the weight ratio of microcrystalline cellulose excipient to colloidal silicone dioxide excipient is about 4 to 800 and preferably 25 to 200.

5

In the immediate release layer that is formulated together with these excipients, the uniformity of the drug substances and excipients increases. Thus, the immediate release layer disintegrates easier and the famotidine is released faster. The pH of the stomach increases with the immediate releasing famotidine. The dissolution profile of the flurbiprofen molecule with an increased dissolution rate, is improved thanks to the increasing pH.

10

As a result, with the multilayer tablet comprising flurbiprofen and famotidine drug substances which are present in the immediate release layers formulated according to the invention, an antiinflammatory, analgesic and antipyretic drug form, which have an increased dissolution profile and decreased side effects, is developed.

15

The multilayer tablet according to the invention comprises the flurbiprofen and famotidine drug substances with a ratio of about 7:1 and preferably 5:1 by weight. The low amount of famotidine in the tablet may cause the famotidine not to disperse homogenously in the formulation. This situation may cause a content uniformity problem and therefore, the non homogenous tablets do not release equal amount of famotidine drug substance when they are disintegrated. That is why the famotidine should disintegrate in an effective manner.

20

When the famotidine is applied in high dosages; it may cause minor side effects such as headache, weakness, fatigue, fever; and especially in patients with kidney failure, it may also cause side effects related with the central nervous system such as anxiety, depression and mental disorders. The multilayer tablet formulation according to the invention comprises famotidine in an amount of about 10 to 50 mg and preferably 15 to 35 mg.

25

The immediate release layer according to the present invention should release equal amounts of famotidin. Therefore, this immediate release layer must be formulated in such a way that it must realize the release of famotidine, which is preferably 5 unit less than flurbiprofen, immediately and effectively.

30

In order to obtain this immediate formulation, microcrystalline cellulose and colloidal silicone dioxide which facilitate the disintegration of the formulation should be present in the formulation as pharmaceutically acceptable excipients. Here, the weight ratio of

35

microcrystalline cellulose to colloidal silicone dioxide is formulated in accordance with the invention and it is about 4-800 and preferably 25-200.

Thus, the immediate release layer containing low amount of famotidine disintegrates efficiently, the positive effect of famotidine on the pH of stomach is actualized rapidly and the dissolution profile and bioavailability of flurbiprofen improve with the increasing pH.

The present invention comprises a first layer that comprises flurbiprofen, a second layer that comprises famotidin and a barrier layer provided between these two layers and it is characterized in that, none of these layers comprise a coating. In order to keep the drug substance and the excipients stable, colloidal silicone dioxide and microcrystalline cellulose are provided in the flurbiprofen and famotidine layers which do not contain coating.

The multilayer tablet according to the present invention comprises famotidine in an amount of 5-25 % by weight and preferably 10-15 % by weight, in the immediate release layer which comprises famotidine and pharmaceutically acceptable excipient.

The multilayer tablet according to the present invention comprises flurbiprofen in an amount of 20-50 % by weight and preferably 30-40 % by weight, in the immediate release layer which comprises famotidine and pharmaceutically acceptable excipient.

The present invention is related to a multilayer tablet that has an immediate release layer comprising famotidine and it comprises;

- a) about 5 to 25% by weight of famotidine,
- b) about 10 to 20 % by weight of pregelatinized starch,
- c) about 60 to 80 % by weight of microcrystalline cellulose,
- d) about 0.1 to 10 % by weight of colloidal silicon dioxide,
- e) about 0.1 to 10 % by weight of magnesium stearate.

The present invention is related to a multilayer tablet that has an immediate release layer comprising flurbiprofen, which comprises;

- a) about 20 to 50% by weight of flurbiprofen,
- b) about 5 to 60% by weight of lactose,
- c) about 5 to 30 % by weight of microcrystalline cellulose,
- d) about 0.5 to 10 % by weight of crosscarmellose sodium,
- e) about 2 to 10 % by weight of hydroxypropyl cellulose,
- f) about 0.1 to 10 % by weight of colloidal silicon dioxide,

g) about 0.1 to 10 % by weight of magnesium stearate.

In another aspect, the present invention is related to a sandwich shaped multilayer tablet which comprises a barrier layer that separates the first immediate release layer comprising flurbiprofen and the second immediate release layer comprising famotidine and characterized in that the barrier layer forms the middle layer of the sandwich shaped multilayer tablet and contains pharmaceutically acceptable excipients. By means of this barrier layer, the incompatibility of flurbiprofen and famotidine molecules within the formulation is minimized or prevented.

10

As a pharmaceutically acceptable excipient, the barrier layer according to the present invention comprises binding agents, dispersants, glidants, lubricants, plasticizers, surface active agents, preservatives or mixtures thereof, it especially comprises;

15

- a) about 0.1 to 10 % by weight of hydroxypropyl cellulose,
- b) about 70 to 99 % by weight of microcrystalline cellulose,
- c) about 0.1 to 10 % by weight of yellow iron oxide,
- d) about 0.1 to 10 % by weight of colloidal silicon dioxide,
- e) about 0.1 to 10 % by weight of magnesium stearate.

20

The multilayer tablet according to the present invention is composed of flurbiprofen immediate release layer, famotidine immediate release layer and barrier layer and in each layer it comprises colloidal silicone dioxide and microcrystalline cellulose as pharmaceutically acceptable excipient.

25

In its each layer, the multilayer tablet according to the present invention comprises colloidal silicone dioxide as excipient, wherein the amount of colloidal silicone dioxide by weight is about 0.1 to 5 mg.

30

In its each layer, the multilayer tablet according to the present invention comprises microcrystalline cellulose as excipient, wherein the amount of microcrystalline cellulose in each layer by weight is about 50 to 150 mg.

35

The ratio of microcrystalline cellulose and colloidal silicone dioxide present as excipients in each layer of the multilayer tablet according to the present invention is between about 4-800 and preferably 25-200 by weight.

According to another aspect, the present invention is related to a method for preparing the said multilayer tablet which comprises the following steps:

a) for the preparation of the first layer;

- i. flurbiprofen, microcrystalline cellulose, lactose monohydrate and a part of hydroxypropyl cellulose are transferred to the fluid bed dryer,
- ii. an aqueous solution is prepared with the remaining part of the hydroxypropyl cellulose, granulated, dried and grinded in the fluid bed dryer and transferred to the container,
- iii. croscarmellose sodium and colloidal silicone dioxide are added to the same container,
- iv. the powder mixture in this container is blended,
- v. magnesium stearate is added to the mixture obtained in step iii) and blended,

b) for the preparation of the second layer;

- i. famotidine, pregelatinized starch and microcrystalline cellulose are picked,
- ii. the mixture obtained in step i) is granulated with water-alcohol mixture, grinded and dried in oven,
- iii. the dried mixture is grinded again and the colloidal silicone dioxide is put to the same container by being sieved,
- iv. the powder mixture in this container is blended,
- v. magnesium stearate is added to the mixture obtained in step iii) and blended,

c) for the preparation of the barrier layer;

- i. a part of microcrystalline cellulose and hydroxypropyl cellulose are transferred to the container,
- ii. remaining part of microcrystalline cellulose, iron oxide yellow and colloidal silicone dioxide are sieved and transferred to the same container,
- iii. the powdered mixture in this container is blended,
- iv. magnesium stearate is added to the mixture obtained in step iii) and blended,

d) the homogeneous mixtures obtained in step a), b) ve c) are compressed to obtain a sandwich shaped tablet.

Examples:

In the present invention, the following examples are defined as the preferred compositions of the present invention. Although the examples are not intended to limit the scope of the present invention, it should be considered in the light of the description detailed above.

Example 1

5 The present example is directed to a sandwich shaped trilayer tablet comprising flurbiprofen and famotidine. The above formulation is prepared by obtaining separately three layers and by compressing them to obtain a sandwich shaped tablet. The preparation process of the tablet is detailed in the description.

	Ingredient	Amount (mg)
First Layer	Flurbiprofen	100
	Lactose monohydrate	124.5
	Microcrystalline cellulose	55
	Croscarmellose sodium	7.3
	Hydroxypropyl cellulose	9.8
	Colloidal silicon dioxide	2.1
	Magnesium Stearate	1.3
	Total	300
Barrier Layer	Hydroxypropyl cellulose	8
	Microcrystalline cellulose	139.1
	Yellow iron oxide	0.6
	Colloidal silicon dioxide	0.8
	Magnesium Stearate	1.5
	Total	150
Second Layer	Famotidine	20
	Microcrystalline cellulose	105.5
	Croscarmellose sodium	7.5
	Hydroxypropyl cellulose	15
	Colloidal silicon dioxide	1
	Magnesium Stearate	1
	Total	150

Example 2

As example 1, the above example is also directed to a sandwich shaped trilayer tablet comprising flurbiprofen and famotidine.

	Ingredient	Amount (mg)
First Layer	Flurbiprofen	100
	Lactose monohydrate	124.5
	Microcrystalline cellulose	55
	Croscarmellose sodium	7.3
	Hydroxypropyl cellulose	9.8
	Colloidal silicon dioxide	2.1
	Magnesium Stearate	1.3
	Total	300
Barrier Layer	Hydroxypropyl cellulose	8
	Microcrystalline cellulose	139.1
	Yellow iron oxide	0.6
	Colloidal silicon dioxide	0.8
	Magnesium Stearate	1.5
	Total	150
Second Layer	Famotidine	20
	Microcrystalline cellulose	105.5
	Pregelatinized starch	23
	Colloidal silicon dioxide	1
	Magnesium Stearate	1
	Total	150

5 **Example 3**

The following Table 1 is about dissolution profile of flurbiprofen depending on the medium pH. This table is obtained by tests which are carried out by USP2 Paddle Dissolution Method. As the pH increases, flurbiprofen has a greater dissolution profile. Table 1 shows
 10 also that flurbiprofen is immediately released from the trilayer tablet of the present invention.

	0.1 N HCl, 900 mL, 50 rpm	pH=4.5 sodium acetate buffer, 900 mL, 50 rpm	pH=7.2, 0.05 M KH₂PO₄ buffer, 900 mL, 50 rpm
Time	Avg.(%)	Avg.(%)	Avg. (%)
0	0	0	0
5	8	20	75
10	10	28	91
15	10	33	96
20	11	35	97
30	11	39	98
45	11	40	99
60	11	40	100

Table 1 – Dissolution profile of flurbiprofen depending on medium pH

CLAIMS

1. A solid oral multilayer tablet comprising
 - i) a first layer (a) comprising flurbiprofen as drug substance and pharmaceutically acceptable excipient,
 - ii) a second layer (c) comprising famotidine as drug substance and pharmaceutically acceptable excipient, and
 - iii) a barrier layer (b) provided between these two layers, comprising pharmaceutically acceptable excipient,wherein these 3 layers are lined up in sandwich form, in such a way that the barrier layer is provided in the middle, and the first and the second layers comprising the drug substances are formulated in way to release the drug substances immediately.
2. The solid oral multilayer tablet according to claim 1 wherein, the first layer (a) comprises 20 to 50% flurbiprofen as drug substance.
3. The solid oral multilayer tablet according to claim 1 wherein, the second layer (c) comprises 5 to 25% famotidine as drug substance.
4. The solid oral multilayer tablet according to claim 1 wherein, the pharmaceutically acceptable excipient in its content comprises at least one of the substances selected among binding agents, disintegrants, glidants, lubricants, plasticizers, surfactants, preservatives or mixtures thereof.
5. The solid oral multilayer tablet according to claim 4, wherein the binders in its content are selected among polymetacrylate, polyvinylpyrrolidone (povidon), hydroxypropyl methyl cellulose (HPMC), hydroxypropyl cellulose (HPC), carboxy methyl cellulose (CMC), methyl cellulose (MC), hydroxy ethyl cellulose, sodium carboxy methyl cellulose (NaCMC), carboxymethyl cellulose calcium, ethyl cellulose, polyethylene oxide, gelatin, starch, xanthan gum, guar gum, alginate, carrageenan, pectin, carbomer, cellulose acetate phthalate, hydroxy propyl starch, polaxomer, poly ethylene glycol or mixtures thereof.
6. The solid oral multilayer tablet according to claim 4, wherein the disintegrants in its content are selected among microcrystalline cellulose, croscarmellose sodium, xylitol, polyplasdone (1-ethenylpyrrolidin-2-one), crospovidone, low-substituted hydroxypropyl cellulose (L-HPC) and sodium starch glycolate or mixtures thereof.

7. The solid oral multilayer tablet according to claim 4 wherein, the glidants in its content are selected among silicon dioxide, magnesium trisilicate, starch, talc, colloidal silicon dioxide or silicon hydrogel or mixtures thereof.
- 5
8. The solid oral multilayer tablet according to any of the previous claims wherein the second layer (c) which comprises famotidine as drug substance and pharmaceutically acceptable excipient comprises preferably colloidal silicone dioxide and microcrystalline cellulose as excipient.
- 10
9. The solid oral multilayer tablet according to claim 8 wherein the colloidal silicone dioxide in the immediate release layer (c) comprising famotidine is present in an amount of about 0.1 to 10 % and preferably 0.1 to 2 %, by weight of the layer.
- 15
10. The solid oral multilayer tablet according to claim 8 wherein the microcrystalline cellulose in the immediate release layer (c) comprising famotidine is present in an amount of about 60 to 80 % and preferably 65 to 75 %, by weight of the layer.
- 20
11. The solid oral multilayer tablet according to claim 8 wherein the weight ratio of excipient microcrystalline cellulose to excipient colloidal silicone dioxide in the immediate release layer (c) comprising famotidine is between about 4 and 800.
- 25
12. The solid oral multilayer tablet according to claim 1 wherein the tablet comprises;
- 30
- a. an immediate release layer (a) comprising flurbiprofen as drug substance and
- i. about 5 to 60% by weight of lactose,
- ii. about 5 to 30 % by weight of microcrystalline cellulose,
- iii. about 0.5 to 10 % by weight of crosscarmellose sodium,
- iv. about 2 to 10 % by weight of hydroxypropyl cellulose,
- v. about 0.1 to 10 % by weight of colloidal silicon dioxide,
- 35
- vi. about 0.1 to 10 % by weight of magnesium stearate,
- as excipient,
- b. an immediate release layer (c) comprising famotidine as drug substance and
- i. about 10 to 20 % by weight of pregelatinized starch,
- ii. about 60 to 80 % by weight of microcrystalline cellulose,
- 35
- iii. about 0.1 to 10 % by weight of colloidal silicon dioxide,
- iv. about 0.1 to 10 % by weight of magnesium stearate,
- as excipient,

- 5 c. a barrier layer (b) provided between these two layers and comprising
- i. about 0.1 to 10 % by weight of hydroxypropyl cellulose,
 - ii. about 70 to 99 % by weight of microcrystalline cellulose,
 - iii. about 0.1 to 10 % by weight of yellow iron oxide,
 - iv. about 0.1 to 10 % by weight of colloidal silicon dioxide,
 - v. about 0.1 to 10 % by weight of magnesium stearate.
- as excipient.

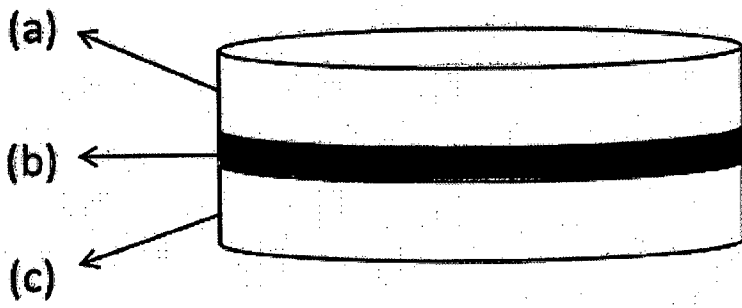


Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2013/000209

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20
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, 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	US 2005/163847 A1 (CHENG XIU X [US] ET AL) 28 July 2005 (2005-07-28) page 1, paragraphs 8, 13 page 2, paragraphs 15-17, 26 page 3, paragraph 46 page 4, paragraphs 52, 54, 57; figure 1 page 5, paragraph 64	1-12
A	----- EP 2 260 837 A1 (POZEN INC [US]) 15 December 2010 (2010-12-15) page 3, paragraphs 11, 12 page 4, paragraph 17; figures 1-3 ----- -/--	1-12

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	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"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 10 October 2013	Date of mailing of the international search report 17/10/2013
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Weiss, Marie-France
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INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2013/000209

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>TAHA ALI S ET AL: "Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs", NEW ENGLAND JOURNAL OF MEDICINE, THE, MASSACHUSETTS MEDICAL SOCIETY, WALTHAM, MA, US, vol. 334, no. 22, 30 May 1996 (1996-05-30) , pages 1435-1439, XP002550689, ISSN: 0028-4793, DOI: 10.1056/NEJM199605303342204 page 1435, column 2, paragraph 2 table 1</p> <p style="text-align: center;">-----</p>	1-12

INTERNATIONAL SEARCH REPORT

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International application No PCT/TR2013/000209

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