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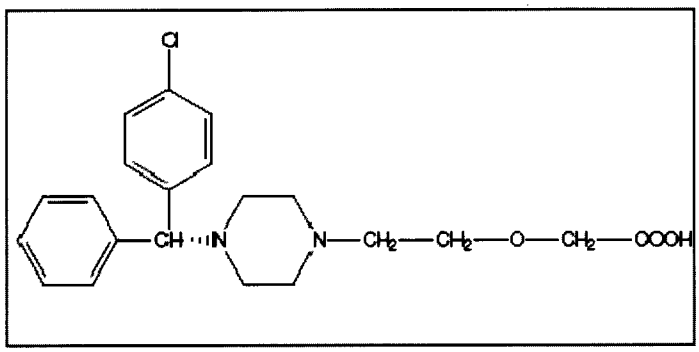
(54) **Title**: FORMULATIONS WITH IMPROVED PHYSICAL CHARACTERISTICS

(57) **Abstract**: The present invention comprises a combination of an Hl-antihistaminic and a leukotriene receptor antagonist which is effective in prevention and/or treatment of allergic and inflammatory diseases of the skin or upper and lower respiratory tracts and relieving the symptoms thereof.

FORMULATIONS WITH IMPROVED PHYSICAL CHARACTERISTICS

The present invention comprises a combination of an H_1-antihistaminic and a leukotriene receptor antagonist which is effective in prevention and/or treatment of allergic and inflammatory diseases of the skin or upper and lower respiratory tracts and relieving the symptoms thereof.

Levocetirizine (Formula I), chemical name of which is 2-[2-[4-[(R)-(4- chlorophenyl)-phenyl- methyl]piperazine-1-yl] ethoxy] acetic acid, is a non-sedating, long-acting H1-histaminic.



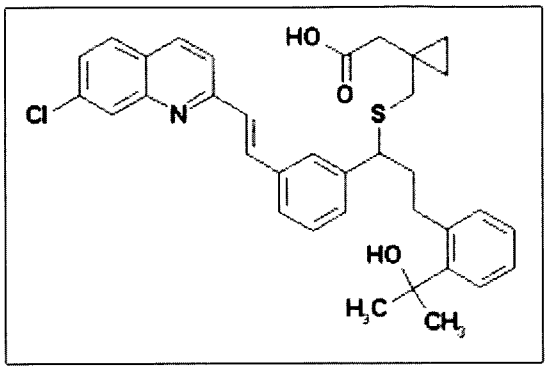
Formula (I)

Cetirizine was first disclosed in the patent numbered EP0058146 A1. The patent numbered GB2225321 A for preparation process of levocetirizine and the patent numbered WO9406429 A1 for use of levocetirizine in treatment of allergic diseases are among the first patents related to levocetirizine which is the R-enantiomer of cetirizine.

Levocetirizine which is the R-enantiomer of cetirizine is a piperazine derivative, potent and selective H1 receptor antagonist. Levocetirizine is a new antihistaminic which binds to H1 receptors with high affinity, even two times higher as compared to cetirizine.

Levocetirizine has anti-allergic and anti-inflammatory activity. The studies conducted have shown that levocetirizine inhibits a comprehensive series of reactions that induce and disseminate allergic inflammation.

As for montelukast (Formula II), chemical name of which is 1-[[[(1R)-1-[3-[(1E)-2-(7-chloro-2-quinolinyl)ethenyl]phenyl3-[2-(1-hydroxy-1-methyl-ethyl)phenyl]propyl]thio]methyl] cyclopropane acetic acid, is a leukotriene receptor antagonist.



Formula (II)

Montelukast was first disclosed in the patent numbered EP480717 A1. Processes for preparation of montelukast and also use of montelukast as leukotriene antagonist are clarified in the patent.

Montelukast is an orally-used, potent and selective antagonist of leukotriene D4 (LTD_4) which is effective on cysteinyl leukotriene receptor ($CysLT_1$) in the respiratory tract. Cysteinyl leukotrienes (LTC_4, LTD_4, LTE_4) are powerful inflammatory eicosanoids which are secreted by various cells including mast cell and eosinophils. These important pro-asthmatics mediators bind to cysteinyl leukotriene receptors ($CysLT_1$) in the respiratory tract and cause a range of respiratory activities such as bronchoconstriction, intensive mucus secretion, vascular permeability and eosinophil accumulation.

Montelukast is a powerful compound which treats asthma inflammation parameters significantly. Montelukast binds to $CysLT_1$ receptor with a high affinity and selectivity and strongly inhibits physiological effects of LTC_4, LTD_4, LTE_4 in $CysLT_1$ receptor without any agonist activity.

Use of levocetirizine and montekulast together is explained in the prior art. For instance, the patent numbered WO2003101434 discloses intranasal use of an antihistamine and a leukotriene inhibitor in the treatment and prevention of allergic rhinitis and symptoms thereof. The antihistaminic group active agent given here is presented as loratadine or desloratadine while the leukotriene inhibitor is presented as montelukast in said patent.

However, as a result of the studies conducted, the inventor has found that the combination product does not have enough hardness in some cases; for instance when said product is produced in tablet dosage form or when the product is required to be used as stored in blisters.

As it is known, tablet hardness relates to resistance of tablets against corrosion, breakage before storing, carrying, coating and use. Low-hardness tablets are exposed to corrosion, disintegration or breakage more. Such situations cause active agent loss.

Furthermore, there is a close correlation between tablet hardness and dispersibility. Since extra hard tablets cannot disintegrate and dissolve as required, the bioavailability of these tablets shall decrease and therefore it shall take longer to get the desired biological response. When all these parameters are taken into consideration, it is aimed that tablet hardness is low enough to enable the tablet to disintegrate fast in stomach while it is high enough to preserve tablet integrity from production to patients' use; during packing, carrying and storing.
There are many patent applications that disclose montelukast formulations and production method thereof. For instance, the patent numbered WO2007092031 (A1) discloses montelukast formulations which have less than 1% of sulfoxide impurity and do not comprise microcrystalline cellulose, and processes for production thereof. Production of montelukast tablet formulations by wet granulation method is also clarified in this patent.

However, it has been seen that the tablet obtained when the formulation and production method of said patent are applied to montelukast and combinations thereof does not have desired mechanical properties.

As montelukast is rather prone to degrade easily, production method and formulation to be used for tablet production should be selected quite carefully in order to provide adequate mechanical properties.

In addition to this, although use of different amounts of various pharmaceutically acceptable excipients in order to improve mechanical properties of the tablet is available in the prior art, this is quite a hard solution offer to be implemented for active agents which are affected by environmental conditions easily and incompatible with most of the pharmaceutical excipients.

When the prior art is taken into consideration, hardness problem of tablet formulations comprising montelukast and combinations thereof has not been referred to and therefore no solution has been suggested.

The present invention aims to provide a pharmaceutical formulation that can be used for preparation of highly stable tablets which have sufficient tablet hardness, also possess sufficient dispersibility and solubility characteristics.

As a result of the studies they conducted, the inventors have surprisingly achieved to produce stable pharmaceutical tablets which have sufficient hardness value and are also sufficiently well-dispersible and soluble by using two diluents having different features and different rates in montelukast formulations and combinations of these formulations with at least one other active agent.

The diluents in the formulations of the present invention are selected from a group comprising alkali metal carbonates, cellulose derivatives (microcrystalline cellulose, cellulose acetate etc.), dextrin, fructose, dextrose, glyceryl palmitostearate, lactitol, lactose, directly compressible lactose, maltose, mannitol, simethicone, sorbitol, starch, talc, xylitol and/or hydrates, anhydrates and/or derivatives thereof.

One characteristic feature of the formulations of the present invention is that the formulations comprise lactose or pharmaceutically acceptable hydrate or anhydrate and mannitol.

Another characteristic feature of the formulations of the present invention is that the ratio of the two diluents used in the formulations to each other (lactose or a pharmaceutically acceptable hydrate or anhydrate thereof : mannitol) is in the range of 0.1 to 5 by weight.

Another characteristic feature of the formulations of the present invention is that the ratio of the two diluents used in the formulations to each other (lactose or a pharmaceutically acceptable hydrate or anhydrate thereof : mannitol) is in the range of 0.1 to 1 by weight.

Another characteristic feature of the formulations is that the ratio of the two diluents used in the formulations to each other (lactose or a pharmaceutically acceptable hydrate or anhydrate thereof : mannitol) is in the range of 0.6 to 1 by weight.

Another characteristic feature of the formulations of the present invention is that the average particle size (D50) of lactose or a pharmaceutically acceptable hydrate or anhydrate thereof and mannitol used as diluent in the formulations is maximum 150 μm.

Another characteristic feature of the formulations of the present invention is that the average particle size (D50) of lactose or a pharmaceutically acceptable hydrate or anhydrate thereof and mannitol used as diluent in the formulations is maximum 130 μm.

Another characteristic feature of the formulations of the present invention is that the average particle size (D50) of lactose or a pharmaceutically acceptable hydrate or anhydrate thereof and mannitol used as diluent in the formulations is in the range of 1 to 120 μm.

The term ''D (50) particle size'' stated herein refers to particle size including 50% of the particles by volume.

Another characteristic feature of the formulations of the present invention is that the formulations comprise lactose monohydrate and mannitol as diluent.

Another characteristic feature of the formulations of the present invention is that the formulations comprise lactose anhydrate and mannitol as diluent.

Another characteristic feature of the formulations of the present invention is that the formulations are in tablet, film coated tablet or bilayer tablet form.

Montelukast formulations of the present invention are used as combined with at least one other active agent.

The second active agent stated herein is preferably an antihistaminic and selected from a group comprising diphenhydramine, dimenhydrinate, carbinoxamine, chlorphenoxamine, mepyramine, antazoline, triple amine, dexchlorpheniramine, dexbrompheniramine, 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 levocetirizine dihydrochloride.

The second active agent can be used with montekulast simultaneously, sequentially or separately. However, the two active agents are combined in a single dosage form in the preferred embodiment of the present invention.

The term ''montelukast'' stated in the text refers to montelukast and its pharmaceutically acceptable salts, solvates, derivatives, polymorphs, hydrates or enantiomers. Preferably, montelukast used in the formulations of the present invention is in the form of sodium salt.

The formulations of the present invention can comprise other pharmaceutically suitable components such as additives and excipients selected from disintegrants, viscosity enhancing

components, filling agents, drying agents, stabilizing agents, lubricants, diluents, binders, glidants, anti-foaming agents, wetting agents, effervescent mixtures, sweeteners and flavourings agents.

The disintegrant that can be used in formulations of the present invention can be selected from highly dispersive polymers, for instance cross-linked hydroxypropyl cellulose, polyvinylpyrrolidone, high-molecular-weight polymers, microcrystalline cellulose, sodium starch glycolate, povidone, alginic acid, sodium alginate.

The binders that can be used in formulations of the present invention comprise one or more components selected from the group comprising potato starch, wheat starch or corn starch; microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, hypromellose and polyvinylpyrrolidone.

The lubricants that can be used in formulations of the present invention comprise one or more components selected from the group comprising highly metallic stearates (magnesium stearate, calcium stearate, aluminium stearate etc), fatty acid esters (sodium stearyl fumarate etc), fatty acids (stearic acid etc), fatty alcohols, glyceryl behenate, mineral oil, paraffins, L-Leucine, hydrogenated vegetable oil, leucine, polyethylene glycols (PEG), metallic lauryl sulphates (sodium lauryl sulphate, magnesium lauryl sulphate), sodium chloride, sodium benzoate, sodium acetate and talc and/or hydrates thereof.

The stabilizing agent that can be used in formulations of the present invention can be selected from alkaline metal salts such as sodium carbonate, sodium hydrogen carbonate, 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, calcium gluconate, calcium glycerophosphate, magnesium carbonate, magnesium hydroxide, magnesium sulphate, magnesium acetate, magnesium silicate, magnesium aluminate; organic components such as primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzyl ethylenediamine, diethanolamine, ethylenediamine, meglumine, monosodium glutamate, polacrilin sodium, sodium alginate and/or pharmaceutically acceptable hydrates and/or derivatives thereof.

The filling agents that can be used in formulations of the present invention comprises one or more components selected from the group comprising lactose, sugar, starch, modified starch, mannitol, sorbitol, inorganic salts, microcrystalline cellulose, cellulose, calcium sulphate, xylitol and lactitol.

The film coating agent that can be used in formulations of the present invention comprises components such as lactose, hydroxypropyl methyl cellulose, triacetine, titanium dioxide, polyvinyl alcohol, talc, lecithin, polyethylene glycol and/or combinations thereof.

The sweeteners that can be used in formulations of the present invention comprise one or more components selected from the group comprising aspartame, dextrose, fructose, sucralose, sodium cyclamate, mannitol, maltose, saccharine and/or pharmaceutically acceptable salts thereof.

The combined product of the present invention comprising levocetirizine dihydrochloride along with an effective amount of montelukast sodium is preferably in bilayer tablet form; basically composed of two different formulations.

The first formulation comprises an effective amount of levocetirizine dihydrochloride and a specific amount of lactose or a pharmaceutically acceptable hydrate or anhydrate thereof as diluent; the second formulation comprises an effective amount of montelukast sodium and a specific amount of mannitol as diluent.

The ratio of the diluents to each other (lactose or a pharmaceutically acceptable hydrate or anhydrate thereof : mannitol) in these two phases is in the range of 0.1 to 5 by weight, preferably in the range of 0.1 to 1 by weight, more preferably in the range of 0.6 to 1 by weight.

The two different formulations prepared are produced in the form of bilayer tablet by direct compression method by being fed separately to the tablet compression machine. Values of tablet hardness analysis which was run under approximately 15 kN pressure using 10 samples taken from different production lines of the bilayer tablets produced this way are identified and showed in the table below.

Tablets which have enough breaking load and hardness can be produced by providing enough flow rate of the dry powder formulation in direct compression method. Hardness value of the bilayer tablets produced according to the invention is at least 10 kP, preferably in the range of 10-50 kP, more preferably in the range of 10-20 kP.

Sufficient fluidity property and tablet hardness in the formulations of the present invention have been solved by adjusting the amount, the type and particle size of the diluents used in the formulations.

The present invention also provides a production method for production of tablet formulations given above.

Tablet formulations of the present invention can also be produced by any method in the prior art; for instance, wet granulation, dry granulation, dry blending though said production method preferably comprises the following steps:

1. **Preparation of the first formulation**
   a. Mixing and sieving montelukast or a pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof; mannitol and at least one other pharmaceutical excipient,
   b. Adding a pharmaceutically acceptable lubricant into the mixture obtained in the first step and preparing the first formulation by mixing the mixture.
2. **Preparation of the second formulation**
   c. Mixing and sieving levocetirizine or a pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof; lactose or a pharmaceutically acceptable hydrate or anhydrate and at least one other pharmaceutical excipient,
   d. Adding a pharmaceutically acceptable lubricant into the mixture obtained in the first step and preparing the second formulation by mixing the mixture.
3. **Preparation of bilayer tablet dosage form**
   e. Preparing bilayer tablet dosage form by feeding the two formulations to tablet compression machine consecutively.
4. **Coating**
   The bilayer tablet dosage form prepared is coated with film.

The coating agent used in this step is preferably a film-coating agent and preferably comprises an effective amount of titanium dioxide. The coating agent comprising titanium dioxide enables montelukast, which is prone to degrade due to environmental conditions, to remain stabile during its shelf life.

In addition, the inventors have seen that the mixing times of the lubricants in step "b" and "d" of the bilayer tablet formulation which is prepared according to the production method clarified above affect mechanical properties of the end production.

Mixing time for montelukast formulation in step "b" is preferably 1-10 minutes, more preferably 1-5 minutes; mixing time for levocetirizine formulation in step "d" is preferably 1-

20 minutes, more preferably 1-15 minutes in production of the formulations of the present invention.

The bilayer tablet dosage form produced by said method has sufficient mechanical properties.

Hardness values of the bilayer tablet dosage form produced according to example I of the invention are given below:

Table I. Tablet hardness data

Sample no.	**Applied pressure (kN)**	**Tablet hardness (kP)**
1	15,3	12,4
2	15,1	12,8
3	14,5	13,5
4	15,5	13,2
5	15,0	11,7
6	15,2	10,9
7	14,6	11,5
8	15,5	13,8
9	14,7	13,7
10	15,3	12,5
Average	**15,0**	**12,6**

Examples of pharmaceutical tablet formulations of the present invention are presented below. These examples are given in order to clarify the subject of the invention; yet the subject of the invention is not limited to these examples.

EXAMPLES

Example 1: Film Coated Tablet Formulation

Content	Percent (%) by weight
Levocetirizine Dihydrochloride	1.50
Montelukast Sodium	3.50
Mannitol	35.00
Lactose	20.00
Disintegrant	5.00
Binder	5.00
Lubricant	3.00
Other pharmaceutical excipient/excipients	27.00
TOTAL	**100**

The film coated tablet formulation given above is prepared according to the production method explained in detail in description.

CLAIMS

1. A bilayer tablet formulation comprising montelukast and levocetirizine and/or pharmaceutically acceptable salts thereof characterized in that at least two different diluents having an average particle size of maximum 150 μm are used in the formulations.
2. The bilayer tablet formulation according to claim 1 characterized in that at least two different diluents having an average particle size of maximum 130 μm are used in the formulations.
3. The bilayer tablet formulation according to claim 2 characterized in that at least two different diluents having an average particle size in the range of 1 - 120 μm are used in the formulations.
4. The bilayer tablet formulation according to any preceding claims characterized in that at least two different diluents selected from a group comprising alkali metal carbonates, cellulose derivatives, dextrin, fructose, dextrose, glyceryl palmitostearate, lactitol, lactose, directly compressible lactose, maltose, mannitol, simethicone, sorbitol, starch, talc, xylitol and/or hydrates, anhydrates and/or derivatives thereof are used in the formulations.
5. The bilayer tablet formulation according to any preceding claims characterized in that lactose or a pharmaceutically acceptable hydrate or anhydrate thereof and mannitol are used as diluent in the formulations.
6. The bilayer tablet formulation according to claim 5 characterized in that lactose monohydrate and mannitol are used as lubricant in the formulations.
7. The bilayer tablet formulation according to claim 5 characterized in that lactose anhydrate and mannitol are used as diluent in the formulations.
8. The bilayer tablet formulation according to any preceding claims characterized in that the ratio of the two different diluents in the formulations to each other is in the range of 0.1 to 5 by weight.
9. The bilayer tablet formulation according to claim 8 characterized in that the ratio of the two different diluents in the formulations to each other is in the range of 0.1 to 1 by weight.
10. The bilayer tablet formulation according to claim 9 characterized in that the ratio of the two diluents in the formulations to each other is in the range of 0.6 to 1 by weight.

11. The bilayer tablet formulation according to any preceding claims characterized in that said formulation comprises montelukast sodium and levocetirizine dihydrochloride.
12. A method for production of the bilayer tablet formulation according to any preceding claims characterized in that the production method is composed of the following steps;
    a. Mixing and sieving montelukast or a pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof; mannitol and at least one other pharmaceutical excipient,
    b. Adding a pharmaceutically acceptable lubricant into the mixture obtained in the first step and preparing the first formulation by mixing the mixture,
    c. Mixing and sieving levocetirizine or a pharmaceutically acceptable salt, ester, solvate, derivative, polymorph or hydrate thereof; lactose or a pharmaceutically acceptable hydrate or anhydrate thereof and at least one other pharmaceutically acceptable excipient,
    d. Adding a pharmaceutically acceptable lubricant into the mixture obtained and preparing the second formulation by mixing the mixture,
    e. Preparing bilayer tablet dosage form by feeding the two formulations to tablet compression machine consecutively,
    f. Coating the bilayer tablet dosage form prepared with film.
13. The tablet formulation according to any preceding claims characterized in that said formulation is used for prevention and/or treatment of allergic and inflammatory diseases of the skin or upper and lower respiratory tract diseases such as seasonal allergic rhinitis, perennial allergic rhinitis, allergic sinusitis, atopic dermatitis, urticaria, allergic asthma, aspirin induced asthma, exercise induced asthma and for relieving the symptoms thereof.