complex formulation comprising levocetirizine and montelukast as active ingredients. Due to the physicochemical properties of these compounds, however, there were difficulties in storage and administration of such formulation. When prepared in the form of a tablet, there remained a problem of reduced patient compliance in patients having difficulties in swallowing or chewing or those who do not prefer such type of formulation, *e.g.*, children.

SUMMARY OF THE INVENTION

The invention is defined in the independent claim. Some optional features of the invention are defined in the dependent claims.

Therefore, as disclosed herein, there may be provided a taste-masked complex granule formulation having improved stability and good bioavailability comprising levocetirizine and montelukast.

There is also provided a complex granule formulation comprising (a) a first granular part comprising levocetirizine or its pharmaceutically acceptable salt, cyclodextrin or its derivative, and an alkalinizing agent; and (b) a second granular part comprising montelukast or its pharmaceutically acceptable salt, cyclodextrin or its derivative, and an alkalinizing agent.

One complex granule formulation contains levocetirizine and montelukast, each of which forms clathrate complexes with cyclodextrin, and employs an alkalinizing agent. Thus, any possible contact between two main ingredients can be prevented; the production of related compounds can be inhibited during a long-term storage; and bioavailability of the active ingredients can be improved as well. Moreover, the bitter taste of levocetirizine can be masked so as to improve patient compliance.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 shows the result of a stability test of complex granule formulations obtained in Examples 1 to 8 and Comparative Examples 1 to 7, comparing the amount of levocetirizine related compound A produced under accelerated condition (40ºC/75% RH) for 6 months with its initial amount.

comparing the amount of montelukast related compounds produced under accelerated condition (40ºC/75% RH) for 6 months with their initial amount.

Fig. 10 shows the change in bioavailability of levocetirizine, measured from complex granule formulations obtained in Example 1 and Comparative Example 3.

Fig. 11 shows the change in bioavilability of montelukast, measured from complex granule formulations obtained in Example 1 and Comparative Example 3.

DETAILED DESCRIPTION OF THE INVENTION

Examples of present invention are explained in detail hereinafter.

The current disclosure may provide a complex granule formulation comprising (a) a first granular part comprising levocetirizine or its pharmaceutically acceptable salt, cyclodextrin or its derivative, and an alkalinizing agent; and (b) a second granular part comprising montelukast or its pharmaceutically acceptable salt, cyclodextrin or its derivative, and an alkalinizing agent.

A complex granule formulation as disclosed herein may employ an antihistamine agent (levocetirizine) as a first active ingredient to effectively reduce early responses of allergic rhinitis or asthma, and as an anti-leukotriene agent (montelukast) as a second active ingredient for the treatment or prevention of asthma and one of the major symptoms of late allergic rhinitis, *i.e.*, nasal obstruction.

A complex granule formulation may contain the following parts.

A. First granular part

(1) Levocetirizine or its pharmaceutically acceptable salt

In the present invention, levocetirizine or a pharmaceutically acceptable salt thereof contained in the first granular part as an active ingredient is, for

cyclodextrin as compared to the amount of pharmacologically active levocetirizine. Also, excessive cyclodextrin is not completely dissolved during the manufacturing process and it undesirably hinders masking of bitter taste.

(3) Alkalinizing agent

In accordance with an exemplary formulation of the present invention, the first granular part contains an alkalinizing agent as a stabilizing agent (or pH regulator). The alkalinizing agent not only improves the stabilities of drugs from related compound by maintaining the inside of the granular part at a neutral or basic condition, but also makes the manufacturing process easier by increasing the solubility of montelukast when preparing a montelukast binding solution. The alkalinizing agent may be meglumine, sodium bicarbonate, sodium carbonate monohydrate, ammonia water, sodium citrate, dried sodium carbonate, or a mixture thereof. The alkalinizing agent may be used in an amount of 0.2 to 0.6 wt% based on the total weight of each granular part. If the amount of the alkalinizing agent exceeds 0.6 wt% based on the total weight of the granular part, the alkalinizing agent has no additional effect on the stabilities and it adds unpleasant feeling caused by the alkalinizing agent.

(4) Other pharmaceutically acceptable additive

A first granular part of the formulation may further contain one or more pharmaceutically acceptable additives. The additive may be selected from the group consisting of a diluent, a sweetener, a flavor, a colorant, a binder, and a mixture thereof.

The diluent may be selected from the group consisting of microcrystalline cellulose, lactose, ludipress, mannitol, calcium dihydrogen phosphate, starch, low-substituted hydroxypropyl cellulose and a mixture thereof. The diluent may be employed in an amount of 1 to 99 wt%, preferably 5 to 95 wt% based on the total weight of the granular part.

The sweetener may be selected from the group consisting of aspartame, acesulfame salt, sucralose, saccharin salt, neotame, cyclamate, thaumatin, LuoHan Guo extract, glycyrrhizin, steviten light (at least 98% stevioside), steviten rich (100% enzymatically modified stevia), sugar,

glucose, maltose, oligosaccharide, dextrin, invert sugar, fructose, lactose, galactose, corn syrup, sorbitol, maltitol, xylitol, erythritol, high fructose corn syrup and trehalose. The sweetener may be used in an amount of 0.1 to 10 wt% based on the total weight of the granular part.

Examples of the flavor include natural flavors, synthetic flavors, and a mixture thereof. The natural flavors may be spearmint oil, cinnamon oil, peppermint oil, lemon oil, clove oil, bay oil, thyme oil, cedar leaf oil, nutmeg oil, sage oil, almond oil, and the like. Also, the synthetic flavors may be synthetic fruit flavors such as lemon, orange, grape, lime and strawberry, and synthetic flavors such as vanilla, chocolate, coffee, cocoa, pine needle, ginseng, red ginseng and citrus. The flavors may be used in an amount of 0.1 to 10 wt% based on the total weight of the granular part.

The colorant may be any colorant that has the maximum absorption wavelength in the 400 nm to 550 nm range, for example, one or more selected from the group consisting of Food Red No. 40 (maximum absorption wavelength in the 497 nm to 501 nm range), Food Yellow No. 5 (maximum absorption wavelength in the 480 nm to 484 nm), Yellow No. 4 (maximum absorption wavelength in the 426 nm to 430 nm), and a safflower yellow dye (maximum absorption wavelength at 400 nm), preferably Food Red No. 40. The colorant may be used in an amount of 0.01 to 1 wt% based on the total weight of the granular part.

The binder may be selected from the group consisting of hydroxypropyl cellulose, hypromellose, polyvinyl pyrrolidone, copovidone, macrogol, light anhydrous silicic acid, synthetic aluminum silicate, calcium silicate or silica derivatives magnesium metasilicate aluminate, phosphate salts such as calcium phosphate dibasic, carbonate salts such as calcium carbonate, and a mixture thereof. The amount of binder employed may be, based on the total weight of the granular part, 0.5 to 30 wt%, preferably 2 to 20 wt%.

B. Second granular part

(1) Montelukast or its pharmaceutically acceptable salt

A pharmaceutically acceptable salt of montelukast comprised in the second granular part as an active ingredient is, for example, non-toxic, inorganic and organic acid addition salts of acetic acid, citric acid, maleic acid, succinic acid, ascorbic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and the like, metal salt thereof (*e.g.*, sodium salt or calcium salt), ammonium salt, amine salt and amino acid salt. In one embodiment, montelukast sodium is employed. The daily dosage amount of montelukast or its pharmaceutically acceptable salt is 0.4 to 100 mg, preferably 1 to 50 mg, more preferably 2.5 to 20 mg.

(2) Cyclodextrin or its derivative

The cyclodextrin or its derivative in the second granular part and the amount thereof are the same as described in the first granular part.

(3) Alkalinizing agent

The alkalinizing agent in the second granular part and the amount thereof are the same as described in the first granular part.

(4) Other pharmaceutically acceptable additives

The pharmaceutically acceptable additives in the second granular part and the amount thereof are the same as described in the first granular part.

Granules which are formed in the first and second granular parts may be further coated so as to completely separate active ingredients. The coating process may be carried out on either one of levocetirizine and montelukast granules, or both.

Coating agents that can be used in the coating process may be conventional polymers, for example, hypromellose, methyl cellulose, ethyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, hydroxyethylcellulose, hydroxypropyl methylcellulose, but not limited thereto. The amount of the

coating agent is preferably kept at minimum so as to improve efficiency in production and provide a formulation size optimal for administration. The amount is, based on the total weight of each granular part, 0.5 to 20 wt%, preferably 1 to 10 wt%.

There is no specific limitation of the mixing ratio of the first and second granular parts. The first and the second granular parts may be mixed in a weight ratio of 20:80 to 80:20, which may be administered to a patient at various dose levels.

Further, a complex granule formulation may be prepared in a package so as to protect the formulation from light and moisture. Examples of suitable packaging materials include foil (*e.g.*, aluminum) pouch or sachet. The foil may be laminated with a polyester film, which protects children from biting and tearing the package, on its outer surface. Linear low density polyethylene may act as a heat-sealable layer for pouch.

A complex granule formulation may be used in the prevention or treatment of allergic rhinitis and asthma, and the allergic rhinitis may be selected from the group consisting of rhinorrhea, nasal obstruction, nasal itching, sneezing and ocular pruritis.

Meanwhile, a complex granule formulation may be manufactured by a method, which comprises the steps of (i) preparing a first granular part by dissolving cyclodextrin or a derivative thereof in purified water, and mixing with levocetirizine or a pharmaceutically acceptable salt thereof and an alkalinizing agent to prepare a levocetirizine binding solution, followed by granulation of the binding solution; (ii) preparing a second granular part by dissolving an alkalinizing agent in purified water, dissolving montelukast or a pharmaceutically acceptable salt thereof and then mixing with cyclodextrin or a derivative thereof to prepare montelukast binding solution, followed by granulation of the binding solution; and (iii) mixing the first and second granular parts prepared.

A complex granule formulation may prevent a possible contact between two active ingredients by allowing each of levocetirizine and montelukast to form clathrate complexes with cyclodextrin and using an alkalinizing agent as a stabilizing agent. Thus, possible reactions among related compounds are minimized, thereby improving the stability and efficacy. Also, the complex granule formulation effectively masks the bitter taste by allowing levocetirizine to form clathrate complexes with cyclodextrin, which improves patient compliance, especially in children and elderly patients.

Hereinafter, the present invention is described more specifically by the following examples, but these are provided only for illustration purposes and the present invention is not limited thereto.

Examples 1 to 3 and Comparative Examples 1 and 2: Preparation of complex granule formulations having various amounts of alkalinizing agent

Complex granule formulations were prepared by varying the amount of an alkalinizing agent listed in the Table 1 below.

Specifically, hydroxypropyl β-cyclodextrin, different amounts of meglumine, and levocetirizine dihyhydrochloride were, in sequence, dissolved in distilled water to prepare a levocetirizine binding solution. The binding solution thus obtained was mixed with D-mannitol, dried, and then sieved to obtain a levocetirizine granular part.

Meanwhile, various amounts of meglumine were dissolved in distilled water, and montelukast and hydroxypropyl β-cyclodextrin were sequentially added thereto to prepare a binding solution. Since montelukast has a low aqueous solubility, meglumine was dissolved first for easier dissolution of montelukast. The binding solution thus obtained was mixed with D-mannitol, dried, and then sieved to obtain a montelukast granular part.

The two granular parts thus obtained were mixed in a same proportion, packaged in a sachet per unit dosage to prepare complex granule formulations comprising 5 mg of montelukast and 5 mg of levocetirizine.

What is claimed is:

1. A complex granule formulation comprising:

(a) a first granular part comprising levocetirizine or a pharmaceutically acceptable salt thereof, cyclodextrin or a derivative thereof, and an alkalinizing agent; and

(b) a second granular part comprising montelukast or a pharmaceutically acceptable salt thereof, cyclodextrin or a derivative thereof, and an alkalinizing agent,

wherein the cyclodextrin or its derivative is β-cyclodextrin or hydroxypropyl β-cyclodextrin.

2. The complex granule formulation of claim 1, wherein the cyclodextrin or its derivative is contained in an amount of 3 to 7 wt % based on the total weight of each granular part.

3. The complex granule formulation of claim 1, wherein the alkalinizing agent is selected from the group consisting of meglumine, sodium bicarbonate, sodium carbonate monohydrate, ammonia water, sodium citrate, dried sodium carbonate, and a mixture thereof.

4. The complex granule formulation of claim 1, wherein the alkalinizing agent is contained in an amount of 0.2 to 0.6 wt % based on the total weight of each granular part.

5. The complex granule formulation of claim 1, wherein each of the first and the second granular parts further comprises a pharmaceutically acceptable additive.

6. The complex granule formulation of claim 5, wherein the pharmaceutically acceptable additive is selected from the group consisting of a diluent, a sweetener, a flavor, a colorant, a binder, and a mixture thereof.

7. The complex granule formulation of claim 1, wherein the complex granule formulation is used for the treatment of allergic rhinitis or asthma.

8. The complex granule formulation of claim 7, wherein the allergic rhinitis is selected from the group consisting of rhinorrhea, nasal obstruction, nasal itching, sneezing and ocular pruritis.