(51) International Patent Classification:
A61K 9/20 (2006.01)    A61K 31/785 (2006.01)

(21) International Application Number:
PCT/EP2010/059149

(22) International Filing Date:
28 June 2010 (28.06.2010)

(25) Filing Language:    English

(26) Publication Language:    English

(30) Priority Data:
200930368     26 June 2009 (26.06.2009)    ES
P 20100102272     25 June 2010 (25.06.2010)    AR


(72) Inventors; and
(75) Inventors/Applicants (for US only): LLORET PÉREZ, Sergio [ES/ES]; Fructuós Gelabert, 6-8, 5°, Sant Joan Despi, E-08970 Barcelona (ES); DÍAZ GUASCH, Laura [ES/ES]; Fructuós Gelabert, 6-8, 5°, Sant Joan Despi, E-08970 Barcelona (ES).

(74) Agent: ILLESCAS TABOADA, Manuel; Calle Recoletos nº 13 -5° Izq., E-28001 Madrid (ES).


Published:  without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: NOVEL PHARMACEUTICAL COMPOSITION COMPRISING POLY (ALLYLAMIN-CONH-DIALLYL-1,3-DI-AMINO-2-HYDROXYPROPA)

(57) Abstract: A solid, pharmaceutical composition for oral administration comprising from about 80% to about 94% by weight of sevelamer including the water of hydration and at least one pharmaceutically acceptable excipient.
The present invention relates to a solid pharmaceutical composition for oral administration comprising poly(allylamin-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane) or its pharmaceutically acceptable salt, in amount from about 80% to about 94% by weight including the water of hydration, and to process for the preparation and utilization thereof.

BACKGROUND OF THE INVENTION

Hyperphosphatemia plays a role in the development of secondary hyperparathyroidism in renal insufficiency. Treatment of hyperphosphatemia includes reduction in dietary intake of phosphate, inhibition of intestinal phosphate absorption with phosphate binders, and removal of phosphate with dialysis.

Poly(allylamine-co-N,N'-diallyl-1,3-diamino-2-hydroxypropane), commonly known as sevelamer (see formula below) is a non-absorbed binding crosslinked polymer. It contains multiple amines separated by one carbon from the polymer backbone. These amines exist in a protonated form in the intestine and interact with phosphate molecules through ionic and hydrogen bonding. By binding phosphate in the dietary tract and decreasing absorption, sevelamer lowers the phosphate concentration in the serum.

\[
\text{Sevelamer}
\]

\[
\text{H}_2\text{C} \equiv \text{CH}_2\text{NH}_2 \text{CO} \left[ \text{O} \right] \text{Cl} \]

Sevelamer
According to the United States Food & Drug Administration information, two salts of sevelamer are currently approved and commercialized—sevelamer hydrochloride and sevelamer carbonate. Sevelamer hydrochloride is currently marketed as a phosphate binder in the dosage and form of 400 mg and 800 mg film-coated tablets for oral administration, and marketed under the trade name Renagel®. Sevelamer carbonate is a phosphate binder in the dosage and form of 800 mg film-coated tablets and also of 0.8 g and 2.4 g packets of powder for preparation of oral suspension. The sevelamer carbonate products are marketed under the trade name Renvela®. Both products Renagel® and Renvela® are indicated for the control of serum phosphorus in patients with chronic kidney disease.

EP 1 239 837 B1 discloses a tablet, which composition comprises an aliphatic amine polymer in amount at least 95% by weight of the core, assuring minimum amount of excipients in the pharmaceutical composition to provide a tablet that is as small as possible and easy to administer. This reference also describes that for sevelamer the compressibility is strongly dependent upon the degree of hydration (moisture content), therefore the process of preparation of the pharmaceutical composition requires hydrating or drying sevelamer in order to achieve the required degree of hydration.

EP 1 304 104 B1 discloses a tablet which comprises a phosphate-binding polymer, together with crystal line cellulose and/or low substituted hydroxypropylcellulose, which ensures sufficient hardness and shows rapid dispersibility. This patent further indicates difficulties that can occur during development of the pharmaceutical composition comprising sevelamer, which are caused by the hygroscopic nature of the active ingredient and the high dose of the active principle in the tablet core.

Therefore there is still a need to provide an alternative pharmaceutical composition which is easy to manufacture, has an excellent product
characteristic like wide range of compressibility and rapid disintegration time, and is independent of the water content of sevelamer or its salt.

DESCRIPTION OF THE INVENTION

The invention provides an alternative pharmaceutical composition which is easy to manufacture, has a broad range of compressibility and rapid disintegration time, and is independent of the water content of sevelamer. The term sevelamer according to the present application includes all pharmaceutically acceptable salts, such as, for example, hydrochloride, carbonate, sulfate, nitrate or phosphate salt of sevelamer.

In one aspect, the invention provides a solid pharmaceutical composition for oral administration comprising from about 80% to about 94% by weight of sevelamer including the water of hydration, and at least one pharmaceutically acceptable excipient. This composition is useful for the therapeutic treatment of mammals, including humans. It was observed that the exact concentration of sevelamer in the pharmaceutical solid dosage form is crucial, and affects final properties of the pharmaceutical composition. Pharmaceutical compositions, with the concentration of sevelamer below 80%, demonstrated problems with uniformity of mass. In particular, it was observed that the problem with uniformity of mass in pharmaceutical composition occurred because of the hygroscopic nature of sevelamer. The particles of sevelamer were forming aggregates between each other, inhibiting therefore appropriate distribution of active ingredient in the blend with the excipient and thus in the final dosage form. It was surprising as normally, when the concentration of an active ingredient is low no interactions like aggregation between particles occur. Another observed inconvenience of a pharmaceutical composition with a sevelamer content of below 80%, was that as the single dose of sevelamer is 400mg or 800mg in dosage unit, thus a big tablet size was necessary. A big tablet size is very unsatisfactory for the patients, considering that the therapeutically effective dosages of sevelamer are 4g to 6g per day. On the
other hand it was observed that the pharmaceutical composition, with the concentration of sevelamer above 94%, demonstrated problems during manufacturing process, because of low content of excipients. Pharmaceutical blends with pharmaceutically acceptable excipients content in the range of about 0% to 6% could not assure the flexible, proper and robust process, what had negative influence on pharmaceutical composition properties and also on pharmaceutical equipment. It was also observed that the compositions with very low concentration of pharmaceutical excipients and the concentration of sevelamer above 94%, demonstrated problems with long disintegration time, what could affect the therapeutic response and activity of sevelamer.

The inventors have surprisingly found that exact content of about 80% to about 94% of sevelamer in pharmaceutical composition of the present invention provides excellent product’s characteristics. It was surprising that the exact content of about 80% to about 94% by weight of sevelamer in a pharmaceutical composition, solved problems related to aggregates formation, poor uniformity of mass, bad processing and slow disintegration time and thus therapeutic response time.

In order to formulate a pharmaceutical composition of the present invention, at least one pharmaceutically acceptable excipient needs to be added along with active ingredient. Excipients are inactive ingredients used to formulate active ingredients into finished dosage forms, which can for example aid in the processing of the drug delivery system during its manufacture. Excipients protect, support and/or enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attribute of the overall safety, effectiveness or delivery of the drug during storage or use. During the manufacturing process of a pharmaceutical product, adequate selection of pharmaceutically acceptable excipients provides improved blend properties, good flowability and therefore compressibility. The solid composition of the invention preferably includes a therapeutically acceptable
quantity of sevelamer (e.g. 400 mg and/or 800 mg and/or 2400 mg) and further includes one or more pharmaceutically acceptable excipients.

In a preferred embodiment, the solid pharmaceutical composition of the invention comprises from about 84% to about 90% by weight of sevelamer including the water of hydration, and one or more pharmaceutically acceptable excipient. The above mentioned advantages have shown to be achieved to a maximum in this range.

Preferably, at least one pharmaceutically acceptable excipient of the pharmaceutical composition of the present invention is a pharmaceutically acceptable starch. The applicants have found that the use of a pharmaceutically acceptable starch in the pharmaceutical composition of the invention stabilizes and facilitates the manufacturing process of said pharmaceutical composition. The use of the starch in the pharmaceutical composition of the present invention prevents segregation of ingredients in pharmaceutical blend, provides good flowability and compressibility of the blend. Particles of sevelamer deform under the effect of pressure in a die, and it is known for the one skilled in the art that elastic material, such as sevelamer, is less suitable for pharmaceutical process. It was observed that, when pharmaceutically acceptable starch is used to form a blend with sevelamer, the processed blend maintain its surface and conformational characteristics. This avoids that capping, lamination and/or friability problems occur during the tabletting process and facilitates therefore obtaining the pharmaceutical product with adequate hardness, and also permits easy, flexible, robust and cheap pharmaceutical manufacturing process. It was also observed, that the use of the pharmaceutically acceptable starch in the pharmaceutical composition of the present invention allows avoiding a static charge on the surface of the sevelamer. The absence of static charge on surface of the active ingredient in the present invention is important because of the following reasons: it assures uniformity of mass and good flowability, prevents segregation during blending process and even more, charged active
pharmaceutical ingredient may adhere to feed frame and result in serious
damage to tablet equipment.

Furthermore, it was surprisingly found that forming the blend, by combining sevelamer with a pharmaceutically acceptable starch avoids the need of controlling the water content in the active ingredient. It is already known, that the moisture content is very important for sevelamer solid pharmaceutical compositions. Moisture content has to be optimized and controlled, because of the following reasons: lack of moisture results into brittle tablet and affects flowability, which in turns affect uniformity of mass. High amount of moisture gives stickness, making compaction process unachievable. In case of active ingredients which are very hygroscopic like sevelamer, low moisture content excipients are of the first choice for a pharmaceutical formulation. That is why also the marketed products Renvela and Renagel warn in the information leaflet, that sevelamer products should be protected from moisture. Thus it was surprising that the combination of hygroscopic sevelamer with a pharmaceutically acceptable starch in the pharmaceutical composition of present invention solved all above mentioned problems relating to the moisture content, as the pharmaceutical acceptable starches are characterized by having high water content, up to about 20%. It has been found that this water can migrate from the starch molecule and can be adsorbed up to desired level and bounded by the hygroscopic sevelamer. This assures the appropriate content of water in sevelamer, avoiding therefore the need of additional drying or moistening the active ingredient and gives excellent properties of pharmaceutical blend, improves tabletting process, and guaranties excellent properties and stability of the final pharmaceutical product. It was also found that the use of pharmaceutically acceptable starch with sevelamer in the pharmaceutical composition assures faster disintegration time in comparison with the marketed products. Improved disintegration time makes the sevelamer solid composition more advantageous over existing products, as it concedes a faster therapeutic response, thus a more efficient acting.
Special attention should be given to the quantity of the pharmaceutically acceptable starch in the solid pharmaceutical composition comprising sevelamer. It was observed by the applicants that the quantity of around or below 6% by weight of pharmaceutically acceptable starch is too low to demonstrate the improvements of the present invention. It was observed that, the more quantity of starch is added to the pharmaceutical composition of the present invention, the more properties of advantages described above are present in the obtained pharmaceutical product.

In the preferred embodiment of the present invention, the pharmaceutical composition comprises from about 6% to about 20%, even more preferably from about 7% to about 18%, still preferred 8% to 15%, by weight of pharmaceutically acceptable starch.

In another embodiment of the present invention, the pharmaceutically acceptable starch preferably is a pregelatinized starch, corn starch, wheat starch, rice starch and/or potato starch. Even more preferably, the pharmaceutically acceptable starch of the pharmaceutical composition of the invention is pregelatinized starch. For the purpose of present invention the term "pregelatinized starch" is defined as a starch that has been chemically and/or mechanically processed to rupture all or part of the starch granules and so render the starch flowable and directly compressible. Typically, pregelatinized starch contains 5% of free amylase, 15% of free amylopectin and 80% unmodified starch. In the present invention the commercially available "Starch 1500®" has been used. Another commercially available trade marks according to "Handbook of Pharmaceutical Excipients" are the following:"Sepistab ST200", "Instastarch", "Lycatab PGS", "Lycatab C", "National 78-1 551 ®", "Pharma-Gel", "Prejel", "Merigel", "Spress B820", "Tablitz", "Unipure LD", "Unipure WG 220"

Furthermore, in a preferred embodiment of present invention the solid pharmaceutical composition comprises a pharmaceutical acceptable excipients selected from the following group: one or more binding agents, one or more disintegrants, one or more surfactants, one or more stabilizing agents,
one or more lubricants, one or more glidants (improving fluidity), and mixtures thereof. Preferably the composition of the invention further comprises colloidal silicon dioxide in concentration of about 0.1% to 2% as a glidant. Furthermore, as a lubricant the composition of the invention preferably comprises, sodium stearyl fumarate and/or stearic acid and/or it's salt like magnesium stearate, zinc stearate, calcium stearate, polyoxyethylene stearate in concentration of about 0.5% to 3%. Optionally, the pharmaceutical compositions of the present invention may further comprise a coating layer.

Preferably, the solid pharmaceutical composition of the invention is in the form of tablets, coated tablets, orodispersible tablet, pellets, pills, granules, capsules, or mini-tablets in capsules. Preferably, the solid pharmaceutical composition of the invention is in the form of tablets or coated tablets.

In another aspect, the present invention relates to a process for preparing the solid pharmaceutical compositions of the invention, said process comprising blending the sevelamer with the at least one pharmaceutically acceptable excipient. The solid pharmaceutical composition of the invention may be in any known solid dosage form such as, for example tablets, coated tablets, orodispersible tablet, pellets, pills, pellets, granules, sachets, capsules, mini-tablets in capsules, and the like. Preferably, the solid pharmaceutical composition of the invention is in the form of tablets or coated tablets. The applicants have found that the use of a pharmaceutically acceptable starch in the solid pharmaceutical composition of the invention is especially advantageous when producing tablets or coated tables. Precisely, the use of pharmaceutically acceptable starch facilitates the manufacturing process as it does not require a previous hydrating or drying step of the active ingredient, while providing a tablet with excellent hardness and fast disintegration time.

In preferred embodiment, the invention relates to a process for preparing the solid pharmaceutical composition of the invention in the form of tablets or coated tablets, said process comprising the steps of blending the sevelamer with the at least one pharmaceutically acceptable excipient, to obtain a blend, compressing the blend to obtain a tablet, and optionally coating the tablet to obtain a coated tablet. Preferably, the at least one pharmaceutically
acceptable excipient is starch. This provides the process and the composition with the above mentioned advantages. The pharmaceutical composition of the invention can be obtained by direct compression process, dry granulation process, wet granulation process, hot-melt granulation process or any other pharmaceutical process known in the art. Preferably, the process of the present invention is direct compression, which is easier to control, and saves time and energy. The term direct compression is used to define the process by which tablets are compressed directly from powder blend of the sevelamer and at least pharmaceutically acceptable excipient, which will flow uniformly into a die cavity and form into a firm compact. No pretreatment of the powder blends by wet or dry granulation procedures is necessary in direct compression process of the present invention.

Throughout the description and claims the word "comprise" and variations of the word, are not intended to exclude other technical features, additives, components, or steps. The term "about" preceding a value is meant to include non significant variations of the value given, preferably variations of not more than 5% of the given value, preferably the exact given value.

Additional objects, advantages and features of the invention will become apparent to those skilled in the art upon examination of the description. The following examples are provided by way of illustration, and they are not intended to be limiting of the present invention. Furthermore, the present invention covers all possible combinations of particular and preferred embodiments described herein.

EXAMPLE 1
Preparation of sevelamer hydrochloride tablets wherein the used sevelamer hydrochloride has a water content of 4.90%.

This example shows a tablet composition comprising from about 84% to about 90% by weight of sevelamer hydrochloride, and pharmaceutically acceptable excipients, wherein one of these excipients was pregelatinized starch, which
stabilized the pharmaceutical composition and facilitated its manufacturing process.

This example further shows a process for preparing a solid pharmaceutical in accordance with an embodiment of the invention.

The tablets were prepared using the materials listed in Table 1.

<table>
<thead>
<tr>
<th>Composition</th>
<th>[mg/tablet]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer hydrochloride</td>
<td>841.22</td>
</tr>
<tr>
<td>Pregelatinized starch</td>
<td>128.98</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>9.90</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>9.90</td>
</tr>
</tbody>
</table>

Tablets were manufactured using the following procedure comprising the following steps: i) blending sevelamer hydrochloride with pregelatinized starch and colloidal silicon dioxide, ii) the blend of step i) was lubricated with stearic acid, iii) the resultant mixture was compressed into sevelamer hydrochloride tablets of appropriate weight and hardness, iv) the tablet cores of step iii) could be optionally coated. Obtained tablets had 5min44sec of disintegration time and 293.6 N of hardness.

EXAMPLE 2
Preparation of sevelamer hydrochloride tablets wherein the used sevelamer hydrochloride has a water content of 6.90%.

This example shows a tablet composition comprising from about 84% to about 90% by weight of sevelamer hydrochloride, and pharmaceutically acceptable excipients, wherein one of these excipients was pregelatinized starch, which stabilized the pharmaceutical composition and facilitated its manufacturing process.

This example further shows a process for preparing a solid pharmaceutical in accordance with an embodiment of the invention.
The tablets were prepared using the materials listed in table 2.

Table 2

<table>
<thead>
<tr>
<th>Composition</th>
<th>[mg/tablet]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer hydrochloride</td>
<td>859.29</td>
</tr>
<tr>
<td>Pregelatinized starch</td>
<td>101.11</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>9.80</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>9.80</td>
</tr>
</tbody>
</table>

Tablets were manufactured using the following procedure comprising the following steps: i) blending sevelamer hydrochloride with pregelatinized starch and colloidal silicon dioxide, ii) the blend of step i) was lubricated with stearic acid, iii) the resultant mixture was compressed into sevelamer hydrochloride tablets of appropriate weight and hardness, iv) the tablet cores of step iii) could be optionally coated. Obtained tablets had 3min22sec of disintegration time and 239.4 N of hardness.

EXAMPLE 3
Preparation of sevelamer hydrochloride tablets wherein the used sevelamer hydrochloride has a water content of 7.43%

This example shows a tablet composition comprising from about 84% to about 90% by weight of sevelamer hydrochloride, and pharmaceutically acceptable excipients, wherein one of these excipients was pregelatinized starch, which stabilized the pharmaceutical composition and facilitated its manufacturing process.

This example further shows a process for preparing a solid pharmaceutical in accordance with an embodiment of the invention.

The tablets were prepared using the materials listed in table 3.
Table 3

<table>
<thead>
<tr>
<th>Composition</th>
<th>[mg/tablet]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer hydrochloride</td>
<td>864.21</td>
</tr>
<tr>
<td>Pregelatinized starch</td>
<td>105.99</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>9.90</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>9.90</td>
</tr>
</tbody>
</table>

Tablets were manufactured using the following procedure comprising the following steps: i) blending sevelamer hydrochloride with pregelatinized starch and colloidal silicon dioxide, ii) the blend of step i) was lubricated with stearic acid, iii) the resultant mixture was compressed into sevelamer hydrochloride tablets of appropriate weight and hardness, iv) tablet cores of step iii) could be optionally coated. Obtained tablets had 3minO9sec of disintegration time and 185.1 N of hardness.

EXAMPLE 4

Preparation of sevelamer hydrochloride tablets wherein the used sevelamer hydrochloride has a water content of 8.10%

This example shows a tablet composition comprising from about 84% to about 90% by weight of sevelamer hydrochloride, and pharmaceutically acceptable excipients, wherein one of these excipients was pregelatinized starch, which stabilized the pharmaceutical composition and facilitated its manufacturing process.

This example further shows a process for preparing a solid pharmaceutical in accordance with an embodiment of the invention.

The tablets were prepared using the materials listed in table 3.
Table 4

<table>
<thead>
<tr>
<th>Composition</th>
<th>[mg/tablet]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer hydrochloride</td>
<td>870.51</td>
</tr>
<tr>
<td>Pregelatinized starch</td>
<td>79.00</td>
</tr>
<tr>
<td>Dextrates</td>
<td>21.61</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>9.44</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>9.44</td>
</tr>
</tbody>
</table>

For the purpose of present invention the term "Dextrates" is defined as a purified mixture of saccharides resulting from the controlled enzymatic hydrolysis of starch. It is either anhydrous or hydrated. In addition to dextrose, dextrates contains 3-5% maltose and higher polysaccharides. In present invention the commercially available trade mark of dextrates Emdex®, has been used.

Tablets were manufactured using the following procedure comprising the following steps: i) blending sevelamer hydrochloride with pregelatinized starch, dextrates and colloidal silicon dioxide, ii) the blend of step i) was lubricated with stearic acid, iii) the resultant mixture was compressed into sevelamer hydrochloride tablets of appropriate weight and hardness, iv) the tablet cores of step iii) could be optionally coated. Obtained tablets had 1min47sec of disintegration time and 293 N of hardness.

EXAMPLE 5
Preparation of sevelamer carbonate tablets wherein the used sevelamer carbonate has a water content of 8.79%.

This example shows a tablet composition comprising from about 84% to about 90% by weight of sevelamer carbonate, and pharmaceutically acceptable excipients, wherein one of these excipients was pregelatinized starch, which stabilized the pharmaceutical composition and facilitated its manufacturing process.
This example further shows a process for preparing a solid pharmaceutical in accordance with an embodiment of the invention.

The tablets were prepared using the materials listed in table 5.

Table 5

<table>
<thead>
<tr>
<th>Composition</th>
<th>[mg/tablet]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer carbonate</td>
<td>877.097</td>
</tr>
<tr>
<td>Pregelatinized starch</td>
<td>83.303</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>9.800</td>
</tr>
<tr>
<td>Zinc stearate</td>
<td>9.800</td>
</tr>
</tbody>
</table>

Tablets were manufactured using the following procedure comprising the following steps: i) blending sevelamer carbonate with pregelatinized starch and colloidal silicon dioxide, ii) the blend of step i) was lubricated with zinc stearate, iii) the resultant mixture was compressed into sevelamer carbonate tablets of appropriate weight and hardness, iv) tablet cores of step iii) could be optionally coated. Obtained tablets had 11 sec of disintegration time and 98.3 N of hardness.

EXAMPLE 6

Preparation of sevelamer carbonate tablets wherein the used sevelamer carbonate has a water content of 9.75%.

This example shows a tablet composition comprising from about 84% to about 90% by weight of sevelamer carbonate, and pharmaceutically acceptable excipients, wherein one of these excipients was pregelatinized starch, which stabilized the pharmaceutical composition and facilitated its manufacturing process.

This example further shows a process for preparing a solid pharmaceutical in accordance with an embodiment of the invention.

The tablets were prepared using the materials listed in table 6.
Table 6

<table>
<thead>
<tr>
<th>Composition</th>
<th>[mg/tablet]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer carbonate</td>
<td>886.427</td>
</tr>
<tr>
<td>Pregelatinized starch</td>
<td>83.773</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>9.900</td>
</tr>
<tr>
<td>Zinc stearate</td>
<td>9.900</td>
</tr>
</tbody>
</table>

Tablets were manufactured using the following procedure comprising the following steps:  
i) blending sevelamer carbonate with pregelatinized starch and colloidal silicon dioxide,  
ii) the blend of step i) was lubricated with zinc stearate,  
iii) the resultant mixture was compressed into sevelamer carbonate tablets of appropriate weight and hardness,  
iv) tablet cores of step iii) could be optionally coated. Obtained tablets had 07 sec of disintegration time and 113.8 N of hardness.

**EXAMPLE 7**

Preparation of sevelamer carbonate tablets wherein the used sevelamer carbonate has a water content of 11.00%

This example shows a tablet composition comprising from about 84% to about 90% by weight of sevelamer carbonate, and pharmaceutically acceptable excipients, wherein one of these excipients was pregelatinized starch, which stabilized the pharmaceutical composition and facilitated its manufacturing process.

This example further shows a process for preparing a solid pharmaceutical in accordance with an embodiment of the invention.

The tablets were prepared using the materials listed in table 7.
Table 7

<table>
<thead>
<tr>
<th>Composition</th>
<th>[mg/tablet]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer carbonate</td>
<td>898.876</td>
</tr>
<tr>
<td>Pregelatinized starch</td>
<td>81.124</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>10.000</td>
</tr>
<tr>
<td>Zinc stearate</td>
<td>10.000</td>
</tr>
</tbody>
</table>

Tablets were manufactured using the following procedure comprising the following steps: i) blending sevelamer carbonate with pregelatinized starch and colloidal silicon dioxide, ii) the blend of step i) was lubricated with zinc stearate, iii) the resultant mixture was compressed into sevelamer carbonate tablets of appropriate weight and hardness, iv) tablet cores of step iii) could be optionally coated. Obtained tablets had 11sec of disintegration time and 108.1 N of hardness.

When carrying out the above examples it was shown that the water content of the active ingredient sevelamer didn’t have any negative influence on the processability of the composition. It was shown that - contrary to the prior art - tablets with excellent hardness and disintegration time were produced even when using sevelamer with a lower (for example 4%) or higher (for example 11%) water content. In addition, all formulations could be further processed by direct compression.
CLAIMS

1. A solid pharmaceutical composition for oral administration comprising from about 80% to about 94% by weight of sevelamer including the water of hydration, and at least one pharmaceutically acceptable excipient.

2. The solid pharmaceutical composition for oral administration of claim 1, wherein said solid pharmaceutical composition comprises from about 84% to about 90% by weight of sevelamer including the water of hydration, and at least one pharmaceutically acceptable excipient.

3. The solid pharmaceutical composition for oral administration of claims 1 or 2, wherein the at least one pharmaceutically acceptable excipient is a pharmaceutically acceptable starch.

4. The solid pharmaceutical composition for oral administration of claim 3, wherein said composition comprises from about 6% to about 20% by weight of pharmaceutically acceptable starch.

5. The solid pharmaceutical composition for oral administration of claims 3 or 4, wherein said composition comprises from about 7% to about 18%, preferably from about 8% to about 15% by weight of pharmaceutically acceptable starch.

6. The solid pharmaceutical composition for oral administration of any of claims 3 to 5, wherein the pharmaceutically acceptable starch is a pregelatinized starch, corn starch, wheat starch, rice starch and/or potato starch.

7. The solid pharmaceutical composition for oral administration of claim 6, wherein the pharmaceutically acceptable starch is a pregelatinized starch.

8. The solid pharmaceutical composition for oral administration of any of claims 1 to 7, wherein said solid pharmaceutical composition is in the form of tablets, coated tablets, orodispersible tablets, pills or mini-tablets in capsules.
9. The solid pharmaceutical composition for oral administration of any of claims 1 to 7, wherein said solid pharmaceutical composition is in the form of pellets, granules or capsules.

10. The solid pharmaceutical composition for oral administration of claim 8, wherein said solid pharmaceutical composition is in the form of tablets or coated tablets.

11. The solid pharmaceutical composition for oral administration of claims 1 to 10, wherein the sevelamer is sevelamer hydrochloride.

12. The solid pharmaceutical composition for oral administration of claims 1 to 10, wherein the sevelamer is a carbonate, sulphate, nitrate or phosphate salt of sevelamer.

13. A process for preparing the solid pharmaceutical composition for oral administration of any of claims 1 to 12, said process comprising blending the sevelamer with the at least one pharmaceutically acceptable excipient.

14. A process for preparing the solid pharmaceutical composition for oral administration of claim 13, said process comprising the steps of blending the sevelamer with the at least one pharmaceutically acceptable excipient to obtain a blend, compressing the blend to obtain a tablet, and optionally coating the tablet to obtain a coated tablet.

15. A process for preparing the solid pharmaceutical composition for oral administration of claims 13 or 14, wherein the sevelamer is sevelamer hydrochloride.

16. A process for preparing the solid pharmaceutical composition for oral administration of claims 13 or 14, wherein the sevelamer is a carbonate, sulphate, nitrate or phosphate salt of sevelamer.