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(57) Abstract: The present invention relates to compositions designed to remove negative effects of excipients used in the formulations comprising montelukast and/or a pharmaceutically acceptable salt thereof on the active agent.

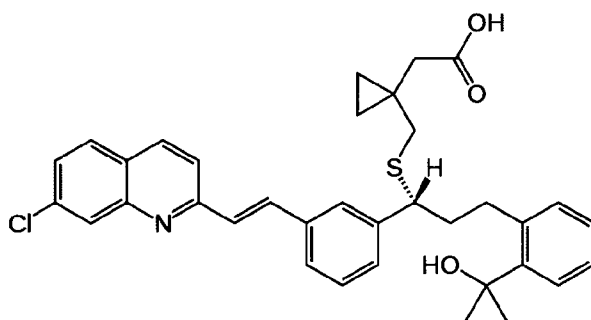


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IMPROVED MONTELUKAST FORMULATIONS

The present invention relates to compositions designed to remove negative effects of excipients used in the formulations comprising montelukast and/or a pharmaceutically acceptable salt thereof on the active agent.

- 5 Montelukast is a leukotriene receptor antagonist which was firstly disclosed in the patent numbered EP480717 A1 (Formula I):

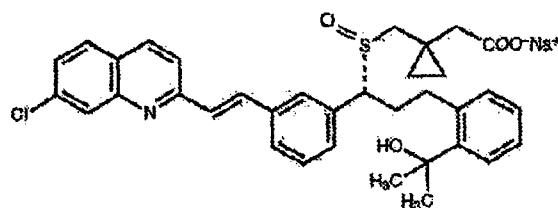


Formula (I)

- Montelukast is a strong and selective antagonist of leukotriene D₄ (LTD₄) which is effective on cysteinyl leukotriene receptor (CysLT₁) in the respiratory tract. Cysteinyl leukotrienes (LTC₄, LTD₄, LTE₄) are strong inflammatory eicosanoids released from various cells including mast cells and eosinophils. These important pro-asthmatic mediators bind to cysteinyl leukotriene (CysLT) receptors located in the respiratory tract and lead to a series of respiratory tract activities such as bronchoconstriction, intensive mucus secretion, vascular permeability and accumulation of eosinophils.

However, the active agent montelukast is highly incompatible with excipients used in pharmaceutical formulations. This incompatibility induces a fast disintegration in the end product.

- The most important impurity that shows up with the disintegration of montelukast sodium is sulfoxide impurity illustrated with the following formula (II):

**Formula (II)**

This sulfoxide impurity appears when the sulphide group in montelukast sodium is oxidized to sulfoxide group and it is not in an active form. However, its presence reduces the effective dose of montelukast sodium in the treatment and therefore it reduces the efficiency of the treatment.

In the prior art stable formulations comprising excipients which are used in montelukast formulations and do not cause stability or incompatibility problems with the active agent have been designed.

For instance, the patent application numbered WO/2010/041277 discloses tablet formulations which comprise montelukast, microcrystalline cellulose and a flavoring agent together with magnesium stearate.

The application WO/2007/092031 discloses pharmaceutical compositions of montelukast which do not comprise microcrystalline cellulose. In this application, magnesium stearate is used as lubricant.

Montelukast sodium is currently marketed in chewable tablet, film coated tablet and pediatric granule form under the trade name Singulair®. Film coated Singulair® formulations comprise microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose as excipient and magnesium stearate as lubricant.

However, the inventors surprisingly found that use of magnesium stearate as a lubricant in the production of montelukast sodium formulations leads to incompatibility in the pharmaceutical composition and also the rate of sulfoxide impurity is higher than expected. Formulations in which magnesium stearate was used were stored with 60% of relative humidity rate and at 45 °C for 4 weeks and the sulfoxide impurity in these formulations appeared to be more than 1%.

As a result, use of magnesium stearate results in faster degradation of montelukast sodium, which is considerably susceptible to and highly incompatible with pharmaceutical excipients, than expected.

5 In addition, magnesium stearate as a lubricant does not provide sufficient flow to formulations; therefore, the formulations produced adhere to metal members through the production line. This kind of adhesion causes loss of active ingredient and thus, reduction of bioavailability.

10 The inventors have developed new formulations using a pharmaceutically acceptable lubricant which would not cause incompatibility and degradation in order to provide sufficient fluidity in montelukast formulations.

Use of silicone oil, siliconized talc and/or liquid paraffin or dual or triple combinations thereof as lubricant in the formulations of the present invention have surprisingly improved fluidity and stability properties of the formulations to a considerable extent.

15 The formulations of the present invention was kept under accelerated storage conditions and the post measurements showed that sulfoxide impurity in the formulations was below 0.6 %.

Detailed Description of the Invention

The present invention relates to stabile montelukast formulations with improved flow characteristics which do not cause incompatibility with excipients.

20 Studies conducted under certain circumstances have indicated that use of silicone oil, siliconized talc and/or liquid paraffin or dual or triple combinations thereof as lubricant in the formulations developed according to the present invention does not cause any incompatibility or degradation in the formulations.

25 The montelukast formulations developed according to the present invention were kept under accelerated storage conditions and post HPLC (High Performance Liquid Chromatography) measurements indicated that sulfoxide impurity remained below 0.6 %.

The pharmaceutical formulation of the present invention characterized in that said formulation comprises sulfoxide impurity less than 0.60 % by weight, preferably less than 0.30 % by weight, more preferably in the range of 0.01 to 0.30 % by weight.

The term “accelerated storage conditions” used throughout the text refers to storage of formulations at 60 % of relative humidity and at 45 °C for 4 weeks.

In addition; use of silicone oil, siliconized talc and/or liquid paraffin or dual or triple combinations thereof as a lubricant in the formulations prevented adhesion of the formulation on the surfaces of the machines during the process and minimized active agent loss. The lubricant or lubricant combinations used formed a considerably smooth film layer on montelukast particles and thus provided to improve flow characteristics.

As a result of the studies they conducted, the inventors of the present invention have surprisingly found that use of silicone oil, siliconized talc and/or liquid paraffin or dual or triple combinations thereof as lubricant in montelukast formulations does not cause any degradation with highly sensitive montelukast and also provides a significant improvement on the flow characteristics of the formulations. Thus, they have obtained montelukast formulations which have both high stability and flow characteristics.

The amount of silicone oil, siliconized talc and/or liquid paraffin or dual or triple combinations thereof used as lubricant in the formulations of the present invention is in the range of 0.1 to 10 % by weight, preferably in the range of 0.1 to 5 % by weight, and more preferably in the range of 2 to 5 % by weight

Formulations of the present invention can comprise at least one other pharmaceutically acceptable lubricant in addition to these lubricants.

Other lubricants that can be used in the formulations of the present invention can be selected from a group comprising lauric acid, palmitic acid, stearic acid, behenic acid and/or pharmaceutically acceptable salts thereof, siliconized talc, simethicone, dimethicone, liquid paraffin, sodium stearyl fumarate, sodium lauryl sulfate, magnesium lauryl sulfate, magnesium lauryl sulfate, magnesium stearate, lecithine, L-leucine, phosphatidylcholines, phosphateidylglycerides, triglycerides and they are comprised in the formulations in the range of 0.1 to 5 % by weight.

The term “montelukast” used throughout the text refers to montelukast or a pharmaceutically acceptable salt, solvate, derivative, polymorph, hydrate or enantiomer thereof though it is preferably in salt form.

Montelukast used in the formulations of the present invention is preferably in sodium salt form and its amount is in the range of 1 to 30 % by weight, more preferably in the range of 1 to 20 % by weight, and most preferably in the range of 1 to 10 % by weight.

The term "siliconized oil" used throughout the text refers to dimethicone and/or silicone analogs of carbon based organic compounds including simethicone which is the activated form of dimethicone.

Montelukast formulations of the present invention are used orally. Pharmaceutical formulations to be used orally can be in the form of tablets, capsules, soluble tablets, layered tablets, effervescent tablets, chewable tablets, coated tablets, soluble granules, soluble powders, emulsions, suspensions, solutions or combinations thereof.

Formulations of the present invention can be combined with a second active agent. The second active agent can be nasal decongestants, leukotriene receptor antagonists, antihistaminics, antidepressants.

The second active agent used in the formulations of the present invention is preferably an antihistaminic substance though it can be selected from a group comprising diphenhydramine, dimenhydrinate, carbinoxamine, chlorphenoxamine, mepyramine, antazoline, trielamine, dexbrompheniramine, dexchlorpheniramine, pheniramine, buclizine, hydroxyzine, cinnarizine, meclizine, alimemazine, promethazine, cyproheptadine, ebastine, astemizole, acrivastine, loratadine, desloratadine, ketotifen, cetirizine, levocetirizine or pharmaceutically acceptable salts, solvates, derivatives, polymorphs, hydrates or enantiomers thereof.

The second active agent used in the formulations is preferably desloratadine or levocetirizine and/or pharmaceutically acceptable salts thereof.

The second active agent can be used with montelukast simultaneously, sequentially or separately.

However, in the preferred embodiment of the invention, the two active agents are combined in a single dosage form by formulating them separately or together.

The pharmaceutical formulations of the present invention comprise other pharmaceutically acceptable components such as additives and excipients selected from disintegrants, viscosity enhancers, filling materials, drying agents, lubricants, diluents, binders, glidants, anti-foam agents, wetting agents, effervescent mixtures, sweeteners and flavoring agents.

The pharmaceutically acceptable disintegrants that can be used in the present invention can be selected from polymers having high disintegrating characteristics, for instance cross-linked hydroxypropyl cellulose, croscarmellose sodium, polyvinylpyrrolidone, high molecular weight polymers, microcrystalline cellulose, corn starch, sodium starch glycolate, povidone, alginic acid, sodium alginate.

The pharmaceutically acceptable binders that can be used in the present invention can be selected from potato starch, wheat starch or corn starch; microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose; hydroxypropylmethyl cellulose and polyvinylpyrrolidone.

The pharmaceutically acceptable diluents that can be used in the present invention can be selected from lactose, microcrystalline cellulose, starch, pregelatinized starch, modified starch, calcium phosphate (dibasic and/or tribasic), calcium sulfate trihydrate, calcium sulfate dihydrate, calcium carbonate, kaolin, lactitol, cellulose powder, dextrose, dextrates, dextrin, sucrose, maltose, fructose, mannitol, direct compression mannitol, direct compression lactose, sorbitol and xylitol.

The pharmaceutically acceptable film coating material that can be used in the present invention is composed of the following components or combinations thereof: lactose, hydroxypropyl methyl cellulose, triacetate, titanium dioxide, polyvinyl alcohol, talc, lecithin, polyethylene glycol.

The pharmaceutically acceptable stabilizing agent and/or agents that can be used in the present invention can be selected from antioxidants, chelating agents, alkalinizing agents and photoprotectives.

Antioxidants can be selected from substances such as butylated hydroxyl anisole (BHA), sodium ascorbate, butylated hydroxyl toluene (BHT), sodium sulfite, gallates (such as propyl gallate), tocopherol, citric acid, malic acid, ascorbic acid, acetylcysteine, fumaric acid, lecithine, ascorbyl palmitate, ethylenediamine tetraacetate.

Chelating agents can be selected from disodium EDTA, edetic acid, citric acid, sodium citrate, potassium citrate or combinations thereof. These agents prevent oxidation by surrounding and masking the metal ions which may catalyze the oxidation process.

Alkalinizing agents can be selected from alkaline metal salts such as sodium carbonate, sodium bicarbonate, sodium hydroxide, sodium silicate, disodium hydrogen orthophosphate, sodium aluminate; alkaline earth metal salts such as calcium carbonate, calcium hydroxide, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulphate, calcium acetate, 5 calcium gluconate, calcium glycerophosphate, calcium hydrogen phosphate dihydrate, magnesium carbonate, magnesium hydroxide, magnesium sulphate, magnesium acetate, magnesium silicate, magnesium aluminate; and organic compounds such as primary, secondary and tertiary amines, cyclic amines; N,N'-dibenzyl ethylenediamine, diethanolamine, ethylenediamine, meglumine, monosodium glutamate, polacrilin sodium, 10 sodium alginate.

The photoprotective agents can be selected from metal oxides such as titanium oxide, iron oxide or zinc oxide.

In addition to these, other pharmaceutically acceptable excipients such as solubility modulators, electrolytes, colorants and coating agents can also be used in the formulation.

15 Formulations of the present invention are used for relieving, preventing and/or treating seasonal allergic rhinitis; perennial rhinitis; asthma; the symptoms of aspirin-sensitive asthma and exercise-induced bronchoconstriction.

Montelukast formulations of the present invention can be produced by any methods in the prior art. These methods include wet granulation, dry granulation, direct compression, dry 20 blending.

Examples of pharmaceutical formulations of the present invention are given below. These examples are given in order to explain the invention, yet the invention is not restricted to these examples.

EXAMPLES**Example 1.** Tablet Formulation Comprising Montelukast Sodium

Composition	Percent (%) by Weight
Montelukast Sodium	6.00
Diluent	85.00
Disintegrant	2.50
Binder	2.00
Simethicone	0.15
Other pharmaceutical excipient/excipients	2.85
Coating Agent	1.50

The method for preparation of the formulation given above preferably comprises the following steps:

1. Montelukast sodium, the diluent, the disintegrant and the binder were mixed and sieved.
2. Simethicone is added to the mixture obtained and mixed.
3. Preferably, another lubricant is added to the simethicone-added composition and mixed.
4. The mixture prepared is loaded to tablet compression machine and the tablets compressed are coated with film.

Table 1. Stability data for Example 1

The montelukast tablet formulations manufactured by formulation and method given above were kept at 60 % of relative humidity and at 45 °C for 4 weeks (under accelerated storage conditions) and the amount of sulfoxide impurity were determined by using HPLC (High
5 Performance Liquid Chromatography) measurements. The results obtained are served below:

Time (Week)	Sulfoxide Impurity (%)
Start	0.07
1	0.08
2	0.08
3	0.09
4	0.10

5.

The results have showed that the sulphoxide impurity is under 0.6 % in the montelukast formulations which were prepared by using simethicone in an amount of 0.15 % by weight.

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CLAIMS

1. A pharmaceutical formulation comprising montelukast or a pharmaceutically acceptable salt, solvate, derivative, polymorph, hydrate or enantiomer thereof as active agent characterized in that the lubricant used in said formulations is silicone oil, siliconized talc and/or liquid paraffin or dual or triple combinations thereof.
2. The pharmaceutical formulation according to claim 1 characterized in that said formulation comprises silicone oil, siliconized talc and/or liquid paraffin or combinations thereof in the range of 0.1 to 10% by weight.
3. The pharmaceutical formulation according to claims 1 to 2 characterized in that said formulation comprises silicone oil, siliconized talc and/or liquid paraffin or dual or triple combinations thereof in the range of 0.1 to 5% by weight.
4. The pharmaceutical formulation according to claims 1 to 3 characterized in that said formulation comprises silicone oil, siliconized talc and/or liquid paraffin or dual or triple combinations thereof in the range of 2 to 5% by weight.
5. The pharmaceutical formulation according to any one of the preceding claims characterized in that silicone oil is dimethicone and/or simethicone.
6. The pharmaceutical formulation according to any one of the preceding claims characterized in that said formulation preferably comprises at least one other pharmaceutically acceptable lubricant.
7. The pharmaceutical formulation according to claim 6 characterized in that the amount of the other lubricant used in the formulation is in the range of 0.1 to 5 % by weight.
8. The pharmaceutical formulation according to any one of the preceding claims characterized in that said formulation comprises montelukast sodium salt as the active agent.
9. The pharmaceutical formulation according to claim 8 characterized in that said formulation comprises montelukast sodium in the range of 1 to 30 % by weight.
10. The pharmaceutical formulation according to claim 9 characterized in that said formulation comprises montelukast sodium in the range of 1 to 20 % by weight.
11. The pharmaceutical formulation according to claims 9 to 10 characterized in that said formulation comprises montelukast sodium in the range of 1 to 10 % by weight.
12. The pharmaceutical formulation according to any one of the preceding claims characterized in that said formulation comprises a second active agent.

13. The pharmaceutical formulation according to claim 12 characterized in that the second active agent is selected from a group comprising nasal decongestants, leukotriene receptor antagonists, anti-histaminics, anti-depressants.
14. The pharmaceutical formulation according to claim 13 characterized in that the second active agent is an anti-histaminic substance.
15. The pharmaceutical formulation according to claim 14 characterized in that the anti-histaminic substance used as a second active agent is selected from a group comprising diphenhydramine, dimenhydrinate, carbinoxamine, chlorphenoxamine, mepyramine, antazoline, tripelemin, dexchlorpheniramine, dexbrompheniramine, pheniramine, buclizine, hidroksizinin, cinnarazine, meclizine, alimemazine, promethazine, cyproheptadine, ebastine, astemizol, acrivastine, loratadine, desloratadine, ketotifen, cetirizine, levocetirizine.
16. The pharmaceutical formulation according to claim 15 characterized in that the second active agent is desloratadine or levocetirizine or a pharmaceutically acceptable salt, solvate, derivative, polymorph, hydrate or enantiomer thereof.
17. The pharmaceutical formulation according to claim 1 characterized in that said formulation is used in the manufacture of a medicament for relieving, preventing and/or treating seasonal allergic rhinitis; perennial rhinitis; asthma; the symptoms of aspirin-sensitive asthma patients and exercise-induced bronchoconstriction.