Title: NOVEL PHARMACEUTICAL COMPOSITION WITH IMPROVED DEFOAMING ACTIVITY

Abstract: A pharmaceutical composition of the present invention comprises dimethylsiloxane or derivatives thereof as a defoaming agent, silicone dioxide, and a polysorbate-based compound. The pharmaceutical composition includes the defoaming agent at a high concentration, and it is suitable for a solid formulation in order to maintain fluidity of solid powders.
NOVEL PHARMACEUTICAL COMPOSITION WITH IMPROVED DEFOAMING ACTIVITY

BACKGROUND OF THE INVENTION

(a) Field of the invention

The present invention relates to a novel pharmaceutical composition with improved defoaming activity, and more particularly, to a novel pharmaceutical composition that maintains defoaming activity in intestines by adsorbing and pulverizing oil phase dimethylpolysiloxane or derivatives thereof in a high concentration on a solid carrier.

(b) Description of the Related Art

Dimethylpolysiloxane (dimethicone) is generally an agent for defoaming in digestive organs to remove gas, is represented as \( \text{CH}_3(\text{Si(CH}_3)_2\text{O})_n\text{Si-(CH}_3)_3 \), and is colorless, transparent, and odorless. The pharmacopoeia of the USA writes that the above compound is soluble in water and alcohol such as methyl alcohol, acetone and the like; it is very slightly soluble in isopropyl alcohol; and it is soluble in amyl acetate, ether, \( n \)-hexane, toluene, and xylene. Dimethylpolysiloxane formulated in oral administration form protects mucosa from attacking factors and removes pain by forming a protective layer in the digestive organs (from the esophagus to the colon), and prevents foaming in the gastrointestinal tract by decreasing the surface tension of gas bubbles and reducing gas in the
gastrointestinal tract.

Simethicone is an activated derivative of dimethylsiloxane (activated dimethicone). Simethicone has similar physiochemical properties to dimethylsiloxane, it has better defoaming activity than dimethicone, and it is more widely used than dimethicone as a gas-removing component in the intestines. Dimethylsiloxane and derivatives thereof are adsorbed in more than 95% liquid carrier with an oil phase and less than 50% solid carrier with a powder phase, and it is used as a pharmaceutical material. It is sold commercially in a solid formulation such as tablets and powders, and as an emulsion and a suspension.

Formulation materials for formulating dimethylsiloxane or its activated derivative, simethicone, can have an effect on medical efficacy and physical properties of the preparation according to the formulation of pharmaceuticals produced therewith. If the formulation of the pharmaceuticals is a suspension or emulsion, formulation materials do not affect the efficacy of pharmaceuticals and physical properties of the preparation even if the pharmaceuticals are formulated in oil or powder phase. However, in the case that the pharmaceuticals are formulated in a solid form such as tablets, it is necessary to solidify by adsorbing on a suitable carrier to solidify material with an oil phase, and a solid carrier to be used for solidifying may affect the adsorbed amount
and the efficacy of pharmaceuticals produced therewith. The properties of the solid formulation such as size, shape, hardness, dissolvability, brittleness, friction loss, and abrasiveness of the resultant product may be changed and the gas-removing activity (defoaming activity) of dimethylpolysiloxane or derivative thereof may not be maintained.

Under these circumstances, the present inventor has developed a pharmaceutical composition as a high concentration solid adsorbent suitable for maintaining gas-removing activity, that is, defoaming activity.

**SUMMARY OF THE INVENTION**

In order to solve the above problems, the present invention provides a pharmaceutical composition being capable of maintaining gas-removing capability (defoaming activity) of dimethylsiloxane and derivatives thereof.

**DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

A more complete appreciation of the invention, and many of the attendant advantages thereof, will be readily apparent as the same becomes better understood by reference to the following detailed description.

The pharmaceutical composition of the present invention comprises dimethylsiloxane and derivatives thereof as gas-removing components for the intestine; silicon dioxide; and a
polysorbate-based compound. The dimethylsiloxane and derivatives thereof are the main gas-removing agents (defoaming agents) for digestive organs. The silicon dioxide acts as a solid carrier, and the polysorbate-based compound acts as a surfactant which maintains suspension of the pharmaceutical composition. The polysorbate-based compound includes polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, polysorbate 85, or a mixture thereof, and among them polysorbate 80 is most preferably used. The pharmaceutical composition can be prepared in the form of a solid powder.

According to a first preferable example, the pharmaceutical composition comprises 60 to 75 wt% of polydimethylsiloxane and derivatives thereof, 25 to 34.5 wt% of silicon dioxide, and 0.5 to 5.0 wt% of a polysorbate-based compound.

According to a second preferable example, the pharmaceutical composition comprises 65 to 70 wt% of dimethicone, 29.5 to 34.5 wt% of silicon dioxide, and 0.5 to 5.0 wt% of a polysorbate-based compound.

According to a third preferable example, the pharmaceutical composition comprises 68 to 75 wt% of simethicone, 24.5 to 31.5 wt% of silicon dioxide, and 0.5 to 5.0 wt% of a polysorbate-based compound.

In the case that the amount of dimethylsiloxane or
derivatives thereof is less than 60 wt%, defoaming activity of the pharmaceutical composition decreases. In the case that it is more than 75 wt%, the oil (liquid phase) component is present in a large amount which decreases the adsorption capability of the solid carrier resulting in deterioration of fluidity of adsorbed solid materials. In the case that the amount of polysorbate-based compound as a suspension agent is less than 0.5 wt%, defoaming activity of the pharmaceutical composition is not sufficient based on the criteria of the U.S.A Pharmacopoeia. In the case that it is over 5.0 wt%, defoaming activity of the pharmaceutical composition is sufficient based on the criteria of the U.S.A Pharmacopoeia, and therefore use of more than 5.0 wt% is not necessary.

The pharmaceutical composition can be formulated as a solid preparation such as a tablet, a sugar-coated tablet, a hard or soft capsule, or powders, but it is not limited thereto.

The pharmaceutical composition can be administrated via oral or parenteral routes such as rectally, intravenously, or intramuscularly, and the oral route is preferable. The dosage and administration frequency can be controlled according to the degree of disorder of the digestive organ, and the weight, sex, and age of the patient.

The following examples further illustrate the embodiment of the present invention. However, it is to be understood that the examples are for illustration only, and that the invention is not limited to the examples.
Example 1

Powders were prepared in the following composition. Dimethicone and polysorbate 80 were put into a mixer, and silicon dioxide was added and then agitated to prepare adsorbed materials. The adsorbed materials were sieved at less than 80 mesh.

**Composition of powders**

- dimethicone: 65.0%
- polysorbate 80: 0.5%
- silicone dioxide: 39.5%

Example 2

Powders were prepared in the following composition according to preparation procedures of powders described in the pharmacopoeia.

**Composition of powders**

- dimethicone: 65.0%
- polysorbate 80: 1.0%
- silicone dioxide: 34.0%

Example 3

Powders were prepared in the following composition according to preparation procedures of powders described in the pharmacopoeia.

**Composition of powders**

- dimethicone: 70.0%
polysorbate 80  5.0%
silicone dioxide  25.0%

Example 4

Powders were prepared in the following composition according to preparation procedures of powders described in the pharmacopoeia.

Composition of powders

Simethicone  60.0%
polysorbate 80  0.5%
silicone dioxide  39.5%

Example 5

Powders were prepared in the following composition according to preparation procedures of powders described in the pharmacopoeia.

Composition of powders

Simethicone  70.0%
polysorbate 80  0.5%
silicone dioxide  29.5%

Example 6

Powders were prepared in the following composition according to preparation procedure of powders described in the pharmacopoeia.
Composition of powders

Simethicone 75.0%
polysorbate 80 1.0%
silicone dioxide 24.0%

Example 7

Powders were prepared in the following composition according to preparation procedures of powders described in the pharmacopoeia.

Composition of powders

Simethicone 70.0%
polysorbate 80 1.0%
silicone dioxide 29.0%

Example 8

Powders were prepared in the following composition according to preparation procedures of powders described in the pharmacopoeia.

Composition of powders

Simethicone 68.0%
polysorbate 80 5.0%
silicone dioxide 27.0%

Example 9

Powders were prepared in the following composition according to preparation procedures of powders described in the
pharmacopoeia.

Composition of powders

Simethicone 75.0%
polysorbate 80 5.0%
silicone dioxide 20.0%

Control 1

Powders were prepared in the following composition according to preparation procedures of powders described in the pharmacopoeia.

Composition of powders

Simethicone 60.0%
silicone dioxide 40.0%

Control 2

Powders were prepared in the following composition according to preparation procedures of powders described in the pharmacopoeia.

Composition of powders

Simethicone 80.0%
silicone dioxide 20.0%

Control 3

Powders were prepared in the following composition according to preparation procedures of powders described in the pharmacopoeia.
Composition of powders

Dimethicone 65.0%
silicone dioxide 35.0%

Experiment Example 1: comparison of defoaming activity of Examples and controls

Experimental procedure of defoaming activity of simethicone

1. foaming solution --- 1 gram of octoxynol 9 was dissolved in 100 mL of purified water.

2. procedure --- 20mg of simethicone powders were put into a 250 mL glass cylinder, foaming solution warmed to 37°C was added, and the cylinder was closed with a cover. The glass cylinder was shaken at 300 ±30 strokes/minute at a 10 degree angle over a distance of 13.3 ±0.4 cm for 10 seconds using a wrist action shaker. The elapsed time when foam disappeared after shaking was measured.

3. Evaluation --- A composition which defoams within 45 seconds can be commercialized as a deforming pharmaceutical composition.
Table 1: Comparison of defoaming activity of Examples and controls

<table>
<thead>
<tr>
<th></th>
<th>Ex. 1</th>
<th>Ex. 2</th>
<th>Ex. 3</th>
<th>Ex. 4</th>
<th>Ex. 5</th>
<th>Ex. 6</th>
<th>Ex. 7</th>
<th>Ex. 8</th>
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As shown in Table 1, pharmaceutical compositions of Examples had defoaming times of 4 to 12 seconds. Pharmaceutical compositions of Controls 1 to 3 had defoaming times of 30 to 45 seconds. These results indicate that pharmaceutical compositions of the present invention have improved defoaming activity.

The pharmaceutical compositions of the present invention can adsorb dimethylsiloxane or derivatives thereof on a solid dispersion material uniformly at a high concentration, and solidify oil materials into powders easily. A preparation of pharmaceutical compositions in solid formulation to be administrated in order to remove gas in a digestive organ realizes a reduced preparation process time, a reduction of preparation cost, a quality improvement of product, and pharmaceutical efficacy along with maintenance of defoaming activity.
WHAT IS CLAIMED IS:

1. A pharmaceutical composition comprising dimethylsiloxane or derivatives thereof as a gas-removing component in intestines, silicone dioxide, and a polysorbate-based compound.

2. The pharmaceutical compositions according to claim 1, wherein the dimethylsiloxane or derivatives thereof are dimethicone or simethicone.

3. The pharmaceutical compositions according to claim 1, wherein the polysorbate-based compound is at least one selected from the group consisting of polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80, and polysorbate 85.

4. The pharmaceutical compositions according to claim 1, comprising 60 to 75 wt% of dimethylsiloxane or derivatives thereof, 24.5 to 34.5 wt% of silicone dioxide, and 0.5 to 5.0 wt% of a polysorbate-based compound.

5. The pharmaceutical compositions according to claim 1, comprising 65 to 70 wt% of dimethicone, 29.5 to 34.5 wt% of silicone dioxide, and 0.5 to 5.0 wt% of a polysorbate-based compound.

6. The pharmaceutical compositions according to claim 1, comprising 68 to 75 wt% of simethicone, 24.5 to 31.5 wt% of silicone dioxide, and 0.5 to 5.0 wt% of a polysorbate-based compound.
7. The pharmaceutical compositions according to one of claims 1 to 6, the composition being prepared in an oral formulation.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 31/74

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)
IPC7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and applications for inventions since 1975

Electronic database consulted during the international search (name of database and, where practicable, search terms used)
MEDLINE, KIPASS, DELPHION

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C. See patent family annex.

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
13 FEBRUARY 2003 (13.02.2003)

Date of mailing of the international search report
17 FEBRUARY 2003 (17.02.2003)

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Facsimile No. 82-42-472-7140

Form PCT/ISA/210 (second sheet) (July 1998)
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