A process for the preparation of granular pharmaceutical composition of montelukast sodium wherein the amount of sulfoxide impurity formed during processing is not more than 0.5% by weight of the initial amount of Montelukast.
Pharmaceutical compositions of Montelukast sodium

Field of invention

The present invention relates to a process for making pharmaceutical composition of montelukast sodium. The present invention relates to an improved process for making oral granules of montelukast.

Background of the invention

Montelukast sodium, the active ingredient in SINGULAIR, is a selective and orally active leukotriene receptor antagonist that inhibits the cysteinyl leukotriene CysLT1 receptor. Montelukast sodium is described chemically as \([\text{[i?-(E)]-l-[[[l-[3-[2-(7-chloro-2-quinoliny1)ethenyl]phenyl]-3-[2-(l-hydroxy-l-methylethyl)phenyl]propyl]thio]}\] methylv]cyclopropaneacetic acid, monosodium salt. Montelukast is represented by the following structural formula

![Formula I](image)

Montelukast is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older. Montelukast is also indicated for the relief of symptoms of allergic rhinitis (seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older, and perennial allergic rhinitis in adults and pediatric patients 6 months of age and older). Montelukast is currently marketed by Merck in the form of film-coated tablets, chewable tablets and oral granules.
U.S. Patent no. 5,565,473 (the '473 patent) is listed in the orange book for Montelukast. The patent claims a broad class of leukotriene antagonist, which included several compounds. Montelukast is among the many compounds claimed in the '473 patent. The '473 patent also discloses pharmaceutical composition for the class of leukotriene antagonist with pharmaceutically acceptable carriers.

U.S. patent application 20030096840 claims oral granules of Montelukast, which may be ingested directly or mixed with food. The granule formulation is advantageous for use by patients who have either difficulty in swallowing or chewing tablets.

PCT application WO 2007/092031 claims a stable pharmaceutical composition of montelukast which does not contain microcrystalline sodium and the amount of sulfoxide impurity does not exceed more than 1% by weight from the initial amount if montelukast after storage at about 40°C at about 75% RH for 3 months.

The article entitled "Fluidized bed processing and drying" published in Pharmaceutical Engineering in March 1991; discloses that the bed temperature is always less then the inlet temperature.

Montelukast is prone to oxidation and forms the sulfoxide impurity. Montelukast also undergoes oxidation during the pharmaceutical manufacturing process. Hence, there is a need in the art to reduce the oxidation of montelukast during pharmaceutical processing and thus improve the stability of the composition.

Summary of the invention

The present invention relates to a process for making montelukast granules comprising montelukast or a salt thereof and a pharmaceutically acceptable carrier, wherein the amount of sulfoxide impurity formed during processing at high temperature is not more than 0.5% by weight of the initial amount of montelukast.
In an embodiment of the present invention the process for making granules of Montelukast Sodium wherein, the solution of montelukast is sprayed at high inlet and bed temperature to reduce the granulation time.

In another embodiment of the present invention the process for making granules of montelukast sodium wherein the granulation occurs at high inlet and bed temperature thereby reducing the granulation time and time for which it is exposed to air which would result in reduced sulfoxide impurity.

**Detailed description of the invention**

The present invention relates to a process for making montelukast granules comprising montelukast or a salt thereof and a pharmaceutically acceptable carrier, wherein the amount of sulfoxide impurity formed during processing at high temperature is not more than 0.5 % by weight of the initial amount of montelukast.

Montelukast and its pharmaceutical compositions are subject to degradation during manufacturing or storage. Montelukast degrades into its corresponding sulfoxide. The sulfoxide impurity is an inactive impurity, which reduces the effective dose of montelukast when it is administered to the patient.

The sulfoxide impurity of montelukast is represented by the following structural formula

[Formula II image]

Formula II
The sulfoxide impurity is formed when montelukast is subjected to high temperature for prolonged period. The present invention overcomes this problem by providing a process wherein the processing time for the formulation of montelukast granules is sufficiently reduced such that the amount of sulfoxide impurity formed is less than 0.5 % by weight of the initial amount of montelukast.

As described herein the "sulfoxide impurity" refers to the oxidation product of montelukast sodium wherein the sulfide group in the side chain has been oxidized to the sulfoxide group.

As described, herein "processing time" refers to the time required for the formation of montelukast granules and the loss on drying is not more than 0.5 %

As described, herein "bed temperature" refers to the temperature inside the fluid bed granulator during the granulation process.

Oral granules of the present invention are flowable and dispersible pharmaceutical composition, which comprises granules having a substrate coated with montelukast sodium.

In the present invention, the substrate may be any pharmaceutically acceptable; typically a sugar such as mannitol, sucrose, lactose, xylitol or the like is used. The substrate is preferably used in a form that is free-flowing, a characteristic that facilitates accurate dosing of the final product granules into unit-dose pouches. If the substrate is not free-flowing, it is necessary to agglomerate individual particles into larger granules.

In cases where the substrate is very free-flowing on its own it may be used in producing the drug granules without further agglomeration; or optionally, the substrate may be first agglomerated with a pharmaceutically acceptable binder. Suitable pharmaceutically acceptable binders are for example hydroxypropyl cellulose, hydroxypropyl...
methylcellulose, methylcellulose, ethyl cellulose and polyvinylpyrrolidone. The agglomeration of the substrate particles is carried out by applying an aqueous solution of the binder onto the substrate, for example by spraying a solution of the binder onto a fluidized bed of the substrate. The binder, when used, typically comprises from about 2 to about 5% of the composition. The resultant agglomerated substrate particles are dried and used in the next step.

The substrate particles are coated with montelukast sodium by, for example, spraying an aqueous drug solution directly on to a fluidized bed of the substrate to produce the drug granules. The granulation process results in drug coated granules, which after drying are blended with a lubricant and used to fill the final product container. Suitable lubricants are pharmaceutically acceptable and include, without limitation, magnesium stearate, talc, and the like. The lubricant typically comprises from about 0.25 to about 1% of the composition.

One of skill in the art will appreciate that other inert ingredients may be added to the composition to impart to the final product desired properties such as taste or appearance; for example, sweeteners such as aspartame, flavoring compounds, and food colorings may be added.

The coating of montelukast onto the substrate particles is carried out in fluid bed granulator with top spray assembly.

For the preparation of the drug granules, the substrate is charged into the fluid bed granulator equipped with a top-spray nozzle. The aqueous solution of the binder may be sprayed onto the fluidized substrate at a specific rate to form granules. The granules are dried and the dried granules are sprayed with the aqueous solution of montelukast sodium. The resultant granules are dried and the granule are further sized and blended with the lubricant.
The temperature and the time for which montelukast is exposed to high temperature is critical during processing. If montelukast in solution form is exposed to higher temperature the sulfoxide impurity is formed to a greater extent.

The manufacturing process comprises of granulation with montelukast sodium solution at high inlet and bed temperature that would help to reduce the granulation time and ultimately exposure to air which in turn would help to reduce the oxidative impurity.

The inlet temperature for the granulation of montelukast may be in the range of 75°C to 100°C.

In an embodiment of the present invention inlet temperature for the granulation of montelukast may be in the range of 75°C to 90°C.

The bed temperature for the granulation of montelukast may be in the range of 40°C to 55°C.

In an embodiment of the present invention bed temperature for the granulation of montelukast may be in the range of 43°C to 50°C.

In an embodiment of the present invention, the inlet air of the fluid bed granulator was replaced with Nitrogen.

In an embodiment of the present invention, the amount of sulfoxide impurity formed is less than 0.5% by weight of the initial amount of montelukast.

In another embodiment of the present invention, the amount of sulfoxide impurity formed is less than 0.3% by weight of the initial amount of montelukast.
The granules prepared by the present invention may also be compressed into tablets by the addition of other excipient such as diluents, disintegrates, lubricants, sweetening agents, flavoring agents, coloring agents, wetting agents, glidants.

The invention is further defined by reference to the following examples describing in detail methods for the preparation and testing of montelukast compositions. The following examples further illustrate certain specific aspects and embodiments of the invention in detail and are not intended to limit the scope of the invention.

**Example**

Example 1

Process for making montelukast granules at higher inlet and bed temperature

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Ingredient</th>
<th>mg/unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Montelukast Sodium</td>
<td>4.15</td>
</tr>
<tr>
<td>2.</td>
<td>Hydroxypropyl cellulose (Klucel LF)</td>
<td>10.40</td>
</tr>
<tr>
<td>3.</td>
<td>Mannitol</td>
<td>484.70</td>
</tr>
<tr>
<td>4.</td>
<td>Purified water^*</td>
<td>--</td>
</tr>
<tr>
<td>5.</td>
<td>Magnesium stearate</td>
<td>0.75</td>
</tr>
</tbody>
</table>

^Evaporates during processing.

1. Hydroxypropyl cellulose was dissolved in water with continuous stirring to obtain a clear solution.

2. Mannitol was passed through 20 mesh and transferred into fluid bed granulator and granulated with the solution from step no. 1 by using top spray at an inlet temperature of 80°C and maintaining bed temperature at 45°C-55°C.

3. The granules were dried in a fluid bed granulator till LOD was not more than 0.50%
4. Granules obtained in step 3 were passed through 20 mesh and oversized granules were milled through OG fitted with 1.0mm sieve.

5. Montelukast Sodium was dissolved in purified water with continuous stirring to obtain a clear solution.

6. The granules obtained from step no. 4 were granulated with the solution obtained from step no. 5 by using top spray at an inlet temperature 80°C and maintaining bed temperature 43-50°C.

7. The granules obtained from step 6 were dried in a fluid bed granulator till LOD is not more than 0.50%.

8. The dried granules were passed through 20 mesh and oversized granules were milled through OG fitted with 1.0mm sieve. The undersize and milled oversize granules were mixed in drum blender for 8 minutes.

9. The granules from step no. 8 were lubricated with magnesium stearate in a drum blender for 1 minute.

Example 2

Process for making montelukast granules at lower inlet and bed temperature

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Ingredient</th>
<th>mg/unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Montelukast Sodium</td>
<td>4.15</td>
</tr>
<tr>
<td>2.</td>
<td>Hydroxypropyl cellulose (Klucel LF)</td>
<td>10.40</td>
</tr>
<tr>
<td>3.</td>
<td>Mannitol</td>
<td>484.70</td>
</tr>
<tr>
<td>4.</td>
<td>Purified water*</td>
<td>--</td>
</tr>
<tr>
<td>5.</td>
<td>Magnesium stearate</td>
<td>0.75</td>
</tr>
</tbody>
</table>

*Evaporates during processing.

1. Hydroxypropyl cellulose was dissolved in water with continuous stirring to obtain a clear solution.
2. Mannitol was passed through 20 mesh and transferred into fluid bed granulator and granulated with the solution from step no. 1 by using top spray at an inlet temperature of 70°C and maintaining bed temperature 30°C-35°C.

3. The granules were dried in a fluid bed granulator till LOD was not more than 0.50%.

4. Granules obtained in step 3 were passed through 20 mesh and oversized granules were milled through OG fitted with 1.0mm sieve.

5. Montelukast Sodium was dissolved in purified water with continuous stirring to obtain a clear solution.

6. The granules obtained from step no. 4 were granulated with the solution obtained from step no.5 by using top spray at an inlet temperature 70°C and maintaining bed temperature 30-35°C.

7. The granules obtained from step 6 were dried in a fluid bed granulator till LOD is not more than 0.50%.

8. The dried granules were passed through 20 mesh and oversized granules were milled through OG fitted with 1.0mm sieve. The undersize and milled oversize granules were mixed in drum blender for 8 minutes.

9. The granules from step no.8 were lubricated with magnesium stearate in a drum blender for 1 minute.

Example 3

Determination of sulfoxide impurity in composition

HPLC method for detection of sulfoxide impurity

Sulfoxide impurity in montelukast was detected using HPLC. HPLC was performed on a C18 column [250mm x 4.9 mm, 5 microns]. The mobile phase was a gradient system comprising mobile phase A [1 ml of 3% TFA in water diluted to 2 litres of water] and mobile phase B [1 ml of 3% TFA in acetonitrile diluted to 2 litres with water] at a flow rate of 1.5 ml/min. Detection was done at 225 nm with and the column temperature was 25°C. The amount of sulfoxide impurity formed during processing was determined by HPLC.
Table 1: Effect of bed temperature on the formation of sulfoxide impurity with regards to the granulation time

<table>
<thead>
<tr>
<th>Bed temperature</th>
<th>Time</th>
<th>Sulfoxide impurity % w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>43°C-50°C</td>
<td>15 minutes</td>
<td>0.21</td>
</tr>
<tr>
<td>30°C-35°C</td>
<td>30 minutes</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Example 4

The pharmaceutical compositions prepared according to example 1 and example 2 were exposed to accelerated storage conditions [i.e. storage at about 40°C and about 75% relative humidity] The percentage by weight of sulfoxide relative to montelukast sodium in each sample was measured by HPLC immediately after the compositions were prepared and after 1 month under accelerated storage condition.

Table 2: Stability of montelukast sodium granules under accelerated storage condition

<table>
<thead>
<tr>
<th>Bed temperature</th>
<th>Sulfoxide impurity [% of initial amount of MLK]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
</tr>
<tr>
<td>43°C-50°C</td>
<td>0.21</td>
</tr>
<tr>
<td>30°C-35°C</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Example 5

Process for making montelukast granules in the presence of Nitrogen in the Fluid bed granulator.
Evaporates during processing.

1. Hydroxypropyl cellulose was dissolved in water with continuous stirring to obtain a clear solution.

2. Mannitol was passed through 20 mesh and transferred into fluid bed granulator and granulated with the solution from step no. 1 by using top spray at an inlet temperature of 80°C and maintaining bed temperature at 45°C-55°C.

3. The granules were dried in a fluid bed granulator till LOD was not more than 0.50%

4. Granules obtained in step 3 were passed through 20 mesh and oversized granules were milled through OG fitted with 1.0mm sieve.

5. Montelukast Sodium was dissolved in purified water with continuous stirring to obtain a clear solution.

6. The fluid bed granulator was fitted with the supply of nitrogen.

7. The granules obtained from step no. 4 were granulated with the solution obtained from step no.5 by using top spray at an inlet temperature 80°C and maintaining bed temperature 43-50°C.

8. The granules obtained from step 7 were dried in a fluid bed granulator till LOD is not more than 0.50%
9. The dried granules were passed through 20 mesh and oversized granules were milled through OG fitted with 1.0mm sieve. The undersize and milled oversize granules were mixed in drum blender for 8 minutes.

10. The granules from step no.9 were lubricated with magnesium stearate in a drum blender for 1 minute.

Table 3: Effect of Nitrogen atmosphere on the formation of sulfoxide impurity

<table>
<thead>
<tr>
<th>Bed temperature</th>
<th>Time</th>
<th>Sulfoxide impurity % w/w</th>
</tr>
</thead>
<tbody>
<tr>
<td>43°C-50°C</td>
<td>15 minutes</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Example 6

Process for making tablets by granulating montelukast at high inlet and bed temperature

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Ingredient</th>
<th>mg/unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Montelukast Sodium</td>
<td>10.375</td>
</tr>
<tr>
<td>2.</td>
<td>Microcrystalline cellulose</td>
<td>85.000</td>
</tr>
<tr>
<td>3.</td>
<td>Lactose monohydrate</td>
<td>89.125</td>
</tr>
<tr>
<td>4.</td>
<td>Hydroxypropyl cellulose</td>
<td>4.000</td>
</tr>
<tr>
<td>5.</td>
<td>Purified water*</td>
<td>--</td>
</tr>
<tr>
<td>6.</td>
<td>Croscarmellose sodium</td>
<td>6.000</td>
</tr>
<tr>
<td>7.</td>
<td>Microcrystalline cellulose</td>
<td>4.000</td>
</tr>
<tr>
<td>8.</td>
<td>Magnesium stearate</td>
<td>1.500</td>
</tr>
<tr>
<td>9.</td>
<td>Opadry Beige 03B34627</td>
<td>5.000</td>
</tr>
</tbody>
</table>

*Evaporates during processing.

1. Hydroxypropyl cellulose was dissolved in purified water with continuous stirring till clear solution was obtained.

2. Montelukast sodium, microcrystalline cellulose and lactose monohydrate were co-sifted and transfer to rapid mixer granulator and the material was mixed.
3. Binder solution of step 1 was added to mixer granulator at slow speed of chopper and impeller for approximately 3-4 minutes and the mixture was granulated.

4. The wet granules from step 3 were transferred to the preheated Fluid Bed Dryer and the granules were dried at product temperature NMT 50°C and inlet temperature between 80-90°C. The granules were dried till loss on drying was not more than 3.0% at 90°C for 15 minutes.

5. The dried granules from step no. 4 were passed through 20 mesh and the retained granules was passed through OG fitted with 1.5mm screen.

6. The sifted granules from step 5 were loaded into a bin blender.

7. The remaining parts of microcrystalline cellulose and croscarmellose sodium were sifted and mixed with the sifted granules for 15 minutes.

8. Magnesium stearate was added to the blend obtained from step 7.

9. The blend was further compressed into tablets.

10. The tablets were then coated with Opadry.

Example 7

The pharmaceutical compositions prepared according to example 6 were exposed to accelerated storage conditions [i.e. storage at about 40°C and about 75% relative humidity].

The percentage by weight of sulfoxide relative to montelukast sodium in each sample was measured by HPLC immediately after the compositions were prepared and after 1, 2 and 3 months under accelerated storage condition.

Table 4: Stability of montelukast sodium tablets under accelerated storage condition

<table>
<thead>
<tr>
<th>Time period [Months]</th>
<th>Sulfoxide impurity [% of initial amount of MLK]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>0.19</td>
</tr>
<tr>
<td>1</td>
<td>0.23</td>
</tr>
<tr>
<td>2</td>
<td>0.21</td>
</tr>
<tr>
<td>3</td>
<td>0.26</td>
</tr>
</tbody>
</table>
Claims

1. A process for the preparation of oral montelukast sodium granules, said process comprising granulation in a fluid bed granulator, at high bed temperature such that the content of sulfoxide impurity in the oral montelukast sodium granules is less than 0.5%.

2. The process according to claim 1 wherein the bed temperature is in the range of 40°C to 55°C.

3. The process according to claim 2, wherein the bed temperature is in the range of 43°C to 50°C.

4. The process according to claim 1, wherein the content of sulfoxide impurity formed is less than 0.3%.

5. A process for the preparation of oral montelukast sodium granules, said process comprising granulation in a fluid bed granulator, at high bed temperature in an atmosphere of Nitrogen such that the content of sulfoxide impurity in the oral montelukast sodium granules is less than 0.5%.