AU9460523

(12) PATENT ABRIDGMENT (11) Document No. AU-B-60523/94
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 684745

(54) Title
A METHOD OF IMPROVING THE SWALLOWABILITY OF GELATIN CAPSULES

(51)[5] International Patent Classification(s)
A61K 009/48

(21) Application No. : **60523/94** (22) Application Date : **18.04.94**

(30) Priority Data

(31) Number	(32) Date	(33) Country
5-99593	**26.04.93**	**JP JAPAN**

(43) Publication Date : **27.10.94**

(44) Publication Date of Accepted Application : **08.01.98**

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(56) Prior Art Documents
US 2512192
DE 1767425

(57)

Gelatin capsules, a widely used dosage form of solid preparations, can adhere to the throat and esophagus upon intake and disintegrate there, causing premature release of ingredient chemicals and hence ulcerations [Clin. Pharmac. 18,250 (1984); Clin. Pharmacol. Ther., Jan., 72 (1985); British Medical Journal, 1, 1673 (1979)]. No attempts have been made to solve this problem.

The present inventors investigated a solution to this problem, and found that gelatin capsule adhesion to the throat and esophagus upon intake is due to the high water solubility and hence high adhesion of gelatin, the major component of the capsules, and that the solution is to improve capsule swallowability through throat and esophagus by coating the gelatin capsule surface with a water repellent to such extent that the capsule's rapid disintegratability is not affected.

Accordingly, the present invention relates to a method of improving the swallowability of a gelatin capsule by use of a surface coating of a physiologically acceptable water repellent.

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1. A method for improving the swallowability of a gelatin capsule which comprises coating the surface of the gelatin capsule with a physiologically acceptable water repellent which has a water solubility of not higher than 0.3 g/l at 25°C, to provide a surface coating of said physiologically acceptable water repellent which is solid at room temperature and has a thickness of 0.1 to 100 μm.

3. A method of claim 1 or claim 2, wherein the water repellent is one or more members selected from the group consisting of ① an aliphatic saturated hydrocarbon having 15 to 55 carbon atoms, ② an oil or a fat having a melting point of 60 to 90°C, ③ a silicone having a viscosity of 95 to 1,050cs at 25°C, ④ a fatty acid, ⑤ an ester of fatty acid, ⑥ a polyhydric alcohol having a melting point of 4 to 65°C and ⑦ a film base polymer.

P/00/011
Regulation 3.2

AUSTRALIA

Patents Act 1990

ORIGINAL

COMPLETE SPECIFICATION

STANDARD PATENT

Invention Title: A METHOD OF IMPROVING THE SWALLOWABILITY OF GELATIN CAPSULES

The following statement is a full description of this invention, including the best method of performing it known to us:

GH&CO REF: P09027-LO:VNV:RK

The present invention relates to a method for improving the swallowability of a gelatin capsule.

Gelatin capsules, a widely used dosage form of solid preparations, can adhere to the throat and esophagus upon intake and disintegrate there, causing premature release of ingredient chemicals and hence ulcerations [Clin. Pharmac. 18,250 (1984); Clin. Pharmacol. Ther., Jan., 72 (1985); British Medical Journal, 1, 1673 (1979)]. No attempts have been made to solve this problem.

The present inventors investigated a solution to this problem, and found that gelatin capsule adhesion to the throat and esophagus upon intake is due to the high water solubility and hence high adhesion of gelatin, the major component of the capsules, and that the solution is to improve capsule swallowability through throat and esophagus by coating the gelatin capsule surface with a water repellent to such extent that the capsule's rapid disintegratability is not affected.

Accordingly, the present invention relates to a method of improving the swallowability of a gelatin capsule by use of a surface coating of a physiologically acceptable water repellent.

In the present invention, the physiologically acceptable water repellent is defined as having a water solubility not higher than 0.03 g/l at 25°C. Such water repellents include aliphatic saturated hydrocarbons having 15 to 55 carbon atoms, such as paraffin (liquid paraffin, solid paraffin) and microcrystalline wax, oils and fats having a melting point of 60 to 90°C, such as carnauba wax, hardened oils, bleached beeswax and white wax, silicones having a viscosity of 95 to 1,050 cs, at 25°C such as silicone oil and silicone resin, fatty acids such as stearic acid, esters of fatty acid such as sucrose ester of fatty acid, glycerol ester of fatty acid and polyglycerol ester of fatty acid, polyhydric alcohols having a melting point of 4 to 65°C, such as stearyl alcohol and cetanol, and film base polymers such as

shellac and ethyl cellulose. Paraffin, carnauba wax, white wax, silicone, stearic acid, stearyl alcohol and shellac are preferred.

The gelatine capsule coating can be achieved by first thermally fusing a physiologically acceptable water repellent (hereinafter also referred to as a coating agent) or dissolving it in an organic solvent to prepare a coating solution, then applying the coating solution to the gelatin capsules by a conventional method using a coater. Thermal fusion of the water repellent is achieved by heating it to a temperature exceeding its melting point. The organic solvent used to dissolve the water repellent is exemplified by normal hexane, methylene chloride and alcohols. Although the water repellent is not subject to limitation as to concentration, it is preferable to use it at 5% by weight to saturation concentration, with preference given to concentrations near saturation concentration. Too low concentrations are undesirable for practical use because drying takes longer. Although any conventional coater can be used, the HICORTER (Freund Industrial Co., Ltd.), the ACCELA COATER (Manesty), the DRIACOATER (Powrex Corporation), the sugar coating pan (Kikusui Seisakusho), the VG Coater (Kikusui Seisakusho) etc. are preferable.

The coating solution is typically used in amounts equivalent to coating agent ratios of 0.1 to 10.0% by weight, preferably 0.5 to 1.5% by weight per capsule base. The thickness of the coating agent layer formed on the gelatin capsule surface is 0.1 to 100 μm, preferably 1 to 50 μm. Too thick a coating agent layer is undesirable because capsule disintegration is delayed. Too thin an agent layer hampers the desired effect of the present invention.

In addition to the above-described water repellent, the coating solution may incorporate coating aids (e.g., polyethylene glycol, glycerol, polysorbate 80), taste correctives (e.g., sucrose, lactose, mannitol, maltitol, sorbitol, xylitol, aspartame, stevia, saccharin), odor

correctives (e.g., menthol, peppermint oil, lemon oil, banana oil) and coloring agents (e.g. tar-based food dyes, aluminium lake, iron oxide red, titanium oxide). These coating aids are added to the coating solution in a proportion ranging from 0.1 to 10 weight %.

The thus-obtained gelatin capsules of the present invention are orally used as packed with pharmaceutical powder, granules, semi-solids, liquids etc., as with conventional gelatin capsules.

According to the present invention gelatin capsule swallowability is improved by preventing capsule adhesion to the throat and esophagus upon intake.

[Examples]

The present invention is hereinafter described in more detail by means of the following examples, in which capsule swallowability and disintegratability were evaluated:

1) Swallowability (sensory evaluation)

Each capsule was ingested without water and throat adhesion and residual sensation were evaluated by 5 panelists.

1: Swallowing easy, without adhesion
2: Slight residual sensation, though passage is easy, without adhesion
3: Slight adhesion and residual sensation
4: Swallowing difficult due to adhesion and residual sensation

2) Disintegratability (JP XII)

Time from ingredient granule release start to release completion upon capsule disintegration was determined using a disintegration tester (in water at 37°C, disc used).

Example 1

500 g of granule-packed No. 1 capsules (about 1,119 cp, 447 mg/cp, empty capsules consisting of 85% by weight gelatin and 15% by weight water) were placed in a sugar-coating pan (12 inches), and various coating solutions were added while the pan was rotated at 40 rpm to coat the capsules, followed by drying at 40°C, to yield samples.

Comparative sample		
Packed hard capsules	447.00 mg	
(empty capsules	77.00 mg)	
Inventive sample 1		
Packed hard capsules	447.00 mg	
(empty capsules	77.00 mg)	
Coating Solution Composition	Weight	Ratio to Empty Capsules
Shellac	0.46 mg	0.60 W/W%
Castor oil	0.12 mg	0.16 W/W%
Carnauba wax	0.52 mg	0.68 W/W%
(99% ethanol	4.2 µl)	
(n-hexane	3.1 µl)	
Total		1.44 W/W%

Table 1

	Swallowability	Disintegratability
Inventive sample 1	1	1.5 to 3.3 minutes
Comparative sample	4	2.0 to 3.5 minutes

The inventive sample showed no disintegratability change or adhesion or residual sensation upon intake, demonstrating improved swallowability, while the comparative sample showed adhesion and residual sensation.

Example 2

500 g of granule-packed No. 1 capsules (about 1,119 cp, 447 mg/cp, empty capsules consisting of 85% by weight gelatin and 15% by weight water) were placed in a High Coater (HCT-20), and various coating solutions were sprayed while the coater was rotated at 20 rpm to coat the capsules, followed by drying at 40°C, to yield samples.

Inventive sample 2

Packed hard capsules	447.00 mg	
(empty capsules	77.00 mg)	
Coating Solution Composition	Weight	Ratio to Empty Capsules
Carnauba wax	0.38 mg	0.49 W/W%
White wax	0.04 mg	0.05 W/W%
(n-hexane	8.4 µl)	
Total		0.54 W/W%

Table 2

	Swallowability	Disintegratability
Inventive sample 2	2	2.0 to 3.5 minutes
Comparative sample	4	2.0 to 3.5 minutes

The inventive sample showed a swallowability improving tendency.

Example 3

500 g of granule-packed No. 2 capsules (about 2,000 cp, 255 mg/cp, empty capsules consisting of 85% by weight gelatin and 15% by weight water) were placed in a High Coater (HCT-20), and various coating solutions were added while the coater was rotated at 20 rpm to coat the capsules, followed by drying at 40°C, to yield samples.

Inventive sample 3		
Packed hard capsules	255.00 mg	
(empty capsules	65.00 mg)	
Coating Solution Composition	Weight	Ratio to Empty Capsules
Silicone oil (KS66)	1.79 mg	2.75 W/W%

Table 3

	Swallowability	Disintegratability
Inventive sample 3	2	2.2 to 3.2 minutes
Comparative sample	4	2.0 to 3.5 minutes

The inventive sample showed a swallowability improving tendency.

Example 4

500 g of granule-packed No. 1 capsules (about 1,119 cp, 447 mg/cp, empty capsules consisting of 85% by weight gelatin and 15% by weight water) were placed in a Doria Coater (DC2500), and various coating solutions were sprayed while the coater was rotated at 40 rpm to coat the capsules, followed by drying at 40°C, to yield samples.

Inventive sample 4		
Packed hard capsules	447.00 mg	
(empty capsules	77.00 mg)	
Coating Solution Composition	Weight	Ratio to Empty Capsules
Carnauba wax	0.20 mg	0.26 W/W%
White wax	0.03 mg	0.04 W/W%

Silicone oil (KS66)	4.47 mg	5.81 W/W%
(n-hexane	4.4 µl)	
Total		6.11 W/W%

Inventive sample 5

Packed hard capsules	447.00 mg	
(empty capsules	77.00 mg)	
Coating Solution Composition	Weight	Ratio to Empty Capsules
Carnauba wax	0.20 mg	0.26 W/W%
White wax	0.03 mg	0.04 W/W%
Silicone oil (KS66)	0.89 mg	1.15 W/W%
(n-hexane	4.4 µl)	
Total		1.45 W/W%

Inventive sample 6

Packed hard capsules	447.00 mg	
(empty capsules	77.00 mg)	
Coating Solution Composition	Weight	Ratio to Empty Capsules
Carnauba wax	0.40 mg	0.52 W/W%
White wax	0.06 mg	0.08 W/W%
Silicone oil (KS66)	1.79 mg	2.32 W/W%
(n-hexane	8.8 µl)	
Total		2.92 W/W%

Table 4

	Swallowability	Disintegratability
Inventive sample 4	2	—
Inventive sample 5	2	—
Inventive sample 6	2	1.8 to 3.0 minutes
Comparative sample	4	2.0 to 3.5 minutes

The inventive samples showed a swallowability improving tendency, while the comparative sample showed adhesion and residual sensation after intake.

Example 5

500 g of empty No. 1 capsules (about 6,500 cp, empty capsules consisting of 85% by weight gelatin and 15% by weight water) were placed in a VG Coater, and various coating solutions were sprayed under reduced pressure (about 100 mmHg), followed by drying at 40°C, to yield samples.

Inventive sample 7

Empty hard capsules	77.00 mg	
Coating Solution Composition	Weight	Ratio to Empty Capsules
Solid paraffin	0.89 mg	1.16 W/W%
(n-hexane	89.0 µl)	

Table 5

	Swallowability	Disintegratability
Inventive sample 7	1	1.5 to 3.6 minutes
Comparative sample	5	2.0 to 3.5 minutes

The inventive sample showed an improved swallowability without loss of disintegratability.

Example 6

500 g of granule-packed No. 1 capsules (about 1,119 cp, 447 mg/cp, empty capsules consisting of 85% by weight gelatin and 15% by weight water) were placed in a sugar-coating pan, and various coating solutions were added while the pan was rotated at 40 rpm to coat the capsules, followed by drying at 40°C, to yield samples.

Inventive sample 8		
Packed hard capsules	447.00 mg	
(empty capsules	77.00 mg)	
Coating Solution Composition	Weight	Ratio to Empty Capsules
Carnauba wax	0.20 mg	0.26 W/W%
White wax	0.03 mg	0.04 W/W%
Solid paraffin	0.45 mg	0.58 W/W%
(n-hexane	49.4 µl)	
Total		0.88 W/W%
Inventive sample 9		
Packed hard capsules	447.00 mg	
(empty capsules	77.00 mg)	
Coating Solution Composition	Weight	Ratio to Empty Capsules
Carnauba wax	0.20 mg	0.26 W/W%
White wax	0.03 mg	0.04 W/W%
Solid paraffin	0.89 mg	1.16 W/W%
(n-hexane	93.4 µl)	
Total		1.46 W/W%

Table 6

	Swallowability	Disintegratability
Inventive sample 8	1	—
Inventive sample 9	1	1.5 to 2.8 minutes
Comparative sample	4	2.0 to 3.5 minutes

The inventive samples showed an improved swallowability without loss of disintegratability.

All the above inventive samples showed an improved swallowability; inventive samples 7, 8 and 9, in particular, showed excellent swallowability.

A storage test gave good results, in which capsules showed no mutual adhesion in 4-week storage at 60°C.

Example 7

500 g of granule-packed No. 1 capsules (about 1,119 cp, 447 mg/cp, empty capsules consisting of 85% by weight gelatin and 15% by weight water) were placed in a High Coater (HCT-20), and various coating solutions were sprayed while the coater was rotated at 20 rpm to coat the capsules, followed by drying at 40°C, to yield samples.

Inventive sample 2

Packed hard capsules	447.00 mg	
(empty capsules	77.00 mg)	
Coating Solution Composition	Weight	Ratio to Empty Capsules
Carnauba wax	0.42 mg	0.54 W/W%
(n-hexane	8.4 µl)	
Total		0.54 W/W%

Table 7

	Swallowability	Disintegratability
Inventive sample 9	2	2.0 to 4.0 minutes
Comparative sample	4	2.0 to 3 5 minutes

The inventive sample showed a swallowability improving tendency.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method for improving the swallowability of a gelatin capsule which comprises coating the surface of the gelatin capsule with a physiologically acceptable water repellent which has a water solubility of not higher than 0.3 g/l at 25°C, to provide a surface coating of said physiologically acceptable water repellent which is solid at room temperature and has a thickness of 0.1 to 100 μm.

2. A method of claim 1, wherein said physiologically acceptable water repellent is used at 0.1 to 10% by weight of the capsule base.

3. A method of claim 1 or claim 2, wherein the water repellent is one or more members selected from the group consisting of ① an aliphatic saturated hydrocarbon having 15 to 55 carbon atoms, ② an oil or a fat having a melting point of 60 to 90°C, ③ a silicone having a viscosity of 95 to 1,050cs at 25°C, ④ a fatty acid, ⑤ an ester of fatty acid, ⑥ a polyhydric alcohol having a melting point of 4 to 65°C and ⑦ a film base polymer.

4. A method of claim 1 or claim 2, wherein the water repellent is one or more members selected from the group consisting of paraffin, carnauba wax, silicone, stearic acid, stearyl alcohol, white wax and shellac.

5. A method of claim 1 or claim 2, wherein the water repellent is one or more members selected from the group consisting of solid paraffin, carnauba wax, silicone oil, white wax and shellac.

6. A method according to claim 1 substantially as herein described in conjunction with any one of Examples 1 to 7.

Dated this 10th day of September 1997

TAKEDA CHEMICAL INDUSTRIES, LTD.
By their Patent Attorney
GRIFFITH HACK

Abstract of the Disclosure

A method for improving the swallowability of a gelatin capsule which comprises coating the surface of the gelatin capsule with a physiologically acceptable water repellent which has a water solubility of not higher than 0.3 g/l at 25°C, to provide a surface coating of said physiologically acceptable water repellent having a thickenss of 0.1 to 100 μm.