The present invention relates to a bilayer tablet formulation comprising montelukast sodium and rupatadine fumarate.
BILAYER TABLET FORMULATIONS OF MONTELUKAST AND RUPATADINE

Field of Invention

The present invention relates to a bilayer tablet formulation comprising montelukast sodium and rupatadine fumarate.

Background of Invention

Montelukast sodium has one asymmetric center and is the R-isomer. A crystalline and an amorphous form are known. Montelukast sodium is a leukotriene receptor antagonist approved for the prophylaxis and chronic treatment of asthma. The chemical name of montelukast is \([R-(E)]-1-[[1-3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-3-[2-(1-hydroxy-1-methylethyl)-phenyl]propyl]thio[methyl] cyclopropane acetic acid mono sodium salt and has the structure shown in the following formula I. It works by blocking the action of substances in the body that cause the symptoms of asthma and allergic rhinitis. It is used to prevent wheezing, difficulty breathing, chest tightness, and coughing caused by asthma.

![Chemical structure of Montelukast Sodium](image)

**Formula I:** Montelukast sodium

In patent W0971 6173, tablet formulation of montelukast sodium has been disclosed. It also exists in the market as tablet, chewable tablet and oral granule under the brand name of SINGULAIR® in U.S.

Rupatadine is a second generation antihistamine and PAF (Platelet-activating factor) antagonist used to treat allergies and is marketed under several trade names such as Rupafin, Alergoliber, Rinialer, Pafinur, Rupax and Ralif.
Rupatadine fumarate has been approved for the treatment of allergic rhinitis and chronic urticaria in adults and children over 12 years. The defined daily dose (DDD) is 10 mg orally. The chemical name of rupatadine fumarate is 8-Chloro-6,1 1-dihydro-1 1-[1-((5-methyl-3-pyridyl)methyl]-4-piperidylidene]-5H-benzo[5,6]cyclohepta[1,2-b]pyridine fumarate and has the structure shown in the following formula II.

![Chemical Structure](Image)

**Formula II:** Rupatadine fumarate

Rupatadine is first disclosed in US6803468 (Ranbaxy Laboratories Limited) and there are several patent applications describing, its process and other salt forms.

In prior art, there may have some capsule formulations including montelukast or rupatadine alone or may be in combination. However, a capsule formulation is less effective than a tablet combination and this may cause compatibility and stability problems and moreover dissolution problems of active drug substances.

Thus, there is no combination of montelukast sodium with rupatadine fumarate especially in tablet form in prior art.

It has also been found that the combination of rupatadine and montelukast is more effective compared to rupatadine alone in the control of allergic rhinitis symptoms.

In addition, instead of one per se use, combining more than one molecule in one dosage form increases the patients’ quality of life and patients’ compliance. Considering all these, combinations of montelukast and rupatadine in a suitable pharmaceutical dosage formulation such as a bilayer tablet formulation is needed in the art. However, there are many challenges
while combining two or more molecules in a tablet such as compatibility, dissolution and stability problems.

In this invention, to overcome these problems mentioned above, a bilayer tablet formulation of montelukast and rupatadine has been developed.

In further, in order to overcome stability and especially dissolution problems of active drug substances, a bilayer tablet formulation has been provided to prevent the direct contact of active drug substances.

**Description of the invention**

The main object of the present invention is to obtain a bilayer tablet formulation comprising a stable and compatible combination of montelukast sodium in first layer and rupatadine fumarate in second layer with a desired dissolution of active drug substances separately.

According to this embodiment, the present invention is aimed to obtain a bilayer tablet formulation to prevent an interaction of active drug substances, therefore the incompatibility problem of these agents is eliminated and efficient and desired dissolution and stability are obtained.

In order to combine two different molecules in one dosage form, molecules should be compatible with each other to achieve desired stability and dissolution for the patients' compliance. During the development study to combine montelukast and rupatadine, it has been found that montelukast shows stability and dissolution problems when it is used together with rupatadine in a conventional tablet formulation (one layer) or in capsule form. The analysis results that, the combination in conventional tablet or capsule form shows an increase in impurity and a decrease in dissolution of montelukast. Owing to the incompatibility problem of these active agents, in this invention bilayer tablet has been developed and desired dissolution and stability has been achieved. Dissolution results of the two active drug substances are given in below in Example 2, in more detail.

Thus, the bilayer tablet formulation of the present invention comprises 3.00 to 15.00 % by weight montelukast sodium as active drug substance in the first layer and comprises 5.00 to 20.00 % by weight rupatadine fumarate as active drug substance in the second layer.

In a further embodiment, the bilayer tablet formulation comprises at least one disintegrant.
According to this embodiment, the disintegrant is selected from the group comprising croscarmellose sodium, pregelatinized starch, crospovidone, sodium starch glycolate, low-substituted hydroxypropyl cellulose, polyvinylpyrrolidone (K - 30), hydroxypropyl methyl cellulose, carboxy methyl cellulose calcium, sodium carboxy methyl cellulose, magnesia aluminum silica, sodium dodecyl sulphate, calcium silicate or mixtures thereof. Preferably, the disintegrant is croscarmellose sodium or pregelatinized starch or mixtures thereof. More preferably, the disintegrant is croscarmellose sodium in first layer and pregelatinized starch in second layer.

Due to the use of different disintegrants separately in the layers, the efficient and desired dissolution of both active drug substances are achieved rapidly. Disintegrants give advantages to formulation in terms of binding strength to the layers. With the synergistic effect of disintegrants used in layers separately comprising active drug substances, layers adhere to each other and robust bilayer tablet with desired dissolution has been achieved. Disintegrants used in this present invention are croscarmellose sodium in first layer and pregelatinized starch in second layer.

According to this embodiment, the weight ratio (w/w) of croscarmellose sodium in first layer to pregelatinized starch in second layer is between 0.1 and 1.0. Preferably, the weight ratio (w/w) is 0.5 - 0.7.

In one embodiment, the bilayer tablet of the present invention further comprises at least one excipient. According to this embodiment, the excipients are selected from the group comprising binders, fillers, lubricants and coloring agents or mixtures thereof.

Suitable binders may include but not limited to hydroxypropyl cellulose (Klucel LF), hydroxypropyl methyl cellulose, methyl cellulose, carboxymethyl cellulose, polyethylene glycol, polyvinyl alcohol, polyvinyl acetate, polyvinylpyrrolidone, sugars, glucose syrups, natural gums, guar gum, tragachanti gum, gelatins, pullulan, agar, alginate, sodium algynates, glycyrrhizin, polymetacrylates, collagen, alginate, sodium alginate, hyaluronic acid, pectin, carrageenan, carbomer, poloxamer, polyacrylamide, aluminum hydroxide, bentonite, laponite, cetostearyl alcohol, polyoxyethylene-alkyl ethers, acacia mucilage, polydextrose, polyethylene oxide, xylitol, sucrose stearate or mixtures thereof. Preferably the binder is hydroxypropyl cellulose (Klucel LF).

Suitable fillers may include, but not limited to microcrystalline cellulose (pH 101, pH 102), lactose monohydrate, starch, mannitol, dibasic calcium phosphate, tribasic calcium
phosphate, trehalose, isomalt, sodium carbonate, sodium bicarbonate, calcium carbonate or mixtures thereof. Preferably the filler is microcrystalline cellulose (pH 101).

Suitable lubricants may include but not limited to magnesium stearate, sodium stearyl fumarate, polyethylene glycol, sodium lauryl sulphate, magnesium lauryl sulphate, fumaric acid, glyceryl palmitostearate, hydrogenated natural oils, zinc stearate, calcium stearate, silica, talc, stearic acid, polyethylene glycol, paraffin or mixtures thereof. Preferably, the lubricant is magnesium stearate.

Suitable coloring agents, may include but not limited to yellow iron oxide, Curcumin, Carmine, Indigo Carmine, Chlorophy II, Helindone pink CN, Diiodofluorescein or mixtures thereof. Preferably, the coloring agent is yellow iron oxide.

**Example 1:**

<table>
<thead>
<tr>
<th>1st layer</th>
<th>% by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>montelukast sodium</td>
<td>3.00 - 15.00</td>
</tr>
<tr>
<td>hydroxypropyl cellulose (Klucel LF)</td>
<td>1.00 - 5.00</td>
</tr>
<tr>
<td>microcrystalline cellulose (PH 101)</td>
<td>30.00 - 60.00</td>
</tr>
<tr>
<td>lactose monohydrate</td>
<td>30.00 - 60.00</td>
</tr>
<tr>
<td>croscarmellose sodium</td>
<td>1.00 - 5.00</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>0.10 - 2.00</td>
</tr>
<tr>
<td>pure water</td>
<td>30.00 - 50.00</td>
</tr>
<tr>
<td>montelukast Layer</td>
<td>50.00 - 65.00</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>2nd layer</th>
<th>% by weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>rupatadine fumarate</td>
<td>5.00 - 20.00</td>
</tr>
<tr>
<td>prejelatinized starch</td>
<td>2.00 - 10.00</td>
</tr>
<tr>
<td>microcrystalline cellulose (PH 101)</td>
<td>30.00 - 60.00</td>
</tr>
<tr>
<td>lactose monohydrate</td>
<td>30.00 - 60.00</td>
</tr>
<tr>
<td>yellow iron oxide</td>
<td>0.10 - 2.00</td>
</tr>
<tr>
<td>magnesium stearate</td>
<td>0.10 - 2.00</td>
</tr>
<tr>
<td>pure water</td>
<td>40.00 - 60.00</td>
</tr>
<tr>
<td>rupatadine layer</td>
<td>35.00 - 50.00</td>
</tr>
</tbody>
</table>
The production of the formulation is carried out as follows:

**Montelukast Layer:** montelukast sodium, hydroxypropyl cellulose (Klucel LF), microcrystalline cellulose (PH 101), lactose monohydrate and half amount of croscarmellose sodium are taken into container. Powder mixture is spray-granulated with pure water. The mixture is dried. The rest of the croscarmellose sodium is added to this mixture, and mixed. Then, magnesium stearate is added to this mixture and mixed.

**Rupatadine layer:** rupatadine fumarate, prejelatinized starch, microcrystalline cellulose (PH 101), lactose monohydrate and yellow iron oxide are taken into collete and powder mixture is wet granulated with pure water. Then, the mixture is sieved and dried in fluid-bed dryer. Then, the mixture is sieved again. Magnesium stearate is added and mixed again.

Two powder mixtures, are put into tableting machine separately to form bilayer tablets.

**Example 2 (Dissolution profile test)**

The bilayer tablet formulation of this present invention (Example 1), was tested by its dissolution profile in 0.5% solution of sodium dodecyl sulphate and at 37˚C using a USP apparatus II method in 900 ml, rotating at 75 rpm against the reference product which is mentioned below as conventional (one layer) tablet or capsule form. The results are shown below in Table 1.

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>Example 1 montelukast sodium (%)</th>
<th>Example 1 rupatadine fumarate (%)</th>
<th>Reference Product* montelukast sodium (%)</th>
<th>Reference Product* rupatadine fumarate (%)</th>
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<tbody>
<tr>
<td>5</td>
<td>104.3</td>
<td>85.9</td>
<td>42.2</td>
<td>85.3</td>
</tr>
<tr>
<td>10</td>
<td>104.8</td>
<td>91.9</td>
<td>53.5</td>
<td>89.1</td>
</tr>
<tr>
<td>15</td>
<td>105.2</td>
<td>93.8</td>
<td>59.4</td>
<td>91.3</td>
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<tr>
<td>20</td>
<td>104.8</td>
<td>94.6</td>
<td>64.1</td>
<td>96.8</td>
</tr>
<tr>
<td>30</td>
<td>104.6</td>
<td>95.0</td>
<td>67.9</td>
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<td>45</td>
<td>106.9</td>
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<tr>
<td>60</td>
<td>104.3</td>
<td>94.3</td>
<td>76.4</td>
<td>95.7</td>
</tr>
</tbody>
</table>

*Reference product* (in one layer tablet or in capsule form): montelukast sodium, rupatadine fumarate, hydroxypropyl cellulose (Klucel LF), microcrystalline cellulose (pH101), lactose monohydrate, croscarmellose sodium and magnesium stearate. (The amount of the ingredients are same with the amounts given in example 1, in montelukast layer)
Therefore it is shown that, when these molecules are formulated together in one layer tablet form or in capsule form the dissolution and bioavailability of montelukast is significantly decreased. When they are formulated separately in a bilayer formulation the amounts are increased.
1. A bilayer tablet formulation comprising montelukast sodium in first layer and rupatadine fumarate in second layer.

2. The bilayer tablet formulation according to claim 1, wherein the first layer comprising 3.00 to 15.00 % by weight montelukast sodium as active drug substance and the second layer comprising 5.00 to 20.00 % by weight rupatadine fumarate as drug substance.

3. The bilayer tablet formulation according to claim 1, further comprising at least one disintegrant.

4. The bilayer tablet formulation according to claim 3, wherein the disintegrant is selected from the group comprising croscarmellose sodium, pregelatinized starch, crospovidone, sodium starch glycolate, low-substituted hydroxypropyl cellulose, polyvinylpyrrolidone, hydroxypropyl methyl cellulose, carboxy methyl cellulose calcium, sodium carboxy methyl cellulose, magnesium aluminum silica, sodium dodecyl sulphate, calcium silicate or mixtures thereof.

5. The bilayer tablet formulation according to claim 4, wherein the disintegrant is croscarmellose sodium or pregelatinized starch or mixtures thereof.

6. The bilayer tablet formulation according to claim 5, wherein the disintegrant is croscarmellose sodium in first layer and pregelatinized starch in second layer.

7. The bilayer tablet formulation according to claim 6, wherein the weight ratio (w/w) of croscarmellose sodium in first layer to pregelatinized starch in second layer is between 0.1 and 1.0.

8. The bilayer tablet formulation according to any preceding claims, further comprising at least one excipient.

9. The bilayer tablet formulation according to claim 8, wherein the excipients are selected from the group comprising binders, fillers, lubricants and coloring agents or mixtures thereof.
10. The bilayer tablet formulation according to any preceding claims, comprising:
   a. 3.00 to 15.00 % of montelukast sodium
   b. 1.00 to 5.00 % of hydroxypropyl cellulose
   c. 30.00 to 60.00 % of microcrystalline cellulose
   d. 30.00 to 60.00 % of lactose monohydrate
   e. 1.00 to 5.00 % of croscarmellose sodium
   f. 0.10 to 2.00 % of magnesium stearate
   g. 30.00 to 50.00 % of pure water
      in first layer and

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   a. 5.00 to 20.00 % of rupatadine fumarate
   b. 2.00 to 10.00 % of pregelatinized starch
   h. 30.00 to 60.00 % of microcrystalline cellulose
   i. 30.00 to 60.00 % of lactose monohydrate
   j. 1.00 to 5.00 % of croscarmellose sodium
   k. 0.10 to 2.00 % of yellow iron oxide
   l. 0.10 to 2.00 % of magnesium stearate
   m. 40.00 to 60.00 % of pure water
      in second layer.
**INTERNATIONAL SEARCH REPORT**

**International application No**
PCT/EP2017/059538

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<td>Wo 2015/069203 AI (SANTA FARMA I LAÇ SANAYI AS [TR]) 14 May 2015 (2015-05-14) claims 1-4; example 1</td>
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[X] Further documents are listed in the continuation of Box C.  
[X] See patent family annex.

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  *"P"* document published prior to the international filing date but later than the priority date claimed  
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  *"S"* document member of the same patent family

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Authorized officer  
Kardas-Llorens, Eyip
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