Title: PACKAGING KIT FOR STATINS AND COMPOSITIONS THEREOF

Abstract: This invention relates to a packaging kit comprising a sealed oxygen impermeable container comprising a statin and at least one stabilizer selected from the group consisting of an oxygen absorber, a moisture absorber or a combination thereof. It further relates to a packaging kit for a solid pharmaceutical composition of a statin comprising the composition and at least one stabilizer selected from the group consisting of an oxygen absorber, a moisture absorber or a combination thereof in an oxygen impermeable container.
PACKAGING KIT FOR STATINS AND COMPOSITIONS THEREOF

Field of the Invention

This invention relates to a packaging kit comprising a sealed oxygen impermeable container comprising a statin and at least one stabilizer selected from the group consisting of an oxygen absorber, a moisture absorber or a combination thereof. It further relates to a packaging kit for a solid pharmaceutical composition of a statin comprising the statin composition and at least one stabilizer selected from the group consisting of an oxygen absorber, a moisture absorber or a combination thereof in an oxygen impermeable container.

Background of the Invention

Statins are currently among the most therapeutically effective drugs available for reducing the level of LDL in the blood stream of a patient at risk for cardiovascular disease. Statins are also known to raise HDL cholesterol levels and decrease total triglyceride levels. The mechanism of action of statins has been elucidated in some detail. It is believed that statins disrupt the biosynthesis of cholesterol and other sterols in the liver by competitively inhibiting the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase enzyme ("HMG-CoA reductase"). HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, which is the rate determining step in the biosynthesis of cholesterol. Consequently, its inhibition leads to a reduction in the rate of formation of cholesterol in the liver.

The main statins currently used in therapeutics are: pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin and rosuvastatin. Lovastatin, simvastatin and pravastatin are fully or partially fermentation based products, whereas fluvastatin, rosuvastatin and atorvastatin are entirely synthetic. Simvastatin is a chemically modified 2,2-dimethylbutyrate analogue of lovastatin. Pravastatin is a purified active metabolite of mevastatin with an open hydroxyacid instead of a lactone ring. All the statins are relatively unstable, and their degradation may be catalyzed by several parameters like oxygen, humidity, low pH and temperature.
These statins are known to occur in various crystalline as well as amorphous forms. However, amorphous forms may be susceptible to oxidation, heat, light, moisture and low pH, as compared to crystalline forms. Impurities generated upon degradation of active substances may reduce the therapeutic effects of an active substance and unnecessarily burden the body with degradation products. For example, oxidative degradation of atorvastatin may lead to impurities such as Atorvastatin diepoxide, dihydroxy epoxide or diketoeoxide.

There have been various attempts to stabilize various statins by using various packaging options.

International Patent Publication WO 2004/032920 describes storage of amorphous atorvastatin calcium solid dosage forms in an inert atmosphere and packaging the dosage form in a material that is not permeable to gases. In one example, tablets containing the drug were packaged in aluminum foil blisters, the blisters having an argon atmosphere.

There is still a need for providing a packaging system for a statins so as to enhance their stability. This can be provided by using an oxygen impermeable container along with one stabilizer such as oxygen or moisture absorber. This packaging system may not require controlling the atmospheric conditions during the time of packaging, which is a cumbersome process.

Summary of the Invention

In one general aspect, there is provided a packaging kit comprising a sealed oxygen impermeable container comprising a statin and at least one stabilizer selected from the group consisting of an oxygen absorber, a moisture absorber or a combination thereof.

In another general aspect, there is provided a packaging kit for a solid pharmaceutical composition of a statin comprising a sealed oxygen impermeable container comprising said composition and at least one stabilizer selected from the group consisting of an oxygen absorber, a moisture absorber or a combination thereof.
In another general aspect, there is provided a method of stabilizing a statin by packaging said statin in a sealed oxygen impermeable container along with at least one stabilizer selected from the group consisting of an oxygen absorber, a moisture absorber or a combination thereof.

In another general aspect, there is provided a method of stabilizing pharmaceutical composition comprising a statin by packaging said composition in a sealed oxygen impermeable container along with at least one stabilizer selected from the group consisting of an oxygen absorber, a moisture absorber or a combination thereof.

Description of the Invention

As used herein the term "statin" refers to any crystalline or amorphous form of pravastatin, simvastatin, rosuvastatin, lovastatin, fluvastatin, atorvastatin and cerivastatin. Pharmaceutically acceptable base addition salts of statins are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N, N-1-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine.

The term "oxygen impermeable" as used herein means a material having an oxygen permeability of less than 5 cm³/sqm.day.atm, more particularly 2 cm³/sqm.day.atm.

The container as used herein include air-tight drums or bottles made up of oxygen impermeable material such as glass or plastic such as polyvinyl chloride, polyethylene terphtalate, ethylene vinylalcohol. Multilayer containers containing polyvinyl chloride, polyethylene terphtalate, ethylene vinylalcohol may additionally comprise layers of oxygen permeable materials for example, polyethylene such as HDPE (high density polyethylene), LDPE (low density polyethylene), polypropylene or polystyrene, however the oxygen barrier properties should not be altered.

Glass container is tamper-proof, transparent, impermeable to gas and resistant to any interaction between containers and the content, and hence provides a total product
safety. Also, for products which are light sensitive amber glass may be used which further protects the product from harmful UV light.

Ethylene vinyl alcohol provides excellent oxygen impermeability, however, it is moisture sensitive, hence a multilayer container may be used wherein ethylene vinyl alcohol may be coextruded with polyethylene or polypropylene, wherein polyethylene or polypropylene help to overcome moisture sensitivity by acting as a barrier to moisture. Coextrusion with polyethylene provides additional advantage of providing transparent container. This coextruded layer comprising ethylene vinylalcohol sandwiched between two layers of HDPE having a total thickness of 1.3 mm was found to have oxygen permeability of 0.45 cm³/sqm.day.atm as measured according to ASTM F1307 (American Society for Testing and Materials). Coextruded layer with polyethylene terpthalate as disclosed US 6,521,159 may also be used.

The container may be sealed using heat induction seal wherein the sealing liner is additionally made up of oxygen impermeable film such as aluminum.

The term "oxygen absorbers" as used herein, means agents used to trap oxygen that is present in the overhead space of closed container. Concerning the chemical and physical mechanisms of active oxygen absorbers, they can be classified into the following categories:

• inorganic, metal based oxygen absorber

• ascorbic acid based absorber

• enzymatic absorber

• polymer based oxygen absorber

Inorganic, metal-based oxygen absorbers are inexpensive, available with different $O_2$-scavenging capacities in sachets and are commonly used in foods and beverages. The broadest range of iron-based products are offered by Mitsubishi Gas Chemicals Ageless™. Similar products are also offered by Multisorb under the trade name Fresh Pax™.
reaction is based on the well-known corrosion of iron. Another variant for oxygen absorbers is self-activated oxygen absorbers which involve combining moisture-retaining additives to metals such as iron. Another modification of metal absorbers is "stealth absorbers", which is also based on corrosion of iron but the metal is embedded in an extendable plastic. Ascorbic acid is a well-known preserving agent and may also be used as one of the options. There are also available enzymatic oxygen absorber which are based on glucose/glucose oxidase.

Polymer based scavengers are suitable for moisture protected applications.

Polymer-based compounds consist of high molecular weight, ethylenically-unsaturated hydrocarbons. An activation step often enables the user to start the oxygen scavenging when desired.

Commercially available sachets include D Series FreshPax™ (available from Multisorb Technologies Inc), Ageless™ Z (Ageless-Z is designated as Z-1000, Z-1000, etc., to indicate the milliliters of oxygen with which a single packet will react), StabilOx D (available from Multisorb Technologies Inc) and ZPT™ sachets (both available from Mitsubishi Gas Corporation), O-Buster™ (available from Hsiao Sung Non-Oxygen Chemical Co., Ltd), Bioka™ Oxygen Absorber (available from Bioka Ltd) and the like.

The moisture absorbers include activated carbon, silicas, zeolites, molecular sieves, hydrogels, calcium oxide and diatomaceous earth. The particular moisture-retaining materials used will depend upon the humidity level of the environment. For example, in a very low-humidity environment, a moisture-carrying material such as a hydrogel that partially binds water may be preferred. The moisture absorber can be supplied in the form of a sachet, cartridge or canister. A preferred form is a canister of silica gel, such as SorBit™ (commercially supplied by Sud-Chemie Corporation). Multisorb provides variety of moisture absorbers under trade name of Natrasorb M, Natrasorb S, Natrasorb C, and Hi-dry, which comprise diatomaceous earth, silica gel, calcium oxide and molecular sieve, respectively.

Further, there are certain commercially available packets or sachets which comprise a combination of oxygen absorber and moisture absorber such as Pharmakeep
oxygen- and moisture-absorbing packets (PharmaKeep KD or KC) (distributed jointly by Sud-Chemie and Mitsubishi Gas Chemical Company).

In addition, combination of oxygen absorber and moisture absorber can be used together in a packaging kit. Oxygen absorbers usually lead to an increase in moisture levels, hence a combination of moisture absorber and oxygen absorber will regulate moisture levels as well as oxygen levels.

The moisture/oxygen absorber may be in the form of packet, sachet, strips or canisters. The packet, sachet, strips or canisters may additionally comprise a moisture-indicating card.

In one of the embodiments, a packaging kit for a statin can be obtained by

i) putting the statin and oxygen absorber and/or a moisture absorber into a oxygen impermeable drum; and

ii) sealing the drum with heat induction seal.

In another embodiment, a packaging kit for a solid pharmaceutical composition comprising statin is obtained by:

i) putting the composition into impermeable bottle along with an oxygen absorber and/or a moisture absorber;

ii) sealing the bottle with heat induction seal.

The composition as used herein includes both immediate and extended release compositions. The statin may be present in the composition between 1% to about 50% by weight of the composition.

The solid pharmaceutical composition includes tablet, capsule, pills, dry powder, dragees or granulate.

The composition may further contain other pharmaceutically acceptable excipients, such as antioxidants, chelating agents, alkali metal salt additives, alkaline earth metal salt additives, binders, diluents, disintegrants, surfactants or lubricants.
Examples of suitable pharmaceutically acceptable antioxidants may include butylated hydroxyanisole (BHA), sodium ascorbate, butylated hydroxytoluene (BHT), sodium sulfite, propyl gallate, tocopherol, citric acid, malic acid, and ascorbic acid.

The chelating agents may be selected from amongst one or more of those suitable chelating agents known in the art. Examples of suitable chelating agents include disodium edetate (EDTA). The chelating agents can be present at a concentration of up to approximately 5% by weight of the composition.

Alkali metal salt additives may be, for example, one or more of sodium carbonate, sodium hydroxide, sodium silicate, disodium hydrogen orthophosphate, sodium aluminate or other suitable alkali metal salts. In particular, the stabilizing alkali metal salt additive may be, for example, sodium carbonate or disodium hydrogen orthophosphate, although the other alkali metal salt additives may also be selected. Alkaline earth metal salt additives can include one or more of calcium carbonate, calcium hydroxide, magnesium carbonate, magnesium hydroxide, magnesium silicate, magnesium aluminate, and aluminum magnesium hydroxide.

The binders may be, for example, one or more binders known in the art. Examples of suitable binders include starch, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, and carboxymethylcellulose.

The diluents may be, for example, one or more diluents known in the art. Examples of suitable diluents include lactose, mannitol, pregelatinized starch, microcrystalline cellulose, corn starch, sucrose, and silicic anhydride.

The disintegrant may be, for example, one or more disintegrants known in the art. Examples of disintegrants include croscarmellose sodium, crospovidone, sodium starch glycolate and starch.

The surfactants may be, for example, one or more surfactants known in the art. Examples of surfactants include polysorbate 80, polyoxyethylene sorbitan, polyoxyethylene-polyoxypropylene copolymer, and sodium lauryl sulphate.
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The lubricants may be, for example, one or more lubricants known in the art. Examples of lubricants include magnesium stearate, stearic acid, palmitic acid and talc.

The glidants may be, for example, one or more glidants known in the art. An example of a pharmaceutically acceptable glidant includes colloidal silicon dioxide.

The pharmaceutical composition may be prepared by a wet or dry granulation technique or by a direct compression technique.

The composition may be optionally coated with film forming polymers and/or coating additives. The coating may be, for example, one or more coating materials known in the art. For example, the coating material can be Opadry or Opadry AMB (aqueous moisture barrier).

EXAMPLES

Composition 1

A composition of amorphous statin may be prepared by formula and method given in the PCT application WO 03/068191 Example 2 as follows.

The amorphous atorvastatin was milled to reduce its mean particle size $d_{50}$ to approximately 20-50 $\mu$m and $d_{10}$ to approximately 80-100 $\mu$m. Butylated hydroxy anisole (0.12 mg/tablet) and butylated hydroxy toluene (0.12 mg/tablet) were dissolved in isopropyl alcohol and applied on to lactose under high shear mixing. The lactose was dried at 40-45°C in a fluidized bed dryer. Amorphous atorvastatin (80 mg/tablet), microcrystalline cellulose (300 mg/tablet) and lactose (628 mg/tablet) were mixed. Following the mixing, the dry binder, hydroxypropyl cellulose-L, (24 mg/tablet) and disintegrant, croscarmellose sodium, (72 mg/tablet) were added to the mixture. Following this addition, an alkali metal salt, sodium carbonate (52 mg/tablet), surfactant, sodium lauryl sulphate (2 mg/tablet), and colloidal silicon dioxide (24 mg/tablet) were added.

Next, the mixture was lubricated with magnesium stearate (12 mg/tablet) and compressed into tablets. The tablets then were coated with Opadry AMB. The values given above are per tablet and can be adjusted appropriately to provide the desired batch size.
Composition 2

Another representative composition may be prepared by the formula and method given below:

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Qty (in mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin calcium (amorphous) equivalent to Atorvastatin 80 mg</td>
<td>82.88</td>
</tr>
<tr>
<td>Mannitol</td>
<td>80.00</td>
</tr>
<tr>
<td>Pregelatinized starch</td>
<td>50.00</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>441.14</td>
</tr>
<tr>
<td>Sodium carbonate anhydrous</td>
<td>25.00</td>
</tr>
<tr>
<td>Butylated Hydroxy Anisole (BHA)</td>
<td>4.58</td>
</tr>
<tr>
<td>Butylated Hydroxy Toluene (BHT)</td>
<td>0.40</td>
</tr>
<tr>
<td>Hydroxypropyl cellulose – low viscosity</td>
<td>16.00</td>
</tr>
<tr>
<td>Colloidal silicon dioxide</td>
<td>16.00</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>48.00</td>
</tr>
<tr>
<td>Sodium lauryl sulphate</td>
<td>24.00</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>12.00</td>
</tr>
<tr>
<td>Isopropyl alcohol</td>
<td>q.s.</td>
</tr>
<tr>
<td>Tablet core weight</td>
<td>800.00</td>
</tr>
<tr>
<td>Opadry AMB</td>
<td>32.00</td>
</tr>
</tbody>
</table>

5 Procedure:

1. Butylated hydroxyanisole and butylated hydroxytoluene were dissolved in isopropyl alcohol.

2. About 3/4th quantity of microcrystalline cellulose, pregelatinized starch and colloidal silicon dioxide were passed through a screen and transferred to a rapid mixer granulator.

3. The solution of step 1 was added to the bulk of step 2 and mixed.

4. The wet mass was dried at 40° C - 45° C in a fluidized bed drier and passed through a sieve.

5. Sodium carbonate was milled and passed through a sieve.

6. The remaining 1/4th quantity of microcrystalline cellulose was passed through
7. Atorvastatin calcium, sodium lauryl sulphate and hydroxypropylcellulose were passed through the screen of a quadro comil.

8. Mannitol and croscarmellose sodium were passed together through a screen.

9. The blends of step 5-7 were added to the blend of step 8 and mixed together.

10. The blend of step 4 was added to the blend of step 9 and mixed together.

11. The blend of step 10 was lubricated with magnesium stearate and compressed into tablets.

12. The compressed tablets of step 11 were coated with a dispersion of Opadry AMB in water.

The following list of materials was used in examples:

Moisture absorber - Molecular sieve Trisorb sachet (SudChemie);

Oxygen absorber - StabilOx D-I00 (Multisorb);

Bottle - Multilayered bottle made up of ethylene vinyl alcohol in between two layer of polyethylene having a total thickness of 1.3 mm.

Example 1

Atorvastatin tablets of Composition 1 were packaged in following packaging options:

1. Tablets and moisture absorber were packaged into multilayered bottle.

2. Tablets and oxygen absorber were packaged into multilayered bottle.

3. Tablets, moisture absorber and oxygen absorber were packaged into impermeable multilayered bottle.
Example 2

Atorvastatin tablet composition 2 along with moisture absorber were packaged into impermeable multilayered bottle.

Bottled compositions of Example 1 (option 3) and Example 2 were subjected to stability studies at 40° C and 75% RH.

The stability studies indicate the atorvastatin tablets are stable under the given stability conditions when packaged as per the present invention.
WE CLAIM:

1. A packaging kit comprising a sealed oxygen impermeable container comprising a statin and at least one stabilizer selected from the group consisting of an oxygen absorber, a moisture absorber or a combination thereof.

2. A packaging kit for a solid pharmaceutical composition comprising a statin comprising a sealed oxygen impermeable container comprising said composition and at least one stabilizer selected from the group consisting of an oxygen absorber, a moisture absorber or a combination thereof.

3. The packaging kit according to claim 1 or 2 wherein the statin is selected from the group consisting of pravastatin, simvastatin, lovastatin, rosuvastatin, fluvastatin, atorvastatin and cerivastatin or pharmaceutically acceptable salts thereof.

4. The packaging kit according to claim 1 or 2 wherein the oxygen absorber is selected from the group consisting of inorganic oxygen absorber, ascorbic acid based absorber, enzymatic absorber, polymer based oxygen absorber, and mixtures thereof.

5. The packaging kit according to claim 1 or 2 wherein the moisture absorber is selected from the group consisting of activated carbon, silicas, zeolites, molecular sieves, hydrogels, calcium oxide, diatomaceous earth, and mixtures thereof.

6. The packaging kit according to claim 1 or 2 wherein the oxygen impermeable container is selected from a glass container or a plastic container.

7. The packaging kit according to claim 6 wherein the plastic container is made up of oxygen impermeable material selected from polyvinyl chloride, polyethylene terpthalate, ethylene vinylalcohol container, or mixtures thereof.

8. The packaging kit according to claim 6 wherein the oxygen impermeable container has an oxygen permeability of less than 5 cm$^3$/m$^2$.day.atm.

9. The packaging kit according to claim 6 wherein the plastic container is a multilayered container.
10. The packaging kit according to claim 9 wherein, in addition to oxygen impermeable material, the multilayered container further comprises layers of oxygen permeable material selected from polyethylene, polypropylene or polystyrene.

11. The packaging kit according to claim 10 wherein multilayered container comprises a layer of ethylene vinyl alcohol between two layers of high density polyethylene.

12. The packaging kit according to claim 1 or 2 wherein the oxygen impermeable container is sealed using heat induction.

13. The packaging kit according to claim 2 wherein the solid pharmaceutical composition is the form of tablets, capsules, pills, dry powder, dragees or granulates.