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(54) Title: COMPOSITION FOR SOLID PHARMACEUTICAL PREPARATIONS CONTAINING VITAMIN D3 DERIVATIVE AND PROCESS FOR PREPARATION THEREOF

(57) Abstract

A composition for solid pharmaceutical preparations containing a vitamin D3 derivative capable of permitting the derivative to be uniformly distributed in the composition while being stabilized. The composition contains an excipient consisting of mannitol and sugar, a degradative agent consisting of hydroxypropyl cellulose, and a binder consisting of polyvinyl pyrrolidone and hydroxypropylmethyl cellulose.
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TITLE OF THE INVENTION

COMPOSITION FOR SOLID PHARMACEUTICAL
PREPARATIONS CONTAINING VITAMIN D₃ DERIVATIVE
AND PROCESS FOR PREPARATION THEREOF

BACKGROUND OF THE INVENTION

This invention relates to a composition for solid pharmaceutical preparations containing a vitamin D₃ derivative and a process for the preparation thereof, and more particularly to a composition for solid pharmaceutical preparations containing a vitamin D₃ derivative in which mannitol and sugar are used as an excipient.


As will be noted from the above, vitamin D₃ derivatives
are labile to heat and light and apt to be readily oxidized, so that a suitable means such as refrigeration, light shielding, replacement with inert gas or the like is employed to prevent deterioration of pharmaceutical preparations containing a vitamin D₃ derivative.

In particular, 26, 26, 26, 27, 27, 27-hexafluoro-1\(\alpha\), 25-dihydroxycholecalciferol (Kobayashi et al, Chem. Pharm. Bull, 30, 4297 (1982)) prepared by replacing each of six hydrogen atoms at positions 26 and 27 of 1\(\alpha\), 25-dihydroxycholecalciferol with a fluorine atom has a extremely high vitamin D-like activity and is merely contained in a very small amount in solid pharmaceutical preparations. Thus, it is highly required to develop techniques of dispersing a trace unstable component in solid pharmaceutical preparations and stabilize the unstable component in the preparations in order to prevent deterioration of the preparations.

Accordingly, it is highly desirable to provide solid pharmaceutical preparations in which a vitamin D₃ derivative is stabilized and the content of a vitamin D₃ derivative is rendered uniform.

SUMMARY OF THE INVENTION

The present invention has been made in view of the foregoing disadvantage of the prior art.

The inventors have made a careful study, for the purpose of providing a composition for solid pharmaceutical preparations which is capable of permitting a vitamin D₃ derivative to be stabilized during the manufacture and storage and the particle size distribution and content of the vitamin D₃.
derivative to be rendered uniform and constant, on stability of
the vitamin D₃ derivative when it is mixed with additives
(excipient, degradative agent, binder and lubricant) applicable
to the preparation of solid pharmaceutical preparations. As a
result, it has been found that the use of lactose, corn starch
or crystalline cellulose as an excipient for the composition
causes a vitamin D₃ to be highly decomposed, whereas the use of
D-mannitol or white sugar as the excipient exhibits an effect of
stabilizing the derivative.

Also, it has been found that the use of carboxymethyl
cellulose as the degradative agent results in the vitamin D₃
derivative to be highly decomposed, whereas hydroxypropyl
cellulose contributes to stabilizing of the derivative.

Thus, the present invention has been made while taking
notice of the fact that solid pharmaceutical preparations
obtained using mannitol and/or white sugar as a base prevents
decomposition of the vitamin D₃ derivative.

Accordingly, it is an object of the present invention
to provide a composition for solid pharmaceutical preparations
containing a vitamin D₃ derivative which is capable of
permitting the vitamin D₃ derivative to be significantly
stabilized and the content of the derivative in the preparations
to be rendered uniform.

It is another object of the present invention to
provide a method of granulating a composition for solid
pharmaceutical preparations containing a vitamin D₃ derivative
which is capable of permitting the vitamin D₃ derivative to be
significantly stabilized and the content of the derivative in the preparations to be rendered uniform.

In accordance with one aspect of the present invention, a composition for solid pharmaceutical preparations containing a vitamin D₃ derivative is provided. The composition comprises an excipient comprising mannitol and/or sugar; a degradative agent comprising hydroxypropyl cellulose; and/or a binder comprising polyvinyl pyrrolidone and/or hydroxypropylmethyl cellulose.

In accordance with another aspect of the present invention, a method of granulating the above-described composition. The method uses a solvent for dissolving mannitol or sugar, hydroxypropylmethyl cellulose or polyvinyl pyrrolidone, and a vitamin D₃ derivative.

DETAILED DESCRIPTION OF THE INVENTION

25-hydroxy-28-trifluoroalciferol; 25-hydroxy-26, 27-
hexafluoroepicalciferol; 1\(\alpha\), 25-dihydroxy-24-
difluorohomocholecalciferol; 1\(\alpha\), 25-dihydroxycholecalciferol-
26, 23-lactone; 1\(\alpha\), 25-dihydroxy-22-oxacholecalciferol; 1\(\alpha\) -
hydroxy-22-oxacholecalciferol; and ergocalciferols corresponding
to the above.

Mannitol and/or sugar used as the excipient in the
composition of the present invention are loaded in an amount of
from 0.1% to 99.9% by weight and preferably from 65% to 95% by
weight in the composition. Hydroxypropyl cellulose of a low
degree of substitution used as the degradative agent is loaded
in an amount of from 0.1% to 99.9% by weight and preferably from
5% to 30% by weight.

Polyvinyl pyrrolidone and/or hydroxypropylmethyl
cellulose used as the binder is loaded in an amount of from 0.1%
to 99.9% by weight and preferably from 1% to 30% by weight.

The composition for solid pharmaceutical preparations
of the present invention is obtained in the form of granules.
It may be prepared into pharmaceutical preparations in the form
of powders, granules, pellets, capsules or tablets as it is or,
if necessary, while being mixed with at least one of any
suitable additives known in the art. The additives include an
excipient, a degradative agent, a binder, a lubricant, an anti-
oxidant, a coating agent, a coloring agent, a corrigent, a
surface active agent and the like.

The excipient includes, for example, lactose,
crystalline cellulose, calcium hydrogenphosphate, starch, light
silica, titanium oxide, magnesium metasilicate aluminate, polyethylene glycol and the like.

The degradative agent includes, for example, carboxymethyl cellulose, calcium carboxymethylcellulose, sodium carboxymethylcellulose, croscarmellose sodium, Type A (Ac-Di-Sol®), starch, crystalline cellulose, hydroxypropyl starch, starch partially modified into α-starch and the like.

The binder includes, for example, hydroxypropyl cellulose, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan and the like.

The lubricant includes, for example, stearic acid, magnesium stearate, calcium stearate, talc, hardened oil, fatty saccharide and the like.

The anti-oxidant includes, for example, dibutyl hydroxytoluene (BHT), gallic propyl, butylhydroxy anisole (BHA) α-tocopherol, citric acid and the like.

The coating agent includes, for example, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose phthalate, polyvinylacetel diethylaminoacetate, aminoalkyl methacrylate copolymer, hydroxypropylmethylcellulose acetate succinate, methacrylic acid coplymer, cellulose acetate trimellitate (CAT), polyvinyl acetate phthalate, and the like.

The coloring agent includes, for example, a tar pigment, titanium oxide and the like.

The corrigent includes, for example, citric acid, adipic acid, ascorbic acid, menthol and the like.
The surface active agent includes, for example, glycerin monostearate, polysorbates, sodium lauryl sulfate, lauromacrogol, fatty saccharide, and the like.

The composition for solid pharmaceutical preparations according to the present invention may be generally prepared according to a conventional wet granulation process.

A solvent used is preferably lower alcohol such as ethanol, isopropanol or the like from a viewpoint of safety in operation. Also, the granulation is preferably carried out using a solvent which is capable of dissolving all the components of the composition such as mannitol, sugar, hydroxypropyl cellulose, polyvinyl pyrrolidone and hydroxypropylmethyl cellulose, as well as a vitamin D₃ derivative, to thereby the composition with uniformity. In particular, it is essential to use a solvent which is capable of dissolving mannitol or sugar and a vitamin D₃ derivative, because a relatively large amount of excipient such as mannitol, sugar or the like is contained in the composition.

In view of the fact that mannitol and sugar are readily soluble in water but is slightly soluble in lower alcohol, the inventors have made a study on a wet granulation process using a mixed solvent of water and lower alcohol. As a result, it has been found that wet granulation of the composition using lower alcohol containing 20% or more water and preferably from 20% to 50% water permits the vitamin D₃ derivative to be uniformly distributed in the composition.

More particularly, the wet granulation is carried out
in such a manner that mannitol and hydroxypropyl cellulose having a low degree of substitution are fully mixed together and a solution prepared by dissolving cellulose in lower alcohol containing from 20% to 50% purified water is used as a binder, to thereby provide a composition of the present invention and then the composition is dried.

As can be seen from the foregoing, the composition for solid pharmaceutical preparations of the present invention permits the vitamin D₃ derivative to be significantly stabilized. Also, the method of the present invention provides a composition for solid pharmaceutical preparations in which a vitamin D₃ derivative is uniformly contained, to thereby ensure the quality of the composition.

The present invention will be further described hereinafter with reference to the following examples and test examples.

Example 1

11.888kg of mannitol and 2.25kg of hydroxypropyl cellulose of a low degree of substitution were fully mixed and pulverized to prepare a mixture, which was dried while spraying, by means of a vacuum granulation apparatus, a solution obtained by dissolving 375g of hydroxypropynethyl cellulose and 18.75g of BHT in 7.125kg of 80% ethanol onto the mixture under reduced pressure. Subsequently, the mixture was dried while spraying a solution prepared by dissolving 15mg of ST-630 in 3.375kg of ethanol onto the mixture under reduced pressure. Then, the mixture was dried while spraying a solution prepared by
dissolving 375g of polyvinyl pyrrolidone (hereinafter referred to as "PVP") K30 and 18.75g of BHT in 3.375kg of ethanol onto the mixture under reduced pressure, resulting in a composition for solid pharmaceutical preparations being obtained.

Thereafter, 0.5 part of calcium stearate was added to 99.5 parts of the composition thus obtained and then tablet preparation was carried out to obtain tablets having a diameter of 6mm, a thickness of 3mm and a weight of 100mg and containing about 0.1μg of ST-630.

Example 2

11.888kg of mannitol and 2.25kg of hydroxypropyl cellulose of a low degree of substitution were fully mixed together and pulverized to prepare a mixture, which was dried while spraying, by means of a vacuum granulation apparatus, a solution obtained by dissolving 375g of hydroxypropylmethyl cellulose and 18.75g of BHT in 3.375kg of 80% ethanol onto the mixture under reduced pressure. Subsequently, the mixture was dried while spraying a solution prepared by dissolving 15mg of ST-630 in 3.375kg of ethanol onto the mixture under reduced pressure. Then, the mixture was further dried while spraying a solution prepared by dissolving 375g of hydroxypropylmethyl cellulose and 18.75g of BHT in 7.125kg of 80% ethanol onto the mixture under reduced pressure, resulting in a composition for solid pharmaceutical preparations being obtained.

Thereafter, 0.5 part of calcium stearate was added to 99.5 parts of the composition thus obtained and then tablet preparation was carried out to obtain tablets having a diameter
of 6mm, a thickness of 3mm and a weight of 100mg and containing about 0.1μg of ST-630.

Example 3

11.888kg of mannitol and 2.25kg of hydroxypropyl cellulose of a low degree of substitution were fully mixed together and pulverized to prepare a mixture, which was dried while spraying, by means of a vacuum granulation apparatus, a solution obtained by dissolving 0.375kg of PVP-K30 and 18.75g of BHT in 3.375kg of ethanol onto the mixture under reduced pressure. Subsequently, the mixture was dried while spraying a solution prepared by dissolving 15mg of ST-630 in 3.375kg of ethanol onto the mixture under reduced pressure. Then, the mixture was further dried while spraying a solution prepared by dissolving 375g of PVPP-K30 and 18.75g of BHT in 3.375kg of ethanol onto the mixture under reduced pressure, resulting in a composition for solid pharmaceutical preparations being obtained.

Thereafter, 0.5 part of calcium stearate was added to 99.5 parts of the composition thus obtained and then tablet preparation was carried out to obtain tablets having a diameter of 6mm, a thickness of 3mm and a weight of 100mg and containing about 0.1μg of ST-630.

Example 4

79.3g of mannitol and 15g of hydroxypropyl cellulose of a low degree of substitution were fully mixed together and pulverized to prepare a mixture, to which a solution obtained by dissolving 2.5g of PVP-K30 and 0.125g of BHT in 10g of ethanol
was added, followed by kneading and drying. Then, an ethanol solution containing 0.001g of ST-630 was added to the mixture, which was then kneaded and dried. Subsequently, a solution obtained by dissolving 2.5g PVP-K30 and 0.125g of BHT in 10g of ethanol to the mixture, which was then kneaded and dried, resulting in a composition for solid pharmaceutical preparations containing about 10μg of ST-630 per 0.95g of the composition.

Example 5

793g of mannitol and 150g of hydroxypropyl cellulose of a low degree of substitution were fully mixed and pulverized to prepare a mixture, to which a solution obtained by dissolving 0.01g of ST-630, 50g of PVP-K30 and 2.5g of BHT in 450g of 80% ethanol was added, followed by granulation by means of a stirring granulation apparatus, resulting in a composition for solid pharmaceutical preparations. Then, the composition was dried on a fluidized bed and then pulverized. Thereafter, 5.0g of calcium stearate was added to the composition, which was then subject to tablet preparation, to thereby prepare tablets having a diameter of 6mm, a thickness of 3mm and a weight of 100mg and containing about 0.1μg of ST-630.

Example 6

793g of mannitol and 150g of hydroxypropyl cellulose of a low degree of substitution were fully mixed together and pulverized to prepare a mixture, to which a solution obtained by dissolving 0.001g of ST-630, 50g of PVP-K30 and 2.5g of BHT in 450g of 80% ethanol was added, followed by granulation. Then, the mixture was dried on a fluidized bed and pulverized.
Thereafter, 5.0g of calcium stearate was added to the mixture, which was then subject to tablet preparation, resulting in tablets which have a diameter of 6mm, a thickness of 3mm and a weight of 100mg and contains about 0.1µg of ST-630 being obtained.

Example 7

80g of mannitol and 15g of hydroxypropyl cellulose of a low degree of substitution were fully mixed together and pulverized to prepare a mixture. Then, a solution obtained by dissolving 0.001g of ST-630 and 5g of hydroxypropyl cellulose in 30g of 80% ethanol was added as a binder to the mixture, which was then kneaded in a mortar and dried, so that a composition containing 1µg of ST-630 per 100mg was obtained.

Example 8

80g of mannitol and 15g of hydroxypropyl cellulose of a low degree of substitution were fully mixed together and pulverized to prepare a mixture. Then, a solution obtained by dissolving 0.001g of ST-630 and 5g of PVP-K30 in 45g of 50% ethanol was added as a binder to the mixture, which was then kneaded in a mortar and dried, resulting in a composition which contains 1µg of ST-630 per 100mg being obtained.

Example 9

80g of mannitol and 15g of hydroxypropyl cellulose of a low degree of substitution were fully mixed together and pulverized to prepare a mixture. Then, a solution obtained by dissolving 5g of PVP-K30 in 25g of purified water was added as a binder to the mixture, which was then kneaded and dried.
Thereafter, 10ml ethanol solution containing 1mg of ST-630 was added to the mixture, which was fully mixed and dried, resulting in a composition which contains 1µg of ST-630 per 100mg being obtained.

Example 10

80g of mannitol and 15g of hydroxypropyl cellulose of a low degree of substitution were fully mixed together and pulverized to prepare a mixture. Then, a solution obtained by dissolving 5g of hydroxypropylmethyl cellulose in 45g of purified water was added as a binder to the mixture, which was then kneaded and dried. Thereafter, 10ml ethanol solution containing 1mg of ST-630 was added to the mixture, which was fully mixed and dried, resulting in a composition which contains 1µg of ST-630 per 100mg being obtained.

Example 11

80g of mannitol and 15g of hydroxypropyl cellulose of a low degree of substitution were fully mixed together and pulverized to prepare a mixture. Then, a solution obtained by dissolving 1mg of ST-630, 5g of PVP-K30 and 0.25g of BHT in 45g of 80% ethanol was added to the mixture, which was then kneaded in a mortar and dried, resulting in a composition which contains 1µg of ST-630 per 100mg being obtained.

Example 12

76.25g of mannitol and 14g of hydroxypropyl cellulose of a low degree of substitution were fully mixed together and pulverized to prepare a mixture. Then, a solution obtained by dissolving 5g of PVP-K30 and 0.25g of BHT in 30g of ethanol was
added to the mixture, which was then kneaded and dried. Thereafter, 10ml ethanol solution containing 1mg of ST-630 was added to the mixture, which was fully mixed and dried, resulting in a composition which contains about 10μg of ST-630 per 0.955g being obtained.

Test Example 1 (Test on uniformity of content)

(Specimen)

Specimen No. 1: 1μg tablet prepared in Example 5
Specimen No. 2: 0.1μg tablet prepared in Example 6

(Test Procedure)

Specimen No. 1:

To one tablet of specimen No. 1 was accurately added an internal standard solution (1) in a volume of 1ml, which was then subject to an ultrasonic treatment for 30 minutes, followed by a centrifugal treatment (3000rpm) for 10 minutes to obtain a supernatant. Then, the supernatant was passed through a membrane filter to obtain a sample solution (n=10). 50ml sample solution was subject to determination described hereinafter, so that a peak area of ST-630 relative to a peak area of the internal standard substance was obtained to calculate an average deviation in n=10.

Specimen No. 2:

To one tablet of specimen No. 2 was accurately added 0.5ml water, which was then subject to an ultrasonic treatment for 10 minutes. Then, an internal standard solution (2) was added in a volume of 0.5ml thereto, which was then subject to an ultrasonic treatment for 20 minutes and a centrifugal treatment.
(3000 rpm) for 10 minutes to obtain a supernatant. Then, the supernatant was passed through a membrane filter to obtain a sample solution (n=10). 50ml sample solution was subject to liquid chromatography as described hereinafter, so that a peak area of ST-630 relative to a peak area of the internal standard substance was obtained to calculate an average deviation in n=10.

Internal standard solution (1): Estradiol benzoate
4μg/ml

Internal standard solution (2): Estradiol benzoate
0.5μg/ml

Operating Conditions
Detector: Ultraviolet absorptiometer (wavelength for measurement: 265nm)
Column: Stainless tube of 4mm in inner diameter and 15mm in length (SK-GEL, ODS-80TM)
Temperature: 50°C
Mobile phase: methanol : water (77:23)

(Result)
Results were as indicated in Table 1.
Table 1 (Test on uniformity of content)

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Maximum Deviation: 2.2% for Specimen No. 1, 6.4% for Specimen No. 2

Test Example 2 (Test on change with time)

(Specimen)

Specimen No. 1: Lactose (Japanese Pharmacopoeia)
Specimen No. 2: Corn starch (Japanese Pharmacopoeia)
Specimen No. 3: Crystalline cellulose (Japanese Pharmacopoeia)
Specimen No. 4: D-mannitol (Japanese Pharmacopoeia)
Specimen No. 5: White sugar (Japanese Pharmacopoeia)
Specimen No. 6: Anhydrous lactose (Japanese Pharmacopoeia)
Specimen No. 7: Calcium carboxymethylcellulose (Japanese Pharmacopoeia)
Specimen No. 8: Hydroxypropylmethylcellulose of low
degree of substitution (Japanese Pharmacopoeia)

(Preparation of sample)
5ml ethanol solution containing ST-63 in a concentration of 100μg/ml was added to 50g of each of the specimens and mixed therewith in a mortar to prepare a mixture. Then, the mixture was dried at 70°C and passed through a 50-mesh screen, resulting in obtaining a sample.

(Test procedure)
5g of each of the samples obtained as described above was sealedly placed in a 4K glass bottle and stored at a temperature of 40°C.

(Determination procedure)
Each of the samples was precisely weighed in an amount of 1g and 4ml internal standard solution (1) was accurately added to the weighed sample, which was then subject to an ultrasonic treatment for 30 minutes, vibration for 10 minutes and a centrifugal treatment (3000 rpm) for 10 minutes in order, to thereby obtain a supernatant. Then, the supernatant was passed through a membrane filter, resulting in a sample solution.

About 20mg of ST-630 was precisely weighed and methanol was added to the weighed ST-630, resulting in a solution of 20ml in total volume. The solution was accurately sampled in a volume of 5ml and the internal standard solution (2) was accurately added in a volume of 2ml to the sampled solution. Then, the mobile phase was accurately added thereto until the
-18-
total volume accurately reaches 20ml, resulting in a standard solution (1) for Specimen No. 1.

50μl of each of the sample solutions and standard solutions was subject to liquid chromatography to obtain peak areas \( Q_t \) and \( Q_s \) of ST-630 relative to a peak area of the internal standard substance.

Internal standard solution (1): Estradiol benzoate
10μg/ml

Internal standard solution (2): Estradiol benzoate
100μg/ml

Then, the content of T-630 in 1g of the sample was calculated according to the following expression:

Amount of ST-630 (μg) contained in 1g of sample

= \( 10(\mu g) \times \text{amount of standard ST-630 (mg)} \)

\( \times \frac{Q_t}{Q_s} \times 50/\text{the amount of sample (mg)} \)

(Result)

The results were as indicated in Table 2.
### Table 2

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<td>99.2</td>
<td>-</td>
<td>100.0</td>
<td>91.2</td>
</tr>
</tbody>
</table>

**Test Example 3 (Test on change with time)**

(Specimen)

Specimen No. 1: 0.1μg tablet prepared in Example 1
Specimen No. 2: 0.1μg tablet prepared in Example 2
Specimen No. 3: 0.1μg tablet prepared in Example 3
Specimen No. 4: Composition prepared in Example 4
Specimen No. 5: 1μg tablet prepared in Example 5
Specimen No. 6: 0.1μg tablet prepared in Example 6
Specimen No. 7: Composition prepared in Example 11
Specimen No. 8: Composition prepared in Example 12

Reference specimen: Composition obtained by adding an ethanol solution containing ST-630 in concentration of 100μg/ml to 50g of lactose, followed by drying in a mortar.

(Test procedure)
50 pieces of each of the specimens in the form of a tablet and 5g of each of the specimens in the form of a composition each were sealedly placed in a 4K glass bottle and stored at a temperature of 40°C.

(Determination procedure)

Liquid specimen No. 1: 10 tablets of Specimen No. 1 were sampled and an internal standard solution (1) was accurately added thereto.

Liquid specimen No. 2: 10 tablets of Specimen No. 2 were sampled and the internal standard solution (1) was accurately added in a volume of 2ml thereto.

Liquid specimen No. 3: 10 tablets of Specimen No. 3 were sampled and the internal standard solution (1) was accurately added in a volume of 2ml thereto.

Liquid specimen No. 4: 1g of Specimen No. 4 was sampled and an internal standard solution (2) was accurately added in a volume of 4ml thereto.

Liquid specimen No. 5: 10 tablets of Specimen No. 5 were sampled and the internal standard solution (2) was
accurately added in a volume of 4ml thereto.

Liquid specimen No. 6: 10 tablets of Specimen No. 6 were sampled and the internal standard solution (1) was accurately added in a volume of 2ml thereto.

Liquid specimen No. 7: 1g of Specimen No. 7 was sampled and the internal standard solution (2) was accurately added in a volume of 4ml thereto.

Liquid specimen No. 8: 1g of Specimen No. 8 was sampled and the internal standard solution (2) was accurately added in a volume of 4ml thereto.

Reference liquid specimen: 1g of the reference specimen was precisely weighed and the internal standard solution (2) was accurately added in a volume of 4ml thereto.

Each of the liquid specimens prepared as described above was subject to an ultrasonic treatment for 30 minutes, vibration for 10 minutes and a centrifugal treatment for 10 minutes in order, to thereby obtain a supernatant. Then, the
supernatant was passed through a membrane filter, resulting in a sample solution being obtained.

Also, about 20mg of ST-630 was precisely weighed and methanol was added thereto, resulting in the total volume being accurately 20ml. The so-prepared solution was accurately sampled in a volume of 1ml and a mobile phase was added thereto, resulting in a solution of accurately 100ml in total volume. Then, the solution was accurately sampled in a volume of 5ml and an internal standard solution (2) was accurately added in a volume of 2ml thereto and further the mobile phase was added thereto to cause the total volume to be accurately 20ml. This resulted in a standard solution (1) for each of Specimens No. 1, No. 2, No. 3 and No. 6.

Further, the standard solution (1) was accurately sampled in a volume of 4ml and the mobile phase was added thereto, to thereby cause the total volume to be accurately 20ml. This resulted in a standard solution (2) for each of Specimens No. 1, No. 2, No. 3 and No. 6.

Internal standard solution (1): Estradiol benzoate
2μg/ml

Internal standard solution (2): Estradiol benzoate
10μg/ml

Internal standard solution (3): Estradiol benzoate
100μg/ml

50μl of each of the sample solutions and standard solution was subject to liquid chromatography to obtain peak areas \( Q_t \) and \( Q_s \) of ST-630 relative to a peak area of the
internal standard substance.

Then, the content of ST-630 in 1g of the specimen was calculated according to each of the following expressions:

**Expression**

For each of Specimens No. 4, No. 5, No. 7 and No. 8 and Reference specimen:

Amount of ST-630 (μg) contained in 1g of specimen

= 10(μg) x amount of standanrd ST-630 (mg)

x \( Q_t/Q_s \) x 50/the amount of sample (mg)

For each of Specimens No. 1, No. 2, No. 3 and No. 6:

Amount of ST-630 (μg) contained in 1g of specimen

= 1(μg) x amount of standanrd ST-630 (mg)

x \( Q_t/Q_s \) x 50/the amount of sample (mg)

**Operating Conditions**

Detector: Ultraviolet absorptiometer (wavelength for measurement: 265nm)

Column: Stainless tube of 4mm in inner diameter and 15mm in length (SK-GEL, ODS-80TM)

Column temperature: 50°C

Mobile phase: methanol : water (77:23)

(Result)

The results were as indicated in Table 3.
<table>
<thead>
<tr>
<th>Specimen</th>
<th>After 1 month</th>
<th>After 2 months</th>
<th>After 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>100.5</td>
<td>99.1</td>
</tr>
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<td>2</td>
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<tr>
<td>8</td>
<td>98.4</td>
<td>98.8</td>
<td>98.0</td>
</tr>
</tbody>
</table>
What is Claimed is:

1. A composition for solid pharmaceutical preparations containing a vitamin D₃ derivative, comprising:
   an excipient comprising mannitol and/or sugar;
   a degradative agent comprising hydroxypropyl cellulose;
   and/or
   a binder comprising polyvinyl pyrrolidone and/or hydroxypropylmethyl cellulose.

2. A method of granulating a composition for solid pharmaceutical preparations as defined in Claim 1, wherein a solvent is used for dissolving:
   mannitol or sugar;
   hydroxypropylmethyl cellulose or polyvinyl pyrrolidone;
   and
   a vitamin D₃ derivative.

3. A method as defined in Claim 2, wherein a lower aqueous alcoholic solution containing 20% or more water is used as said solvent.
INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/02843

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: A 61 K 31/59,9/14,9/20,47/26,47/32,47/38

II. FIELDS SEARCHED

Classification System Classification Symbols

IPC5 A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *

III. DOCUMENTS CONSIDERED TO BE RELEVANT *

Category * Citation of Document, ** with indication, where appropriate, of the relevant passages *** Relevant to Claim No. ****

A EP, A, 0116755 (TEIJIN)
29 August 1984
see claims; page 5, lines 21-24, 30-35; page 6, lines 5-10; page 10, lines 5-37 cited in the application

A EP, A, 0215596 (TEIJIN)
25 March 1987
see claims; page 2, lines 47-63; page 3, lines 1-4

P, X EP, A, 0387808 (SS PHARMACEUTICAL)
19 September 1990
see claims 1-4; page 2, lines 51-54; page 3, lines 25-38; page 4, examples 2, 5

P, A EP, A, 0413828 (TEIJIN)
27 February 1991
see claims; page 4, lines 38-55; page 5, lines 7-26

* Special categories of cited documents: 16
** "A" document defining the general state of the art which is not considered to be of particular relevance
*** "E" earlier document but published on or after the international filing date
**** "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
***** "O" document referring to an oral presentation, use, exhibition or other means
****** "P" document published prior to the international filing date but later than the priority date claimed

**** Relevant to Claim No.
1-3
1-3
1-3
1-3

IV. CERTIFICATION

Date of the Actual Completion of the International Search
9th July 1991

International Searching Authority
EUROPEAN PATENT OFFICE

Date of Mailing of this International Search Report 07.08.91

Signature of Authorized Officer miss T. MORTENSEN

Form PCT/ISA/210 (second sheet) (January 1985)