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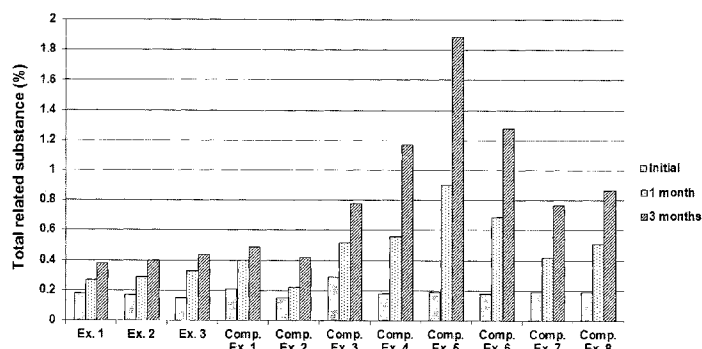
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(54) Title: LIQUID FORMULATION WITH ENHANCED STABILITY COMPRISING MONTELUKAST OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF AND METHOD FOR PREPARING SAME

FIG. 2



(57) Abstract: The present invention relates to a liquid formulation comprising an electrolyte compound, and montelukast or a pharmaceutically acceptable salt thereof as an active ingredient, and a method for preparing the above liquid formulation. According to the present invention, montelukast or a pharmaceutically acceptable salt thereof is substantially dissolved and present in a solution state, thereby improving stability over time, preventing decrease of dissolution and stability over time and increasing its bioavailability. And, owing to its enhanced stability and superior taste and flavor, the liquid formulation of the present invention shows improved medication compliance, and can be effectively used for the treatment of asthma and allergic rhinitis.

## DESCRIPTION

### LIQUID FORMULATION WITH ENHANCED STABILITY COMPRISING MONTELUKAST OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF AND METHOD FOR PREPARING SAME

#### FIELD OF THE INVENTION

The present invention relates to a liquid formulation comprising montelukast or a pharmaceutically acceptable salt thereof and a method for preparing the formulation. More particularly, the present invention relates to a syrup formulation for the prevention and treatment of asthma, which is a liquid formulation comprising montelukast or a pharmaceutically acceptable salt thereof in a solution state, having enhanced stability. The present invention also relates to a method for preparing the above syrup formulation.

#### BACKGROUND OF THE INVENTION

Asthma is an inflammatory airway obstructive disease with symptoms of dyspnea and severe cough caused by swelling of bronchial mucosa due to bronchial inflammation, and bronchial obstruction due to bronchial muscle spasm. Patients with asthma show symptoms such as wheezing, dyspnea and cough etc. due to airway obstruction, and the symptoms tend to get worse at night than in daytime. Also, they may have difficulties in breathing due to excessive sputum production. In severe cases, asthmatic attacks may be life-threatening.

Asthma is a problematic disease prevalent worldwide, and about 300 million asthma patients are estimated to be present. A half of childhood asthma cases persists until adulthood and continues as adult asthma. The prevalence of asthma among children and adults confirmed by a standard survey method amounts to 1 to 18%, albeit with differences among countries.

Therapeutic agents of asthma are mainly divided into disease-controlling agents

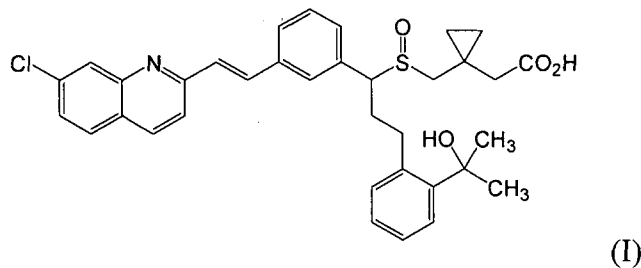
and symptom-alleviating agents. The disease-controlling agents are used for controlling symptoms of asthma mainly by anti-inflammatory effects. The symptom-alleviating agents are medications used in order to alleviate symptoms in a short time period by rapidly dilating airway.

5 Montelukast, one of the disease-controlling agents, is an antagonist that inhibits cysteinyl leukotriene CysLT1 receptor, and has been used for the treatment and prevention of leukotriene-mediated diseases and disorders. Specifically, montelukast is known to be effective for allergic rhinitis, atopic dermatitis, chronic urticaria, sinusitis, nasal polyps, chronic obstructive pulmonary disease, conjunctivitis including rhino-  
10 conjunctivitis, migraine, cystic fibrosis, and viral bronchiolitis, etc. (SE Dahlen, Eur. J. Pharmacol., 533 (1-3), 40-56 (2006)). Also, montelukast has a great advantage that it is effective for aspirin-sensitive asthma patients and has very few side effects. At present, Singulair<sup>TM</sup> (MSD), an agent employing sodium montelukast as its pharmacologically active ingredient, is approved for the treatment of asthma for adults and children over 6  
15 months of age, and commercially available.

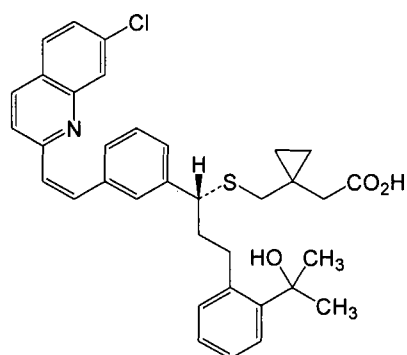
Regarding dosage regimens, doses and dosage forms, Singulair<sup>TM</sup> is commercially available with dosage forms of 10 mg tablets to be taken once a day by adults aged over 15 years, 4 to 5 mg chewable tablets to be chewed and taken once a day by children aged 2 to 14 years, and 4 mg fine granules to be taken once a day by  
20 children aged 6 months to 2 years. Among them, the fine granule has a disadvantage that it should be taken orally itself, or mixed in small amount (e.g. 5 mL or less) of soft foods such as baby food, mother's milk or porridge which is colder than room temperature and be taken immediately (i.e., within 15 minutes).

Furthermore, being unstable to light, humidity and heat, montelukast produces  
25 degradation products such as montelukast sulfoxide (as shown in Formula 1 below) and montelukast cis-isomer (as shown in Formula 2 below) when it is degraded. Also, it has been reported that upon exposure of a commercially available chewable tablet, Singulair<sup>TM</sup> employing sodium montelukast as its main ingredient to sunlight, montelukast sulfoxide increases up to 2.4% in 3 weeks, and upon exposure of  
30 montelukast in 0.1 M solution of hydrochloric acid to sodium, etc. for 6 hours,

montelukast cis-isomer increases up to 14.6% (M. M. Al Omari et al., *J. Pharm. and Biomed. Anal.*, 45, 465-471 (2007)). These results indicate that it is not easy to maintain stability of montelukast-containing products over time.



(I)



(II)

5

Among the dosage forms of the therapeutic agents, oral liquid formulations, such as syrups, suspensions, elixirs, and spirits, have several advantages. They allow patients to control doses easily and can be conveniently taken by toddlers, children and the elderly patients. In comparison to solid formulations such as tablets, chewable tablets and granules, the bioavailability of the oral liquid formulations can be increased and individual variations can be decreased. Also, medication compliance of patients can be enhanced by improving taste and flavor by addition of sweeteners and flavoring agents.

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Montelukast has high solubility in water, but it has disadvantage in that its pharmacological component can be degraded rapidly and produce related substances when dissolved in water, making it difficult to maintain the feature of montelukast. As such, there have been difficulties in developing a liquid formulation comprising montelukast or a pharmaceutically acceptable salt thereof, and there is no product commercially available or developed yet.

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The present inventors have endeavored to develop a liquid formulation comprising montelukast with improved stability, bioavailability and medication

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compliance, and without decrease of dissolution over time, by employing a stabilizer thereto.

## SUMMARY OF THE INVENTION

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Therefore, it is an object of the present invention to provide a liquid formulation comprising montelukast or a pharmaceutically acceptable salt thereof as a pharmacologically active ingredient in a solution state, having enhanced stability over time and improved medication compliance.

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It is another object of the present invention to provide a method for preparing the above liquid formulation.

In accordance with one object of the present invention, there is provided a liquid formulation comprising an electrolyte compound, and montelukast or a pharmaceutically acceptable salt thereof as an active ingredient.

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In accordance with another object of the present invention, there is provided a method for preparing a liquid formulation comprising: (1) adding at least one pharmaceutically acceptable additive selected from the group consisting of a sweetener, a flavoring agent, a preservative, a solubilizing agent, an emulsifying agent, a pH adjusting agent, an antioxidant and a coloring agent, to purified water and then stirring them to prepare solution 1; (2) adding at least one electrolyte compound to purified water and stirring them, and then adding montelukast or its pharmaceutically acceptable salt thereto and stirring them to prepare solution 2; and (3) mixing solution 1 with solution 2, and adding purified water thereto to adjust the concentration.

The liquid formulation comprising montelukast or a pharmaceutically acceptable salt thereof according to the present invention allows its pharmacological ingredients to be substantially dissolved and present in a solution state, thereby preventing decrease of dissolution over time and increasing its bioavailability. Further, owing to superior taste, flavor and easy dosage control, the liquid formulation of the present invention can be easily taken by patients and its medication compliance can be enhanced. And, due to the addition of an electrolyte compound it shows improvement in stability and homogeneity

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of drug effect by preventing recrystallization, precipitation, separation of layers or production of related substances does not take place even when stored for a long time, and can be effectively used for asthma and allergic rhinitis patients.

## 5 BRIEF DESCRIPTION OF THE DRAWING

The above and other objects and features of the present invention will become apparent from the following descriptions of the invention, when taken in conjunction with the accompanying drawings:

10 Fig. 1 shows the amount of montelukast sulfoxide produced in the liquid formulations in Examples 1 to 3 and Comparative Examples 1 to 8 when stored under the accelerated conditions; and

Fig. 2 shows the amount of total montelukast related substances of the liquid formulations in Examples 1 to 3 and Comparative Examples 1 to 8 when stored under  
15 the accelerated conditions.

## DETAILED DESCRIPTION OF THE INVENTION

The liquid formulation according to the present invention comprises an  
20 electrolyte compound, and montelukast or a pharmaceutically acceptable salt thereof as an active ingredient.

The active ingredient can be selected from the group consisting of montelukast, montelukast sodium, montelukast potassium, montelukast strontium, montelukast  
25 calcium, montelukast magnesium, montelukast ammonium, and a mixture thereof, among which montelukast sodium is preferred.

The active ingredient can be employed in the liquid formulation in an amount of 0.005 to 10 weight%, preferably 0.008 to 5 weight%, more preferably 0.01 to 2 weight% based on the total weight of the liquid formulation (i.e., montelukast in the active  
30 ingredient is employed in the above preferred amount). With the amount of the

montelukast being in the above preferred range, a patient can avoid the inconvenience of taking too large or small amount of liquid formulation, and the quality test and analysis of a prepared liquid formulation can be performed more easily.

The liquid formulation comprising montelukast or a pharmaceutically acceptable salt thereof can be used for the treatment or prevention of asthma, allergic rhinitis, atopic dermatitis, chronic urticaria, sinusitis, nasal polyps, chronic obstructive pulmonary disease, conjunctivitis including rhino-conjunctivitis, migraine, cystic fibrosis, and viral bronchiolitis, etc.

The liquid formulation can comprise at least one electrolyte compound which can function as a stabilizer.

In particular, the stabilizer may be a property stabilizer.

In the present invention, the term "property" refers to a physicochemical feature or characteristics of a liquid formulation or a pharmacologically active ingredient comprised therein. And, "property stability" means that a stable solution state is maintained over time without deterioration change of the physicochemical feature or characteristics of the liquid formulation or the pharmacologically active ingredient employed therein. Further, "property stabilizer" refers to an agent to improve the property stability.

The "solution state" in the present invention means that the solubility of the montelukast or a pharmaceutically acceptable salt thereof measured at room temperature is 70 to 100%, specifically 80 to 100%, more specifically 90 to 100%, and more specifically 95 and 100%.

And, the term "room temperature" in the present invention refers to a temperature range of approximately 15 °C to 25 °C.

The electrolyte compound may be neutral or weak alkaline by being dissociated in a solvent. Specifically, the electrolyte compound can have pKa of 6.0 to 12.0, more specifically pKa of 6.5 to 11.0, and more specifically pKa of 7.0 to 10.0. With pKa of the electrolyte compound being within the above preferred range, the stimulation

imposed on the active ingredient by the electrolyte compound can be minimized, which is advantageous in preventing deterioration of the characteristics of the active ingredient.

Further, the solubility of the electrolyte compound at room temperature (e.g., 20 °C) can be 100 to 900 g/L. Specifically, the solubility of the liquid formulation in a solvent at room temperature can be 200 to 750 g/L, more specifically 300 to 600 g/L.

In one specific embodiment, the electrolyte compound is at least one selected from the group consisting of alkali metal chloride and alkali earth metal chloride.

In a more specific embodiment, the electrolyte compound can be selected from the group consisting of potassium chloride, sodium chloride, calcium chloride and a mixture thereof.

The electrolyte compound can be employed in the liquid formulation in an amount of 0.5 to 20 parts by weight, preferably 1 to 15 parts by weight, more preferably 2 to 10 parts by weight based on 1 part by weight of montelukast. With the content of the electrolyte compound being within the above preferred range, a pharmacologically active ingredient in liquid formulation can be solubilized with its solubility effectively maintained, while the increase of related substances in the liquid formulation is prevented.

Such electrolyte compound lets montelukast or a pharmaceutically acceptable salt thereof maintain its stable feature in a solution state without recrystallization or precipitation over time. Further, the electrolyte compound also plays the role of maintaining proper pH, moisture equilibrium, osmotic pressure control, and acid-base equilibrium.

The liquid formulation of the present invention can further comprise a pharmaceutically acceptable additive. The pharmaceutically acceptable additive can be, for example, at least one selected from a group consisting of a sweetener, a flavoring agent, a preservative, a solubilizing agent, an emulsifying agent, a pH adjusting agent, an antioxidant and a coloring agent. By comprising the pharmaceutically acceptable additive, the solution state of the liquid formulation can be effectively maintained even

when it is stored for a long time, or medication compliance can be enhanced by improving its taste and flavor.

The sweetener improves taste of the liquid formulation, which may be, for example, at least one substance selected from the group consisting of white sugar, high fructose, sorbitol, mannitol, xylitol, aspartame, steviol glycosides, sucralose, acesulfame potassium and glycerin. The sweetener can be employed in an amount of 0.001 to 50 weight%, preferably 0.005 to 30 weight% based on the total weight of the liquid formulation.

The flavoring agent makes patients feel a scent when taking the liquid formulation, which improves the medication compliance. It can be, for example, at least one substance selected from the group consisting of a general fruit flavor or various fruit flavors such as apple flavor, cherry flavor, orange flavor, strawberry flavor, banana flavor, grape flavor, mango flavor and peach flavor; vanilla flavor; mint flavor; and honey flavor. The flavoring agent can be employed in an amount of 0.1 to 5 weight%, preferably 0.2 to 3 weight% based on the total weight of the liquid formulation.

The preservative inhibits the growth of microorganisms during storage of the liquid formulation, which may be, for example, at least one substance selected from the group consisting of paraoxybenzoates such as paraoxybenzoic acid methyl, paraoxybenzoic acid ethyl, paraoxybenzoic acid propyl and paraoxybenzoic acid butyl; benzoates such as benzoic acid and sodium benzoate; and sorbates such as sorbic acid and potassium sorbate. The preservative can be employed in an amount of 0.01 to 2 weight%, preferably 0.02 to 1 weight% based on the total weight of the liquid formulation.

The solubilizing agent plays the role of improving the solubility of an active ingredient and the like in the liquid formulation, which may be, for example, at least one substance selected from the group consisting of meglumine, arginine, and lysine. The solubilizing agent can be employed in an amount of 0.001 to 1.0 weight%, preferably 0.005 to 0.5 weight% based on the total weight of the liquid formulation.

The liquid formulation can also employ an emulsifying agent to improve the feature of the liquid formulation, and a pH adjusting agent to adjust the acidity of the

liquid formulation to an appropriate level.

The liquid formulation can comprise a solvent to dissolve an active ingredient and the like. The solvent may be, but not limited to, a polar solvent, preferably a polar aqueous solvent, for example. In a specific embodiment, the solvent can be water (purified water).

The liquid formulation can be alkaline, e.g., neutral or weakly alkaline. Specifically, the liquid formulation can have a pH range of 6.0 to 12.0, more specifically 8.0 to 12.0. With the pH of the liquid formulation being within the above preferred range, the property of the liquid formulation can be improved in terms of property stability by preventing precipitations of montelukast or pharmaceutically acceptable salt thereof.

And, the active ingredient solubilized in the liquid formulation can show a solubility of 70% to 100%, specifically 80% to 100%, more specifically 90% to 100%, even more specifically 95% to 100% under the accelerated conditions of 40 °C, 75% of relative humidity and 3 month period.

Further, in the liquid formulation, the amount of montelukast sulfoxide produced may be 0.9% or less, specifically 0.7% or less, more specifically 0.5% or less, even more specifically 0.4% or less, while the amount of total related substances produced may be 1% or less, specifically 0.8% or less, more specifically 0.6% or less, even more specifically 0.5% or less.

The above liquid formulation can be a liquid formulation for oral administration, such as, but not limited to, a syrup, a suspension, an elixir, and a spirit, preferably a syrup.

The liquid formulation of the present invention allows its pharmacological ingredients to be substantially dissolved and present in a solution state, thereby preventing decrease of dissolution over time and increasing its bioavailability. Further owing to superior taste, flavor and easy dosage control, the liquid formulation of the present invention can be easily taken by patients and its medication compliance can be

enhanced. And, due to the addition of an electrolyte compound it shows improvement in stability and homogeneity of drug effect by preventing recrystallization, precipitation, separation of layers or production of related substances even when stored for a long time, and can be effectively used for asthma and allergic rhinitis patients.

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The liquid formulation of the present invention can be prepared by a method comprising the steps of:

(1) adding at least one pharmaceutically acceptable additive to purified water and stirring them to prepare solution 1;

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(2) adding at least one electrolyte compound to purified water and stirring them, and then adding pharmacologically active ingredient thereto and stirring them to prepare solution 2; and

(3) mixing prepared solution 1 with solution 2, and adding purified water thereto to adjust the concentration.

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In the step (1), the pharmaceutically acceptable additive may be one of the additives exemplified above. In one embodiment, after adding a stabilizer to purified water and stirring them, a sweetener and an antioxidant can be sequentially added thereto and stirred to prepare solution 1. In a specific embodiment, step (1) can comprise the steps of:

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i) adding a solubilizing agent (e.g., meglumine) to purified water of 30 °C or less, preferably 15 °C to 30 °C in a preparation tank, and stirring them;

ii) adding a sweetener to the solution obtained in the step i) and stirring them; and

iii) adding an antioxidant to the solution obtained in the step ii) and stirring them to prepare solution 1.

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In the step (2), the pharmacologically active ingredient is montelukast or a pharmaceutically acceptable salt thereof, specific examples of which have been described above. In a specific embodiment, step (2) can comprise the steps of:

a) adding at least one electrolyte compound to purified water of 30 °C or less, preferably 15 °C to 30 °C and stirring them; and

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- b) adding montelukast sodium to the solution obtained in the step a) and stirring them to prepare solution 2.

In the step (3), the liquid formulation can be prepared by mixing the prepared solution 1 with solution 2 and adding purified water thereto to adjust the concentration, as stated above. In one embodiment, the liquid formulation can be prepared by adding solution 2 to solution 1, and then adding sterilized purified water cooled in room temperature thereto until reaching a preferred volume, followed by stirring them. It is preferable for the liquid formulation prepared as above to be subjected to the step of filtration through 1  $\mu\text{m}$  filter and the like. The final liquid formulation prepared can be stored in a storage tank or an appropriate container.

Hereinafter, the present invention is explained in detail with reference to the following Examples. The following Examples are intended to illustrate the invention, but the scope of the present invention is not limited thereto.

#### **Example 1: Preparation of a liquid formulation comprising montelukast**

0.20 g of meglumine was dissolved in 50 mL of sterile purified water in a preparation tank with stirring. After cooling the preparation tank to 30 °C or lower, 0.50 g of sucralose was added thereto and stirred, and then 0.01 g of sodium edetate was added thereto, to prepare solution 1. Separately, after preparing a solution by adding 0.2 g of potassium chloride to purified water at 25 °C, 0.104 g of montelukast sodium (equivalent to 0.100 g of montelukast alone) was added thereto and stirred, to prepare solution 2. Solution 2 was mixed with solution 1, and sterile purified water was added thereto to prepare a solution with a final volume of 100 mL. The resultant mixture was filtrated through a 1  $\mu\text{m}$  filter to obtain a liquid formulation in a solution state. The prepared liquid formulation showed montelukast solubility of 100%, confirming that montelukast sodium was present in a solution state.

#### **Examples 2 and 3: Preparation of liquid formulations comprising**

**montelukast**

Liquid formulations were prepared by the same method as Example 1, except for the addition of potassium chloride or sodium chloride as a stabilizer in the amount  
5 described in Table 1.

[Table 1]

| Additives                                                                                   | Ex. 1            | Ex. 2            | Ex. 3            |
|---------------------------------------------------------------------------------------------|------------------|------------------|------------------|
| Montelukast sodium (g)<br>(Montelukast)                                                     | 0.104<br>(0.100) | 0.104<br>(0.100) | 0.104<br>(0.100) |
| Meglumine (g)                                                                               | 0.20             | 0.20             | 0.20             |
| Sucralose (g)                                                                               | 0.50             | 0.50             | 0.50             |
| Sodium edetate (g)                                                                          | 0.01             | 0.01             | 0.01             |
| Potassium chloride (g)                                                                      | 0.20             | 1.00             | -                |
| Sodium chloride (g)                                                                         | -                | -                | 0.20             |
| Purified water                                                                              | aa               | aa               | aa               |
| Total volume (mL)                                                                           | 100              | 100              | 100              |
| Amount of a stabilizer added (part by weight)<br>(based on 1 part by weight of montelukast) | 2                | 10               | 2                |
| *aa: appropriate amount                                                                     |                  |                  |                  |

**Comparative Examples 1 to 8: Preparation of liquid formulations  
10 comprising montelukast**

Liquid formulations were prepared by the same method as Example 1, except that the stabilizer was either excluded or potassium chloride, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate or glucose was added as a stabilizer in  
15 the amount described in Table 2.

[Table 2]

| Additives                               | Comp.<br>Ex. 1   | Comp.<br>Ex. 2   | Comp.<br>Ex. 3   | Comp.<br>Ex. 4   | Comp.<br>Ex. 5   | Comp.<br>Ex. 6   | Comp.<br>Ex. 7   | Comp.<br>Ex. 8   |
|-----------------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Montelukast sodium (g)<br>(Montelukast) | 0.104<br>(0.100) | 0.104<br>(0.100) | 0.104<br>(0.100) | 0.104<br>(0.100) | 0.104<br>(0.100) | 0.104<br>(0.100) | 0.104<br>(0.100) | 0.104<br>(0.100) |
| Meglumine                               | 0.20             | 0.20             | 0.20             | 0.20             | 0.20             | 0.20             | 0.20             | 0.20             |
| Sucralose                               | 0.50             | 0.50             | 0.50             | 0.50             | 0.50             | 0.50             | 0.50             | 0.50             |
| Sodium edetate                          | 0.01             | 0.01             | 0.01             | 0.01             | 0.01             | 0.01             | 0.01             | 0.01             |
| Potassium chloride                      | -                | 0.04             | 2.10             | -                | -                | -                | -                | -                |
| Potassium hydroxide                     | -                | -                | -                | 0.01             | 0.20             | -                | -                | -                |
| Sodium hydroxide                        | -                | -                | -                | -                | -                | 0.01             | -                | -                |
| Sodium hydrogen carbonate               | -                | -                | -                | -                | -                | -                | 1.00             | -                |

|                                                                                                   |     |     |     |     |     |     |     |      |
|---------------------------------------------------------------------------------------------------|-----|-----|-----|-----|-----|-----|-----|------|
| Glucose                                                                                           | -   | -   | -   | -   | -   | -   | -   | 10.0 |
| Purified water                                                                                    | aa  | aa  | aa  | aa  | aa  | aa  | aa  | aa   |
| Total volume (mL)                                                                                 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100  |
| Amount of a stabilizer added<br>(part by weight)<br>(based on 1 part by weight of<br>montelukast) | 0   | 0.4 | 21  | 0.1 | 2   | 0.1 | 10  | 100  |
| *aa: appropriate amount                                                                           |     |     |     |     |     |     |     |      |

### Experimental Example 1: pH measurement of montelukast liquid formulation

5 The pH of the liquid formulations of Examples 1 to 3, and Comparative Examples 1 to 8 was measured with a pH meter. The results are shown in Table 3 below.

[Table 3]

|    | Ex. 1 | Ex. 2 | Ex. 3 | Comp.<br>Ex. 1 | Comp.<br>Ex. 2 | Comp.<br>Ex. 3 | Comp.<br>Ex. 4 | Comp.<br>Ex. 5 | Comp.<br>Ex. 6 | Comp.<br>Ex. 7 | Comp.<br>Ex. 8 |
|----|-------|-------|-------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| pH | 10.1  | 10.2  | 10.6  | 10.0           | 10.1           | 10.8           | 10.4           | 13.5           | 10.8           | 9.8            | 9.0            |

10 As shown in Table 3, pHs of the liquid formulations of Comparative Examples were in the range of 9 to 11, except for Comparative Example 5. The liquid formulation of Comparative Example 5 showed pH out of a preferred range due to strong alkalinity of potassium hydroxide, although potassium hydroxide was employed in the same amount as potassium chloride in Example 1.

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### Experimental Example 2: Observation of feature stability of montelukast liquid formulation

20 The liquid formulations of Examples 1 to 3 and Comparative Examples 1 to 8 were placed into transparent glass bottles and stored under the accelerated conditions (40 °C, 75% of relative humidity) for 7 days, and 3 months. The liquid formulations were examined visually for any precipitations or other property changes.

The results are shown in Table 4.

[Table 4]

|                                                                                | Evaluation of precipitation and other property changes |              |                                 |              |
|--------------------------------------------------------------------------------|--------------------------------------------------------|--------------|---------------------------------|--------------|
|                                                                                | Accelerated storage for 7days                          |              | Accelerated storage for 3months |              |
|                                                                                | Precipitation formation                                | Transparency | Precipitation formation         | Transparency |
| Ex. 1                                                                          | -                                                      | -            | -                               | -            |
| Ex. 2                                                                          | -                                                      | -            | -                               | -            |
| Ex. 3                                                                          | -                                                      | -            | -                               | -            |
| Comp. Ex. 1                                                                    | +                                                      | +            | +                               | +            |
| Comp. Ex. 2                                                                    | -                                                      | -            | +                               | +            |
| Comp. Ex. 3                                                                    | -                                                      | -            | -                               | -            |
| Comp. Ex. 4                                                                    | -                                                      | +            | +                               | +            |
| Comp. Ex. 5                                                                    | -                                                      | -            | +                               | +            |
| Comp. Ex. 6                                                                    | -                                                      | +            | +                               | +            |
| Comp. Ex. 7                                                                    | -                                                      | +            | +                               | +            |
| Comp. Ex. 8                                                                    | +                                                      | +            | +                               | +            |
| - : No Precipitation, Transparent,<br>+ : Precipitation, Opaque, Discoloration |                                                        |              |                                 |              |

As shown in Table 4, the liquid formulations of Examples 1 to 3 generated no precipitations and showed transparent properties during 3 months of accelerated conditions. However, the liquid formulation of Comparative Example 1, in which no electrolyte compound was added, showed precipitation and opaque property on day 7 of acceleration. And, when the amount of electrolyte compound was insufficient as in the Comparative Example 2, the ionizing capacity on the active ingredient decreased, resulting in opaque property along with precipitation formation. The liquid formulations of Comparative Examples 4 to 6, although their pHs were within the range of 8.0~12.0, showed precipitation and browning phenomenon upon 3 month acceleration, due to the addition of strong alkaline electrolyte compounds which imposed strong stimulation to the main ingredient. The liquid formulation of Comparative Example 7 showed precipitation due to low ionizing capacity of the electrolyte compound.. The liquid formulation of Comparative Example 8 showed precipitation on day 7 of acceleration, due to the addition of non-electrolyte component.

### **Experimental Example 3: Evaluation of solubility of montelukast liquid formulation**

The liquid formulations of Examples 1 to 3, and Comparative Examples 1 to 8 were stored under the accelerated conditions (40 °C, 75% of relative humidity) for 3

months. Each sample was centrifuged at 16,000 rpm for 20 minutes, and the supernatant was filtered through a 0.45  $\mu\text{m}$  filter. Then, the filtrate was diluted 1/4 with methanol. And then, the solubility was analyzed according to the following analysis conditions.

5

<Conditions for analysis of montelukast solubility>

Instrument: HPLC (Hitachi 2000 series, Japan)

Detector: ultraviolet absorption spectrophotometer (wavelength: 225 nm)

Column: stainless steel column (inner diameter: about 4.6 mm; length: about 15  
10 cm) packed with octylsilyl silica gel (particle diameter: 5  $\mu\text{m}$ ) for liquid chromatography (Inertsil C8, GL Science Co.)

Mobile phase: 0.025 mol/L potassium dihydrogen phosphate solution (adjusted to a pH of 6.6 with 10 mol/L sodium hydroxide solution): acetonitrile = 4:6 (v/v)

Flow rate: 1.0 mL/min.

15 Column temperature: 45 °C

Results of solubility test of montelukast liquid formulations measured under the above analysis conditions are shown in Tables 5 and 6.

[Table 5]

|                                                   | Ex. 1 | Ex. 2 | Ex. 3 |
|---------------------------------------------------|-------|-------|-------|
| Amount of montelukast input ( $\mu\text{g/mL}$ )  | 1,000 | 1,000 | 1,000 |
| Solubility of montelukast ( $\mu\text{g/mL}$ )    | 999.5 | 998.1 | 997.3 |
| Solubility relative to the amount of input (w/w%) | 99.9% | 99.8% | 99.7% |

20

[Table 6]

|                                                   | Comp.<br>Ex. 1 | Comp.<br>Ex. 2 | Comp.<br>Ex. 3 | Comp.<br>Ex. 4 | Comp.<br>Ex. 5 | Comp.<br>Ex. 6 | Comp.<br>Ex. 7 | Comp.<br>Ex. 8 |
|---------------------------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Amount of montelukast input ( $\mu\text{g/mL}$ )  | 1,000          | 1,000          | 1,000          | 1,000          | 1,000          | 1,000          | 1,000          | 1,000          |
| Solubility of montelukast ( $\mu\text{g/mL}$ )    | 541.1          | 789.4          | 997.9          | 496.1          | 674.1          | 501.6          | 582.2          | 234.7          |
| Solubility relative to the amount of input (w/w%) | 54.1%          | 79.0%          | 99.8%          | 50.0%          | 67.4%          | 50.1%          | 58.2%          | 23.5%          |

In the liquid formulations of Examples 1 to 3 and Comparative Examples 1 to 8, montelukast sodium was added at a concentration of 1,040  $\mu\text{g/mL}$ , which corresponds to

a concentration of 1,000 µg/mL of montelukast, assuming that the entire amount of inputted montelukast has been dissolved.

As the results of solubility analysis, the liquid formulations of Examples 1 to 3 and Comparative Examples 3, which had favorable properties, showed solubility of 98 to 100 w/w% per input. However, the liquid formulations in the rest of the Comparative Examples showed extraction of montelukast, resulting in decline of its content.

#### **Experimental Example 4: Analysis of related substances in montelukast liquid formulation**

After storing the liquid formulations of Examples 1 to 3 and Comparative 1 to 8 in the light-shielded sealed glass container under the accelerated conditions, the production of montelukast sulfoxide and total montelukast related substances was analyzed according to the following analysis conditions.

##### **<Accelerated storage conditions>**

Storage conditions: 40 °C and 75% of relative humidity, light-shielded sealed glass container

Test timing: initial, after 1 and 3 months

Object to be analyzed: montelukast related substance

##### **<Conditions for analysis of montelukast related substance>**

Instrument: HPLC (Hitachi 2000 series, Japan)

Detector: ultraviolet absorption spectrophotometer (wavelength: 238 nm)

Column: stainless steel column (inner diameter: about 4.6 mm; length: about 25 cm) packed with octylsilyl silica gel (particle diameter: 5 µm) for liquid chromatography (Zorbax SB-Phenyl, Agilent)

Mobile phase:

A - purified water containing 0.1% (v/v) trifluoroacetic acid

B - acetonitrile solution containing 0.1% (v/v) trifluoroacetic acid

## The Eluents dissolution conditions

| Time (min) | A (%) | B (%) |
|------------|-------|-------|
| 0          | 60    | 40    |
| 20         | 10    | 90    |
| 30         | 10    | 90    |
| 31         | 60    | 40    |
| 35         | 60    | 40    |

Flow rate: 1.5 mL/min.

Column temperature: 25 °C

- 5           The amount of production of montelukast sulfoxide and total related substances measured under the above analysis conditions are shown in Table 7, and Figs. 1 and 2.

[Table 7]

|             | Initial   |                          | 1 month   |                          | 3 months  |                          |
|-------------|-----------|--------------------------|-----------|--------------------------|-----------|--------------------------|
|             | Sulfoxide | Total related substances | Sulfoxide | Total related substances | Sulfoxide | Total related substances |
| Ex. 1       | 0.07%     | 0.18%                    | 0.16%     | 0.27%                    | 0.23%     | 0.38%                    |
| Ex. 2       | 0.09%     | 0.17%                    | 0.18%     | 0.29%                    | 0.26%     | 0.40%                    |
| Ex. 3       | 0.06%     | 0.15%                    | 0.20%     | 0.33%                    | 0.30%     | 0.44%                    |
| Comp. Ex. 1 | 0.10%     | 0.21%                    | 0.23%     | 0.40%                    | 0.31%     | 0.49%                    |
| Comp. Ex. 2 | 0.06%     | 0.15%                    | 0.15%     | 0.22%                    | 0.29%     | 0.42%                    |
| Comp. Ex. 3 | 0.15%     | 0.29%                    | 0.34%     | 0.52%                    | 0.50%     | 0.78%                    |
| Comp. Ex. 4 | 0.11%     | 0.18%                    | 0.49%     | 0.56%                    | 0.79%     | 1.17%                    |
| Comp. Ex. 5 | 0.12%     | 0.19%                    | 0.71%     | 0.90%                    | 0.98%     | 1.89%                    |
| Comp. Ex. 6 | 0.11%     | 0.18%                    | 0.52%     | 0.69%                    | 0.82%     | 1.28%                    |
| Comp. Ex. 7 | 0.08%     | 0.19%                    | 0.27%     | 0.42%                    | 0.53%     | 0.77%                    |
| Comp. Ex. 8 | 0.12%     | 0.19%                    | 0.32%     | 0.51%                    | 0.62%     | 0.87%                    |

- As shown in the Table 7, Figs. 1 and 2, it was confirmed that the stabilities of the liquid formulation can be improved by adding an electrolyte compound. And, when excessive amount of electrolyte compounds was added as in Comparative Example 3, property stability was improved but related substances increased to a certain degree. It was found that when a strong alkaline electrolyte compound with high ionizing capacity was added as in Comparative Examples 4 to 6, degradation of main ingredient rapidly occurred, resulting in significant increase of related substance production. And, In Comparative Example 7, in which an electrolyte compound with low ionizing capacity was added, property stability was inferior and related substances increased to a certain degree. Also, in Comparative Example 8, in which glucose, a non-electrolyte component, was added, low stability was shown, as in Comparative Example 7.

**WHAT IS CLAIMED IS:**

1. A liquid formulation comprising an electrolyte compound, and montelukast or a pharmaceutically acceptable salt thereof as an active ingredient.  
5
2. The liquid formulation of claim 1, wherein pH of the liquid formulation ranges from 8.0 to 12.0.
3. The liquid formulation of claim 1, wherein the electrolyte compound is  
10 employed in an amount of 0.5 to 20 parts by weight based on 1 part by weight of montelukast.
4. The liquid formulation of claim 1, wherein montelukast in the active ingredient is employed in an amount of 0.005 to 10% by weight based on the total  
15 weight of the liquid formulation.
5. The liquid formulation of claim 1, wherein the solubility of the active ingredient is 95% to 100% under the accelerated conditions of 40 °C, 75% relative humidity and 3 month period.  
20
6. The liquid formulation of claim 1, wherein the electrolyte compound has pKa of 6.0 to 12.0.
7. The liquid formulation of claim 1, wherein the solubility of the electrolyte  
25 compound is 100 to 900 g/L at 20 °C.
8. The liquid formulation of claim 1, wherein the electrolyte compound is at least one selected from the group consisting of alkali metal chloride and alkali earth metal chloride.  
30

9. The liquid formulation of claim 1, wherein the liquid formulation further comprises at least one pharmaceutically acceptable additive selected from the group consisting of a sweetener, a flavoring agent, a preservative, a solubilizing agent, an emulsifying agent, a pH adjusting agent, an antioxidant and a coloring agent.

5

10. A method for preparing a liquid formulation comprising:

(1) adding at least one pharmaceutically acceptable additive selected from the group consisting of a sweetener, a flavoring agent, a preservative, a solubilizing agent, an emulsifying agent, a pH adjusting agent, an antioxidant and a coloring agent, to  
10 purified water and then stirring them to prepare solution 1;

(2) adding at least one electrolyte compound to purified water and stirring them, and then adding montelukast or its pharmaceutically acceptable salt thereto and stirring them to prepare solution 2; and

(3) mixing solution 1 with solution 2, and adding purified water thereto to  
15 adjust the concentration.

1/2

FIG. 1

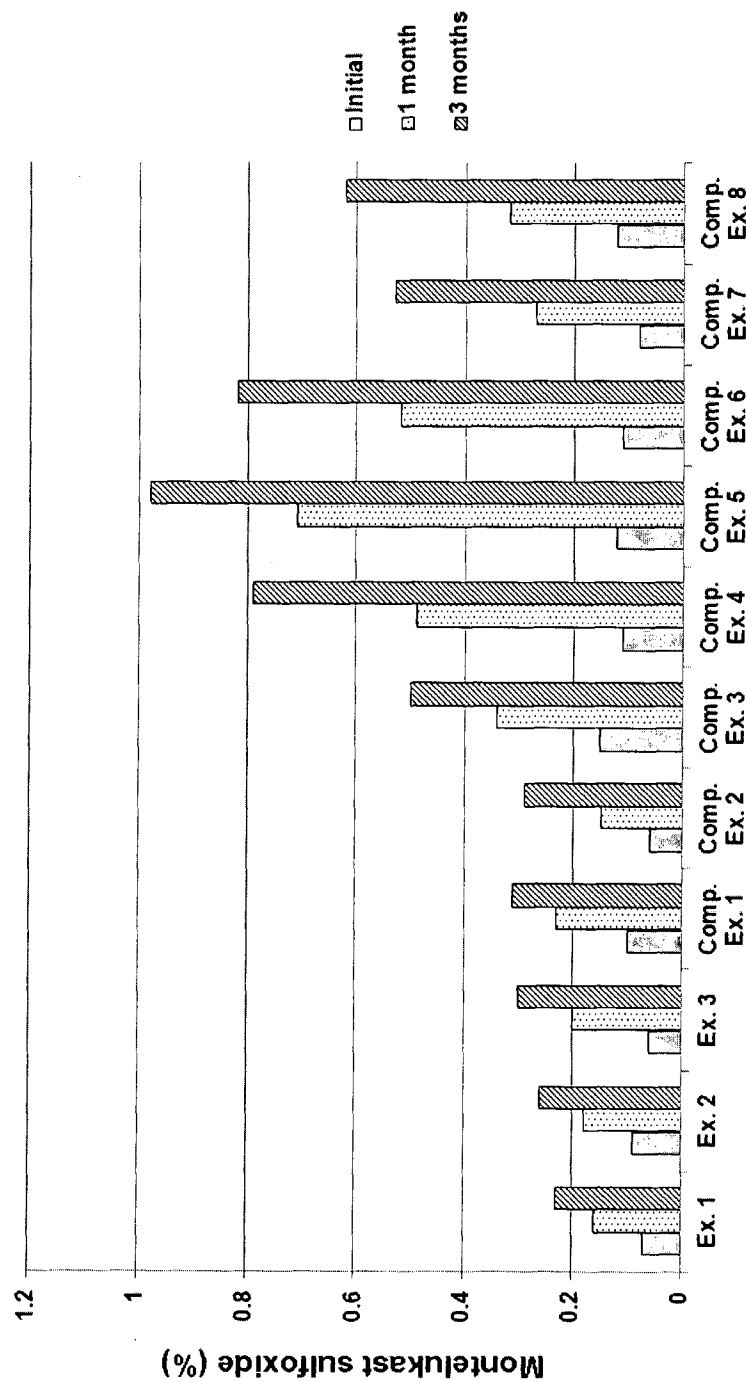
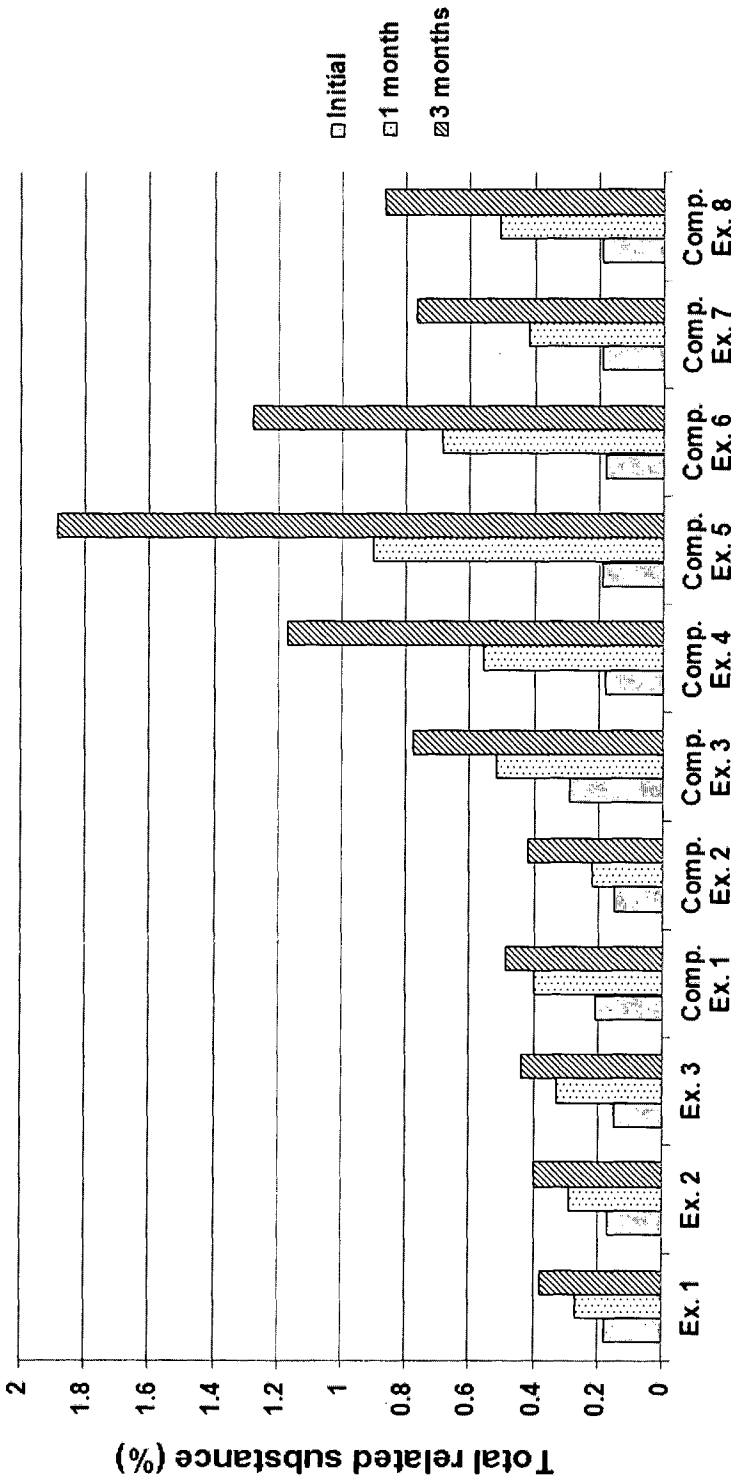


FIG. 2



## INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/KR2015/003529****A. CLASSIFICATION OF SUBJECT MATTER****A61K 47/02(2006.01)i, A61K 9/08(2006.01)i, A61K 31/4704(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61K 47/02; A61K 9/00; A61K 31/00; A61K 9/10; A61P 37/08; A61K 47/38; A61K 31/519; A61K 9/08; C25D 5/40; A61K 31/4704

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) &amp; Keywords: electrolyte, liquid formulation, montelukast

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                         | Relevant to claim No. |
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Further documents are listed in the continuation of Box C.



See patent family annex.

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