

[54] **GLIDANTS AND PROCESS FOR PREPARING THE SAME**

[75] Inventors: **Eiichi Nakajima; Tadashi Morioka; Kozo Kurihara; Takashi Kobayashi,** all of Tokyo, Japan

[73] Assignee: **Sankyo Company Limited,** Tokyo, Japan

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[63] Continuation of Ser. No. 336,372, Feb. 27, 1973, abandoned.

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[58] **Field of Search** **424/14, 22, 44; 252/11, 252/39, 33, 56 R, 56 S, 52**

[56]

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Primary Examiner—Delbert E. Gantz

Assistant Examiner—I. Vaughn

Attorney, Agent, or Firm—Flynn & Frishauf

[57]

ABSTRACT

Improved glidants having excellent gliding properties, i.e., improving or eliminating those disadvantages encountered in the prior art, for example, capping of the finished pharmaceutical preparations, delayed disintegration of the finished pharmaceutical preparations, lowering of the dissolution-out rate of the active ingredient and the like, which comprises certain known glidants wet-treated with a surface active agent, said known glidants being selected from higher fatty acids, the metal salts thereof and hydrogenated vegetable oils. The present glidants are prepared by subjecting the known glidants to wet treatment with a surface active agent.

9 Claims, No Drawings

GLIDANTS AND PROCESS FOR PREPARING THE SAME

This is a continuation of application, Ser. No. 336,372, filed Feb. 27, 1973, and now abandoned.

This invention relates to improved glidants and a process for preparing the same.

More particularly, it is concerned with improved glidants comprising a glidant substance wherein said glidant substance is subjected to wet treatment with a surface active agent, said glidant substance being selected from the group consisting of higher fatty acids, the metal salts thereof and hydrogenated vegetable oils and with a process for the preparation of such improved glidant.

It is well-known in the art that a certain type of adjuvants or glidants which have been widely employed for the production of various pharmaceutical preparations, e.g., powders, capsules, tablets and the like have troublesome disadvantages that they show such undesirable characteristics as poor disintegration of the finished pharmaceutical preparation, prolonged dissolution-out rate of the active ingredient, especially they have a pronounced tendency to cause capping when used in making tablets. In some cases, other types of glidants such as boric acid, sodium benzoate, sodium chloride, leucine, Carbowax (Registered Trade Mark), sodium stearate and the like have been also utilized in the pharmaceutical preparations, especially those required for hydrophilic property, e.g., water-soluble tablets, but these glidant substances were known to exert a poor glidant effect as well as toxicity and hygroscopicity so that they were kept away from general utilizability.

As a result of our extensive studies to develop a new and improved glidant having no disadvantages as seen in the prior art glidants, it has been unexpectedly found that a certain type of the known glidant substances, i.e., those selected from the group consisting of higher fatty acids, the metal salts thereof and hydrogenated vegetable oils exhibit a highly excellent glidant effect when they are subjected to wet treatment with a surface active agent.

The above finding is quite surprising because it has been generally understood in the art that a glidant exhibits its glidant effect due to its surface properties and thus, when treated with a substance having no gliding property per se, such a glidant should lose its inherent glidant property.

However, in contrary to the above-depicted prejudice, the improved glidant of this invention can hold inherent glidant effects such as the improvement in fluidity, the lowering of the excluding force from punches upon making tablets, the increase in bulk density, the prevention of anchoring and the like and simultaneously perform almost complete elimination of the disadvantages accompanied with the prior art glidants, e.g., poor disintegration, lower dissolution-out rate and the like, as compared with the prior art glidants. Still more surprisingly, in the case of making tablets the improved glidant of this invention can effectively prevent the low tablet hardness and the development of capping, which are believed inherent in the prior art glidant.

It is, therefore, a primary object of this invention to provide an improved glidant which shows highly excellent glidant ability without the disadvantages inherent in the prior art, especially capping, delayed disintegration and low dissolution-out rate.

It is another object of this invention to provide a process for the preparation of an improved glidant having desirable characteristics.

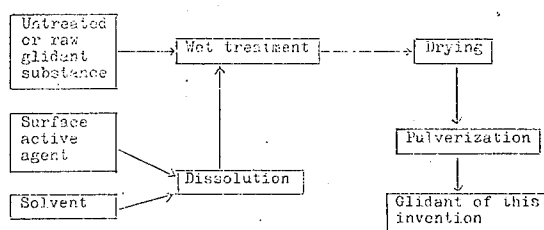
These objects and the advantages of this invention will be apparent to those skilled in the art from the detailed description below.

The glidant of this invention, as explained above, has an essential feature that it comprises a glidant substance known per se, said substance being selected from the group consisting of higher fatty acids, the metal salts thereof and hydrogenated vegetable oils, which substance is subjected to wet treatment (or treatment under a wetting condition) with a surface active agent.

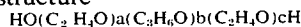
The term "wet treatment" as used herein is contemplated to include kneading procedure and other procedures commonly employed for absorption between solid phase and liquid phase.

In another aspect of this invention, the process of this invention comprises subjecting the selected glidant substance to wet treatment with a surface active agent.

In effecting the process of this invention, the preferred embodiment can be carried out according to the flow sheet as illustrated below.



In the above-mentioned embodiment, the wet treatment may be effected as set forth above. The drying may be suitably effected by a conventional drying procedure, e.g. hot air drying, aeration drying, vacuum drying and the like. The pulverization may be suitably effected by means of a conventional grinder, e.g., impact grinder, pneumatic grinder and the like. It is desirable that the particle size of the ground glidant be in the range of $10\ \mu$ or less, but larger particle size may also be favourably employed. Examples of the glidant substances to be treated according to the process of this invention include stearic acid, magnesium stearate, calcium stearate and hydrogenated castor oil [e.g. "Lubriwax" (trade name, available from Freund Industrial Company, Japan) and "Sterotex" (trade name, available from Capital City Products Company, U.S.A)]. If desired, any combination of the above-illustrated glidant substances may also be employed in this invention. The surface active agents which may be employed in this invention may be of any type of non-ionic, anionic and cationic type surface active agents. Of these surface active agents are preferable polyoxyethylene-polyoxypropylene block polymers, e.g., those having the structure



wherein either the sum of a and c is 30 – 35 and b is 25 – 30 or the sum of a and c is 140 – 150 and b is 25 – 30 and a molecular weight of either ca. 3,000 or ca. 8,000, respectively [e.g. "Pluronic F-68" and "Pluronic L-64"]

(trade names, available from Asahi Denka Kogyo K.K., Japan or from Wyandotte Chemical Co., U.S.A.); polyoxyethylene sorbitan fatty acid esters, e.g., polyoxyethylene monostearate, monolaurate, monopalmitate, monooleate and trioleate; alkyl sulfate salts, e.g., sodium lauryl sulfate; and the like. The amount of the surface active agent to be employed is not critical, but it is usual and effective to employ the surfactant at 20 % by weight or less, preferably at 4 - 5 % by weight, based upon the total weight of the untreated glidant substance. The solvent which may be employed in the above wet treatment may be any of those that could dissolve the surfactant and not the untreated glidant substance. Examples of the solvents which may be employed include water, methanol, ethanol, acetone, chloroform and the like.

The following Examples are given for the purpose of illustrating of the advantages and embodiments of this invention, but they should not be construed to be limiting the scope of this invention. All parts and percentages are given by weight.

Table I

Surface active agent	Solvent
Polyoxyethylene sorbitan monolaurate	A (Ethanol)
Polyoxyethylene sorbitan tristearate	B (Ethanol)
Sorbitan monooleate	C (Ethanol)
Sorbitan monooleate	D (Ethanol)
Pluronic L-64	E (Water)
Pluronic F-68	F (Water)
Sodium lauryl sulfate	G (Water)

Separately, 100 parts of magnesium stearate (hereinafter referred to as "StMg") was placed into a mortar and then 80 parts of each of the above-depicted surfactant solutions was added thereto. After being well kneaded, the mass was dried in vacuum and ball-milled. The lactose samples having incorporated therein 0.5 % or 2 % respectively of the surfactant-treated StMg and the untreated StMg were determined for their physical properties as shown below with the results which are summarized in the following Table II.

Table II

Amount of glidant added	Specific volume	Specific extruding force*	Angle of falling**	Disintegration time of molded product (min.)
	0.5%	0.5%	0.5%	2%
Lactose alone	1.81	1.00	52	1
Lactose + Untreated StMg	1.28	0.11	44	23
Lactose + (A)	1.28	0.15	48	8
Lactose + (B)	1.29	0.11	47	5
Lactose + (C)	1.26	0.10	43	9
Lactose + (D)	1.27	0.11	42	9
Lactose + (E)	1.30	0.25	43	6
Lactose + (F)	1.27	0.15	43	6
Lactose + (G)	1.29	0.15	42	3

*Extruding force from the cylinder upon the pressure-molded product (Kg/cm)

**Angle of repose of the powder flowed out of the funnel.

EXAMPLE 1

The surface active agents indicated in the Table I below were respectively dissolved in the solvents indicated in the Table I to form the 5 % solutions thereof.

It will be seen from the above Table II that the glidants of this invention exhibit excellent properties.

EXAMPLE 2

The molded products from the formulations indicated in the following Table III and the No. 1 capsules filled with the same formulations were tested for their physical properties as below with the results which are summarized in the Table IV below.

Table III

Sample No.	1	2	3	4	5	6	7
Chloramphenicol (parts)	100	100	100	100	100	100	100
Lactose (parts)	40	39.3	39.3	39.3	37.2	37.2	37.2
Untreated StMg (parts)	—	—	0.7	—	—	2.8	2.66
Sodium lauryl sulfate (powder, less than 10 μ , parts)	—	0.7	—	—	—	—	0.14
StMg treated with sodium lauryl sulfate* (less than 10 μ , parts)	—	—	—	0.7	2.8	—	—
Total (parts)	140	140	140	140	140	140	140

*100 parts of StMg was subjected to wet treatment with an 5% aqueous solution of sodium lauryl sulfate, dried and then pulverized.

Table IV

Compound No.	1	2	3	4	5	6	7
Specific extruding force (kg/cm)	1.50	1.05	0.48	0.49	—	—	0.50

Table IV-continued

Compound No.	1	2	3	4	5	6	7
Disintegration time of capsule(min)	8	8	11	8	8	25	18

It will be seen from the above Table IV that the incorporation of the surfactant alone does not provide so much appreciable glidant effect (Sample No. 2), the incorporation of the StMg alone provides a good glidant effect but poor disintegration ability (Sample Nos. 3 and 6) and the incorporation of a simple mixture of the surfactant and the StMg gives an insufficient period of disintegration time (Sample No. 7), whereas the glidants treated with the surfactant solution according to this invention exert the desired effect (Sample Nos. 4 and 5).

EXAMPLE 3

The powdery formulations shown in the following Table V were formed by utilizing the treated StMg prepared in the above Example 1 and filled into No. 0 capsules, which were then subjected to a dissolution-out test.

The results are summarized in the Table VI below.

Table V

Sample No.		8	9	10	11	12
Chloramphenicol	(parts)	500	500	500	500	500
Lactose	(parts)	150	120	120	120	120
Untreated StMg	(parts)	—	30	—	—	—
(B)*	(parts)	—	—	30	—	—
(F)*	(parts)	—	—	—	30	—
(G)*	(parts)	—	—	—	—	30
Total (parts)		650	650	650	650	650

*The same as in the above Table I.

Table VI

Amount of the active ingredient eluted (%)			
Dissolution-out time	10 min.	20 min.	30 min.
Sample No.			
8	81	95	98
9	5	14	23
10	15	45	76
11	10	45	78
12	91	99	100

It will be seen from the above Table VI that, when such a large amount of the glidant is formulated, the formulation containing the conventional or untreated StMg (Sample No. 9) shows much lower dissolution-out rate as compared with that containing no glidant (Sample No. 8), whereas the formulations containing the StMg treated according to this invention (Sample Nos. 10, 11 and 12) undergo little influence with such factors and show a good dissolution-out rate.

EXAMPLE 4

An appropriate amount of lactose was granulated with a 4 % starch paste and then dried. To the so obtained granules was incorporated the glidant indicated in the following Table VII. The resulting granules were molded and tested as follows.

Table VII

Sample No.	13	14	15
Lactose granules (parts)	2000	2000	2000
Untreated StMg (parts)	15	—	—
StMg treated with sodium lauryl sulfate* (parts)	—	15	—
Total (parts)	2015	2015	2000

*The same as in the above Example 2.

Five hundred mg. of the granule sample as obtained above was molded under pressure of 1 ton by means of a conventional compression tester equipped with flat punches of 11 mm. diameter, whereupon the excluding force from the punch was determined with a load cell.

The results are summarized in the following Table VIII.

Table VIII

Sample No.	Excluding force from the punch(kg.)
13	19
14	19
15	92

It will be seen from the above Table VIII that the formulation containing the StMg treated with the surfactant (Sample No. 14) has a reducing action against the force excluding the tablets from the punch, i.e., a glidant action as the formulation containing the untreated StMg (Sample No. 13) has.

EXAMPLE 5

The powdery formulations were prepared having the formulas as indicated in the following Table IX.

Table IX

Sample No.	16	17	18
Ground sugar (parts)	1070	1058	1058
Methyl cellulose (50 c.p.s., parts)	10	10	10
Talc (parts)	120	120	120
Untreated Lubriwax (parts)	—	12	—
Lubriwax treated with sorbitan monolaurate*	—	—	12
Total (parts)	1200	1200	1200

*50 parts of an 10% ethanolic solution of sorbitan monolaurate was mixed and kneaded with 100 parts of Lubriwax, dried in vacuum and then pulverized.

One thousand and two hundred mg. of the sample as obtained above was molded under pressure of 3.3 tons by means of a conventional compression tester equipped with flat punches of 16 mm. diameter, whereupon the excluding force from the punch was determined with a load cell.

Table X

Sample No.	Excluding force from the punch (kg.)
16	58
17	40
18	33

It will be seen from the above Table X that the formulation containing the Lubriwax treated with sorbitan monolaurate (Sample No. 18) exhibits a superior glidant power to that of the formulation containing the untreated Lubriwax (Sample No. 17).

EXAMPLE 6

The granules were prepared by incorporating a 4 % starch paste to an appropriate amount of lactose and then granulating. The so obtained granules were punched to the tablets having a uniform tablet height according to the formulae indicated in the Table XI below.

Table XI

Sample No.	19	20	21
Lactose granule (parts)	987.5	987.5	987.5
Untreated StMg (parts)	12.5	—	—
StMg treated with sodium lauryl sulfate * (parts)	—	12.5	—
StMg treated with polyoxy-** ethylene sorbitan tristearate (parts)	—	—	12.5
Total (parts)	1000	1000	1000

*The same as in the above Example 2.

**Prepared by the same procedure as that of the just above (*).

The test results of the tablets thus prepared are summarized in the following Table XII.

Table XII

Sample No.	19	20	21
Strength of tablet (kg.)	3.2	5.5	5.2
Capping number*	12/20	0/20	0/20
Disintegration time (min.)	25	11	14

*Webster-Abbe abrasion tester, in 2 minutes.

It will be seen from the above Table XII that the tablets containing the glidants treated with a surfactant (Sample Nos. 20 and 21) have no capping, a high strength and a satisfactory disintegration time.

What is claimed is:

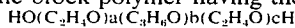
1. A glidant comprising a major amount of a glidant substance selected from the group consisting of a higher fatty acid, a calcium salt thereof, a magnesium salt thereof, and a solid hydrogenated vegetable oil, treated with a solvent solution containing a surface active agent in an amount sufficient to improve dissolution of the glidant substance, said solvent being a solvent for said surface active agent and a non-solvent for said glidant substance, followed by drying and pulverization.

2. The glidant according to claim 1 wherein said glidant substance is stearic acid, magnesium stearate, calcium stearate or hydrogenated castor oil.

3. The glidant according to claim 1 wherein said surface active agent is a non-ionic, anionic or cationic surface active agent.

4. The glidant according to claim 1 wherein said surface active agent is a polyoxyethylene-polyoxypropylene block polymer, a polyoxyethylene sorbitan fatty acid ester or an alkyl sulfate salt.

5. The glidant according to claim 1 wherein said surface active agent is a polyoxyethylene-polyoxypropylene block polymer having the structure

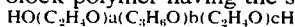


wherein either the sum of a and c is 30 – 35 and b is 25 – 30 or the sum of a and c is 140 – 150 and b is 25 – 30 and having a molecular weight of either about 3,000 or about 8,000; a polyoxyethylene sorbitan mono- or tri-fatty acid ester having 12 – 18 carbon atoms in the fatty acid moiety; or sodium lauryl sulfate.

6. The glidant according to claim 1 wherein said surface active agent is employed in an amount of up to 20% by weight, based upon the total weight of said glidant substance.

7. The glidant according to claim 1 wherein said glidant substance is magnesium stearate and said surface active agent is sodium lauryl sulfate.

8. The glidant according to claim 1 wherein said glidant substance is magnesium stearate and said surface active agent is a polyoxyethylene-polyoxypropylene block polymer having the structure



wherein either the sum of a and c is 30 – 35 and b is 25 – 30 or the sum of a and c is 140 – 150 and b is 25 – 30 and having a molecular weight of either about 3,000 or about 8,000.

9. The glidant according to claim 1 wherein the solvent is water methanol, ethanol, acetone or chloroform.

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