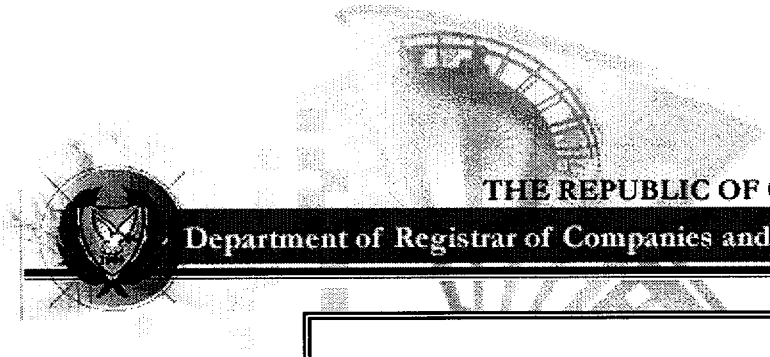

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

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(54) **Organopolysiloxane/silica pharmaceutical compositions**

(57) An antacid chewable tablet containing an antacid, an organopolysiloxane, and silica in an amount of 1 to 70% of the weight of the siloxane/silica mixture has rapid defoaming action. The tablet is prepared by adding the organopolysiloxane and silica, premixed in powder form, to an antacid. Additionally, the premixed powder can be used as an antiflatulent alone or in combination with other medicinal agents.

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SPECIFICATION

Organopolysiloxane compositions

This invention relates to organopolysiloxane compositions useful for preparing improved antacid compositions. More specifically, this invention includes a method for combining the organopolysiloxane with silica resulting in a powder. This powder may then be combined with an antacid and compressed into tablets. The powder can also be used as an antiflatulent alone or in combination with other medicinal agents.

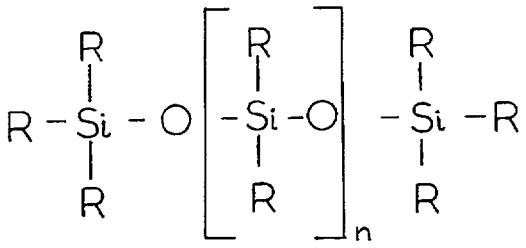
The use of organopolysiloxanes in antacid compositions is known in the art. For instance, U.S. Reissue Patent 25,205 describes the use of organopolysiloxanes with antacids. U.S. Patents 3,210,208 and 3,382,150 describe methods for preparing coated organopolysiloxane particles. Both of these patents utilize an emulsion of organopolysiloxane, a nontoxic coating material and water. The emulsion is spray-dried to form particles of organopolysiloxane which is then coated with the coating material. U.S. 3,501,571 describes a method for absorbing organopolysiloxanes on an inert absorbent filler such as sugar or mannitol, granulating the resulting mixture and then drying the mixture which results in the organopolysiloxane in a powder form.

All of the above methods require either some form of liquid to form an emulsion or granulation of the organopolysiloxane material and use of an inert absorbent filler. The above methods then require a spray drier or oven to dry the material. This is both time consuming and costly.

U.S. 3,422,189 describes anti-flatulent compositions which contain an organopolysiloxane and finely divided silica or a silica aerogel. The finely divided silica is used in amounts sufficient to form a viscous mixture with the organopolysiloxane resulting in a honey-like or salve-like consistency. A weight range, based on the organopolysiloxane employed, of 1-10% is employed with a range of about 3-7% being preferred. British Patent 1,047,470 describes defoaming compositions which are prepared by adding finely divided silica to a polysiloxane component and heating this mixture to disperse the silica. The silica is disclosed as being present in an amount of at least 3% by weight.

It has now been discovered that a uniform powder comprising spherical particles and essentially consisting of an organopolysiloxane and silica can be prepared without the use of liquid or heat. The novel silica and organopolysiloxane powder of this invention consists essentially of organopolysiloxanes, from about 1% to 70%, preferably from about 5% to about 60%, and more particularly about 15% to about 60% by weight of the powder. The novel powder can then be formulated with suitable excipients to form an antiflatulent tablet composition or can be mixed with an antacid and compressed into tablets. The novel powder of the invention can also be mixed with excipients or other medicinal agents and excipients and used in various pharmaceutical forms. The use of this amount of organopolysiloxane results in a uniform powder and distinguishes this formulation from prior combinations of silica and organopolysiloxanes. The expression "uniform powder" is intended herein to mean a powder obtainable by blending the ingredients in a suitable blender until a substantially uniform product is obtained.

The organopolysiloxane type compound that is utilized in this novel formulation is usually a liquid, oily or semi-solid organopolysiloxane represented by the following formula.



wherein R is a lower alkyl group having from 1 to 5 carbon atoms or an organic radical such as phenyl and n can be 0 to 2000. A preferred organopolysiloxane is simethicone which is a mixture of fully methylated linear siloxane polymers containing repeating units of the formula $[-(CH_3)_2\text{-Si O-}]_n$, stabilized with trimethylsiloxy end-blocking units of the formula $[(CH_3)_3\text{-Si O-}]$ and silicon dioxide. Simethicone contains at least 93.0 percent and not more than 99.0 percent of $[-(CH_3)_2\text{-Si O-}]_n$ (dimethylpolysiloxane), and at least 4.0 percent and not more than 7.0 percent of silicon dioxide.

Suitable antacids which can be utilized in this invention include magaldrate, magnesium hydroxide, aluminum hydroxide, magnesium carbonate, calcium carbonate, magnesium oxide, magnesium trisilicate, aluminum phosphate, dihydroxy aluminum aminoacetate, bismuth subcarbonate and combinations thereof. The preferred antacid of this invention is magaldrate. The antacid composition may have a rapid defoaming action.

The finely divided silica used in this invention are available from various commercial sources. A preferred source of silica is sold under the tradename CAB-O-SIL and is a submicroscopic fire-dried fumed silica. The particle size can vary from 70 to 500 angstroms in diameter.

As has been noted before, the organopolysiloxane powder of this invention can be incorporated with an antacid in the formulation of a chewable antacide tablet. A preferred method of preparation of this tablet is to add sucrose to a simethicone-silica powder before mixing with the antacid. A preferred formula for 1000 tablets is listed below:

Ingredient	*Amount*
Magaldrate, U.S.P.	470.0 g
Simethicone N.F.	23.2 g
Silica, Colloidal	17.37 g
Sucrose, Powdered	153.0 g
Methylcellulose, U.S.P., 15 cps	1.34 g
Dextrates, Hydrous	500.0 g
Polyethylene Glycol 6000, U.S.P., Milled	120.0 g
Spearmint, Aromalok 26380, Fritzsche	4.0 g
Magnesium Stearate, U.S.P.	5.4 g
Water, U.S.P., Purified	28.0 ml
Theoretical Tablet Weight	1,294. mg

The term "theoretical tablet weight" is used because all commercial dimethylpolysiloxanes are somewhat volatile. Recently, low volatility dimethylpolysiloxane has been introduced on the market and this product appears to perform better.

As can be seen from the above formulation, pharmaceutically inert ingredients such as extenders, binders, lubricants, coloring agents, flavorings and the like can be added to the antacid formulation. Examples of pharmaceutically inert ingredients which can be added to the antacid formulation include extenders or diluents such as lactose, mannitol, sorbitol, microcrystalline cellulose and starch. Examples of binders that can be added to the formulation of this invention are natural gums and gum constituents such as acacia, tragacanth, agar, and pectin; proteinaceous materials such as gelatin, casein, and zein; polyvinylpyrrolidone; cellulose compounds; and starch. Examples of lubricants that can be used are calcium stearate, talc, stearic acid, sodium benzoate or mixtures thereof.

The uniform powder of this invention is simply prepared by blending the simethicone with the silica in a suitable blender until uniform. The simethicone silica powder is then as, previously noted preferrably granulated with sucrose prior to formulation of an antiflatulent dosage form alone or formulation of a combination antacid antiflatulent dosage form.

More specifically, the above formulation is prepared in the following manner and is illustrative of the manner of preparation for all the compositions encompassed by this invention.

1. Heat about 14 ml of Purified Water to 80-90°C. Add Methylcellulose, 15 cps, and stir until uniformly dispersed. Bring up to a volume of 28 ml with Purified Water and cool to room temperature.
2. Blend the simethicone with Colloidal Silica in a suitable blender until uniform.
3. Blend the mixture from Step #2 with Powdered Sucrose in a suitable blender until uniform.
4. Granulate the blend from Step #3 with the solution prepared in Step #1, adding additional Purified Water if necessary to obtain suitable granulation.
5. Dry the granulation from Step #4 overnight at 45°C in a forced draft dryer and pass through a Fitz Mill using a #20 screen, medium speed, knives forward.
6. Blend Magaldrate Powder, Dextrates Hydrous, Polyethylene Glycol 6000 Milled and Spearmint Aromalok 26380. Pass through a Fitz Mill using a #16 screen, medium speed, knives forward.
7. Blend the ingredients from Step #5 and #6 in a suitable blender until uniform.
8. Add the Magnesium Stearate and blend.
9. Compress to make a tablet.

Examples of other medicinal agents which can be used in combination with an organopolysiloxane powder include the following:

1. Digestants such as bile constituents, pancreatin, pepsin, and digestive enzymes such as amylase, lipase and protease.
2. Anticholinergic Agents such as atropine sulfate, hyoscyamine sulfate, scopolamine hydrobromide and mixed alkaloidal extracts.
3. Barbiturates such as phenobarbital and butabarbital sodium.

The following examples further illustrate the above described invention:

EXAMPLE I

Simethicone	800 g
Colloidal Silica	600 g

Mix simethicone and the colloidal silica together in a suitable mixer with high shear. The resulting mixture is a powder. It is understood that this powder can be prepared by dissolving simethicone in a suitable solvent as taught by the prior art, dispersing the simethicone on the silica and evaporating the solvent.

EXAMPLE II

The powder as prepared in Example I can be mixed with antacids such as magaldrate and pharmaceutically inert ingredients and compressed into tablets. This example illustrates such a preparation.

Simethicone Powder from Example I	35.0 g
Magaldrate	470.0 g
Powdered Sucrose	70.0 g
PEG 6000	120.0 g
Dextrates, Hydrous	425.0 g
Sorbitol	100.0 g
Saccharin	0.3 g
Spearmint	4.0 g
Magnesium Stearate	5.4 g
Theoretical Tablet Weight	1229.7 mg

All the ingredients except magnesium stearate were mixed in a suitable mixer. The magnesium stearate was blended in and all the ingredients were compressed.

EXAMPLE III

Simethicone powder as described in Example I can first be mixed with a pharmaceutically inert ingredient, granulated with a binder and dried and sized to convert the mixture into granules

Simethicone	–	400.0 g
Colloidal Silica	–	300.0 g
Powdered Sucrose	–	2625 g
5% Methylcellulose (15 cps) Aq.Sol.		–
	450.0 ml	

The simethicone and colloidal silica were mixed in a suitable mixer with high shear. The powdered sucrose was added and mixed well. Granulate the mixture with 450 ml of 5% methylcellulose aqueous solution and dry it in a forced air oven at 45°C. Size the dried material by passing through a suitable screen.

EXAMPLE IV

Simethicone granules as prepared in Example III can be mixed with antacids and pharmaceutically inert ingredients and compressed to make tablets as follows:

Simethicone Granules from Example III	167.38 g
Magaldrate	470.0 g
Dextrates, Hydrous	500.0 g
PEG 6000	120.0 g
Spearmint	4.0 g
Magnesium Stearate	5.4 g
Theoretical Tablet Weight	1266.78 mg

This formulation is prepared as in Example II.

EXAMPLE V

Simethicone Powder from Example I	140.0 g
Dextrates, Hydrous	600.0 g
Polyethylene Glycol 6000	80.0 g
Spearmint Flavor	2.7 g
Magnesium Stearate	2.0 g
Theoretical Tablet Weight	824.7 mg

All the ingredients except Magnesium Stearate were mixed in a suitable mixer. The Magnesium Stearate was blended in and all the ingredients were compressed.

EXAMPLE VI

Simethicon Granulation from Example III	669.5 g
Spearmint Flavor	2.7 g
Magnesium Stearate	2.0 g
Theoretical Tablet Weight	674.2 mg

The Simethicone Granulation and Spearmint were mixed in a suitable mixer. The Magnesium Stearate was blended in and all the ingredients were compressed.

Examples V and VI illustrate anti-flatulent formulations.

CLAIMS

1. A uniform powder comprising substantially spherical particles and consisting essentially of an organopolysiloxane and silica wherein the organopolysiloxane is present in an amount from about 1% to about 70% based on the weight of the powder.

2. A powder as claimed in claim 1, wherein the organopolysiloxane is present in an amount from about 5% to about 60%.

3. A powder as claimed in claim 1, wherein the organopolysiloxane is present in an amount from about 15% to about 60%.

4. A powder as claimed in any one of claims 1 to 3, wherein the organopolysiloxane is simethicone.

5. A powder as claimed in claim 1, substantially as described in Example I.

6. A method for preparing a uniform powder comprising spherical particles, comprising blending in the absence of heat or a solvent about 1% to about 70%, based on the weight of the powder, of an organopolysiloxane with finely divided silica.

7. A method as claimed in claim 6, in which the organopolysiloxane is simethicone.

8. A method as claimed in claim 6 or 7, wherein the organopolysiloxane is present in an amount from about 15% to 60%.

9. A method as claimed in claim 6, carried out substantially as described in Example I herein.

10. A method of preparing a granulation, comprising a method as claimed in any one of claims 6 to 9 and granulating the powder with sucrose.

11. A method as claimed in claim 10, carried out substantially as described in Example III herein.

12. A powder whenever prepared by a method as claimed in any one of claims 6 to 9.

13. A granulation whenever prepared by a method as claimed in claim 10 or 11.

14. A composition comprising a powder as claimed in any one of claims 1 to 5 and 12 and sucrose.

15. A composition as claimed in claim 14, substantially as described in Example III herein.

16. A pharmaceutical composition comprising a powder as claimed in any one of claims 1 to 5 and 12 and pharmaceutically acceptable excipients.

17. A composition as claimed in claim 16, substantially as described in Example V or VI herein.

18. A compressed tablet comprising a powder as claimed in any one of claims 1 to 5 and 12, an antacid and pharmaceutically acceptable excipients.

19. A tablet as claimed in claim 18, wherein the antacid is magaldrate.

20. A tablet as claimed in claim 18, formulated substantially as described with reference to Example II or IV herein.

21. A tablet as claimed in claim 18, formulated substantially as described with reference to the aforesaid "preferred formula for 1000 tablets".

New claims or amendments to claims filed on 29 Feb 1980.

Additional claims:– 22 to 26.

New or amended claims:–

22. As an antiflatulant, a powder as claimed in any one of Claims 1 to 5.

23. A pharmaceutical composition comprising a powder as claimed in any one of Claims 1 to 5 and another medicinal agent.

24. A composition as claimed in Claim 23, which also contains pharmaceutically acceptable excipients.

25. A composition as claimed in Claim 23, wherein the agent is an antacid.

26. A composition as claimed in Claim 25, wherein the agent is magaldrate.

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