TITLE

INCREASED-DOSAGE NELFINAVIR TABLET AND METHOD OF MAKING SAME

FIELD OF THE INVENTION

The present invention is directed to a high-dosage form of nelfinavir tablets and a method of making such tablets. More particularly, the present invention is directed to nelfinavir tablets having a dosage significantly greater than presently available tablets to reduce the patient pill burden.

BACKGROUND OF THE INVENTION

It has been shown that individuals infected with HIV may be treated with HIV-protease inhibitors to prevent or inhibit the rapid proliferation of the virus in the patient. HIV-protease inhibitors block a key enzymatic pathway in the virus, substantially reducing viral loads, and slowing the steady decay of the immune system. Nelfinavir compounds, in particular, nelfinavir mesylate (Viracept®), have been shown to be effective protease inhibitors in the treatment of HIV-infected patients. Nelfinavir mesylate and methods of making nelfinavir are disclosed in U.S. Patent No. 5,484,926 to Dressman et al., the disclosure of which is incorporated by reference herein. Intermediates for making HIV-protease inhibitors, such as nelfinavir mesylate, are disclosed in U.S. Patent No. 5,705,647 to Babu et al., the disclosure of which is incorporated by reference herein.

Nelfinavir mesylate is presently available in tablets that provide a dosage equivalent to 250 mg of the nelfinavir free base. Therefore, as the twice-daily standard dosage is 1250 mg, a patient is required to take five tablets twice a day. As ten tablets a day is a significant pill burden for the patient, it would be advantageous to reduce this high pill burden, and promote compliance. Therefore, a need exists for a nelfinavir tablet providing a higher dosage of nelfinavir than the presently available 250 mg tablet.

SUMMARY OF THE INVENTION

The high-dosage nelfinavir tablet disclosed herein comprises a nelfinavir compound and a binder. The tablets disclosed can have a nelfinavir binder weight ratio of from about 3:1 to about 5:1. Preferably, the nelfinavir to binder weight ratio is greater than about 3.5 to 1 and less than about 5 to 1, and, more preferably, is 4 to 1. The nelfinavir compound is preferably present in an amount sufficient to provide a nelfinavir dosage equivalent to about 625 mg of nelfinavir free base. The nelfinavir compound is preferably nelfinavir mesylate, and the preferred binder is calcium silicate. Where the nelfinavir compound is nelfinavir mesylate, the compound is preferably present in an amount of about 730 mg per tablet. The tablet disclosed may further comprise at least one excipient, which is preferably selected from the group consisting of magnesium stearate, crospovidone, and colloidal silicon dioxide, and is preferably coated. Each tablet preferably comprises at least one of from about 15 to about 20 weight percent crospovidone, from about 0.1 to about 0.5 weight percent silicon dioxide, and from about 0.5 to about 1.5 weight percent magnesium stearate, based on total tablet weight. A preferred tablet comprises about 17.5 weight percent crospovidone, 0.25 weight percent, silicon dioxide and about 1 percent by weight magnesium stearate based on total tablet weight.

The coating is preferably hydroxypropyl methycellulose, which is preferably present in an amount of from about 1 to about 3 percent by weight of the tablet, more preferably in an amount of about 2 percent by weight of the tablet.

The method disclosed comprises forming a granulated mixture of a nelfinavir compound and a binder in a granulating process, and processing the granulated mixture to form a high-dosage nelfinavir tablet, where the granulating process comprises adding moisture and applying mechanical energy to the mixture, and curing the mixture in at least one curing step in which no moisture is added and no mechanical energy is applied to the mixture. Preferably, each curing step is for a cure time of at least about 1 minute, more preferably for a cure time of from about 1 minute to about 30 minutes, and even more preferably for a cure time of from about 10 minutes to about 15 minutes. The nelfinavir compound and the binder may be dry blended before granulating the mixture.

After granulating, the wet granulated mixture may be dried at a temperature of from about 60°C to up to 80°C, preferably to a moisture content of from about 4 to about 8 percent LOD (Loss On Drying). The dried granulate is then preferably milled, and may be blended with at least one excipient, such as, e.g., magnesium stearate, crospovidone, and colloidal

silicon dioxide. Preferably, the granulation mixture is milled with a round-hole screen having a hole size of from about 0.024 inch to about 0.045 inch.

Accordingly, an aspect of the present invention provides a tablet comprising a nelfinavir compound and a binder wherein the nelfinavir compound to binder weight ratio is 4 to 1, and wherein the nelfinavir compound is present in an amount sufficient to provide a nelfinavir dosage equivalent to 625 mg of nelfinavir free base.

Another aspect of the present invention provides a method for making a high dosage nelfinavir tablet, the high dosage nelfinavir tablet containing an amount of a nelfinavir compound equivalent to 625 mg of nelfinavir free base, the method comprising the steps of:

forming a granulated mixture of the nelfinavir compound and a binder in a granulating process; and

processing the granulated mixture to form a high-dosage nelfinavir tablet, wherein the granulating process comprises:

adding moisture and applying mechanical energy to the granulated mixture; and

curing the granulated mixture in at least one curing step in which no moisture is added and no mechanical energy is applied to the mixture.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a flow diagram of the process used in example 1; and

Fig. 2 is a flow diagram of the process used in example 2.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a high-dosage nelfinavir tablet and to a process of making such a tablet. As used herein, the term "nelfinavir compound" means nelfinavir free base (1,1-dimethylethyl) decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4-(phenyl-thio-buty)]-3-isoquinolinecarboxamide) or a pharmaceutically acceptable salt, such as nelfinavir mesylate (1,1-dimentylentyl) decahydro-2-[2-hydroxy-3-[(3-hydroxy-2-methylbenzoyl)amino]-4- (phenyl-thio-buty)]-3-isoquinolinecarboxamide mono-methane sulfone). The term "high-dosage" refers to nelfinavir tablets that provide a therapeutic dosage effectively greater than that provided in a 250 mg tablet. Generally, the dosage of nelfinavir compound in a tablet will be equivalent to about 531 mg to about 719 mg, and, preferably, from about 593 mg to about 656 mg of the nelfinavir free base. More preferably, the dosage of nelfinavir compound is equivalent to 625 mg of nelfinavir free base. That is, the tablets of the invention provide a nelfinavir compound in an amount sufficient to provide the same therapeutic effect as a 625 mg dose of nelfinavir free base. For example, for

nelfinavir mesylate, the preferred nelfinavir compound, the amount of drug required to provide the same therapeutic effect as a 625-mg dose of nelfinavir free base is about 730 mg. It should be noted that, unless otherwise stated, all weights given herein are for anhydrous material. Those of ordinary skill in the art will understand how to adjust the weight of each ingredient used in the tablet to account for any residual moisture or solvent that may be present.

Tablets of the invention comprise a nelfinavir compound ("the drug") and a binder in a drug/binder weight ratio of from about 3 to 1 to about 5 to 1. Preferably, the drug/binder weight ratio is between about 3.5 to 1 and about 5 to 1, more preferably in a range of from about 3.5 to 1 to about 4.5 to 1, and, even more preferably, is about 4 to 1. Preferably, the nelfinavir compound is nelfinavir mesylate, and the binder is calcium silicate ($CaSiO_3$). The

use of calcium silicate as a binder provides optimal dissolution and crystallinity in high-dosage nelfinavir tablets.

Lower-dosage (250 mg) forms of nelfinavir tablets that are commercially available having a drug/binder ratio of about 2 to 1. The higher drug/binder weight ratio of the tablets of the invention makes the absorption of water more difficult during processing. As a result, to obtain an adequate absorption of moisture into the drug-binder matrix, at least one curing step is required during granulation. During each curing step of the granulation process, no moisture is added, and no mechanical energy is applied for a period of time referred to herein as a "cure time". The at least one curing step during granulation is of a time adequate for absorption of the moisture required to allow the product of the granulation to be further processed into tablets. A cure time is not required in the presently available 250-mg nelfinavir tablets, as the larger proportion of binder in the 250-mg tablets allows absorption of moisture without curing. Thus, in contrast to the process of the present invention, the addition of water and the use of a mechanical energy source, e.g., a chopper and/or impeller, is continuous in the production of the 250 mg tablets.

In one embodiment, the high-dosage nelfinavir tablets of the invention are produced in the following process. The amounts of the nelfinavir compound and binder required for a given batch size and drug/binder weight ratio are first determined, accounting for any residual moisture and/or solvent. Preferably the nelfinavir compound and the binder are first screened to remove any lumps.

The nelfinavir compound and binder are then mixed and wet granulated. The drug and binder may be dry blended prior to granulation, or may be mixed in the granulation apparatus. Preferably, the granulation is performed in a high-shear granulator.

During granulation, water is added to the drug/binder mixture under the action of the granulator, e.g., by an impeller and/or a chopper. The granulation process also comprises at least one curing step to allow for the adequate absorption of water by the nelfinavir compound/binder mixture. During the curing step, no water or mechanical energy is added to the mixture, i.e., the addition of water and any impeller and/or chopper action is stopped. The time for a curing step, i.e., the cure time, is typically at least about 1 minute, preferably from about 1 to about 30 minutes, and more preferably from about 10 to 15 minutes. The granulation process may comprise 1or more cure steps. Preferably, the granulation process comprises from 1 to about 6 cure steps, and more preferably comprises from 1 to about 3 cure

steps. The granulation process may further comprise one or more wet massing steps in which mechanical energy is added without the addition of moisture.

Following granulation, the granulated drug/binder mixture is processed into tablets. Processing steps may include (but are not limited to) drying, screening, milling, blending with excipients, pressing, and coating. Useful excipients include (but are not limited to) crospovidone, colloidal silicon dioxide, and magnesium stearate.

EXAMPLES

The following non-limiting examples are illustrative of the preferred embodiments of the invention and are not to be construed as limiting the invention, the scope of which is defined by the appended claims.

Example 1

Batches of 117,490 tablets having a dosage equivalent to 625 mg of nelfinavir free base and a total weight of 140.6 kg were produced using the manufacturing process scheme shown in Fig.1. Each tablet contained, on average, 730.6 mg U.S. Spec. nelfinavir mesylate, 182.7 mg calcium silicate, 196.7 mg crospovidone, NF (Kollidon, CF), 2.8 mg colloidal silicon dioxide, NF, and 11.2 mg magnesium stearate, NF, for a total core weight of 1173 mg, on average. Each tablet was coated with 23.5 mg Oradry Clear YS-2-19114-A for a total average tablet weight of 1,196 mg. Any water used in the processing was essentially removed during the process, such that no more than about four percent residual moisture remained in a tablet.

After screening through a Quadro Comil having a round-edge impeller and a 0.032-inch round-hole screen, 21.47 kg of calcium silicate was added to 88.60 kg (equivalent to 85.85 kg anhydrous and solvent free) nelfinavir mesylate, which had been screened through a 20-mesh screen, in the granulation bowl of a Zanchetta Model Roto F900L granulator. The drug and binder were mixed for about 5 minutes with the impeller at high velocity setting and the chopper at low velocity setting. The impeller velocity was then changed to low for 1 minute.

The mixture of nelfinavir mesylate and calcium silicate was then granulated as follows. Over a period of 5 to 10 minutes, at a rate of 3 to 6 kg/minute, 30 kg of water was added to the mixture with an impeller velocity of high and a chopper velocity of low. The addition of water was then stopped, and the impeller velocity and chopper reduced to low for a period of 1 minute in a wet massing step. The impeller and chopper were then turned off,

and the wet mixture was allowed to cure for a curing time of 10 to 15 minutes. The impeller was then turned back to low, and an additional 6 kg of water was added over a period of 1 to 2 minutes. The chopper was then turned on, and an additional 3 kg of water was then added with both the impeller and chopper velocities set to low. The addition of water was again stopped, and a wet massing step was performed for 30 seconds with both the impeller and chopper velocities set at low. The impeller and chopper were turned off, and the wet mixture was cured for an additional curing time of 10 to 15 minutes. An additional 3.8 kg of water was added over a time of about 1 minute with the impeller and chopper velocities set at low. This was followed by a wet massing step of about 1 minute with the impeller and chopper velocities unchanged.

The granulated mixture was then dried at 60 ±5°C until the moisture content reached 4 to 8 percent LOD with a target of 6 percent LOD. The dried mixture was then milled with a Quadro Comil Model 196-S having a round-edge impeller, a 0.032-inch round-hole screen, and a 0.2-inch spacer.

Approximately half of the total dried and milled granulations was then placed into a type "V" blender, 30 cubic feet, using a vacuum loading, and 23.11 kg of Crospovidone, NF, (Kollidon CL) was added to the blender. The remaining granulation mixture was then added to the blender, and the combined materials were mixed for 30 minutes. A mixture of 1.32 kg magnesium stearate, NF, and 0.32 kg colloidal silicon dioxide, NF, was mixed, and passed through a 20-mesh stainless steel screen before being added to other ingredients in the blender, and mixed for 5 minutes to form a final blend.

The final blend was then compressed into white, oval-shaped, 0.750 x 0.425-inch (19.1 x 10.8 mm) tablet cores debossed on one side with a "V" and "625" on the others. The weight of the tablets ranged from 1.144 g to 1.202 g, with a target of 1.173 g. The thickness of the tablets ranged from 0.322 inch (8.18mm) to 0.342 inch (8.69mm), with a target of 0.332 inch (8.43mm), and the hardness ranged from 22 Kp to 34 Kp, with a target of 28 Kp. Friability was no more than 1.0 percent, and disintegration was no more than 15 minutes.

The tablet cores were then coated with 2.76 kg of Opadry Clear YS-2-19114-A in purified water on a Glatt PC 1500 60" coater and dried. The tablets were found to be bioequivalent to commercially available 250-mg nelfinavir tablets.

Example 2

Nefinavir mesylate tablets of the invention were produced using the manufacturing process scheme shown in Fig.2. Nelfinavir mesylate and calcium silicate were blended in a 500-liter bin-blender for 15 minutes to form a 60-kg blend of nelfinavir mesylate and calcium silicate having a drug/binder weight ratio of 4:1. A correction factor was applied to the nelfinavir mesylate to account for the presence of 3.1 percent volatiles. The height of the blended powder was monitored for changes to determine whether aeration was occurring, but no significant change was observed. The blended powder was discharged into polyethylene bag lined fiber drums, and showed a characteristic fluid-like flow.

Within a few minutes of discharge, a decrease in volume of greater than 10 percent was observed, and a reduction of almost 50 percent was observed following overnight storage. It is believed that the powder blend became aerated during discharge, causing an increase in volume. And, thus, as air in the blend slowly dissipated during storage, the volume decreased.

The powder blend was fed via a side stuffer into a twin-screw wet granulator (34-mm Leistriz Granulator). The components of a screw design of the type used are described below. The screw granulator comprised the following sections, in the direction of flow: a spacer, a first convey section, a first mixing section, a second convey section, a second mixing section, a third convey section, a chopper section, a spacer section, and a torpedo. Water for granulation was injected at the first convey section and the first mixing section. The granulation screw was run at 300 rpm and the side stuffer at 200 rpm. The powder blend had a feed rate of 7.8 kg/hour and water was injected at 47 ml/minute to provide a consistent wet output of at least 10 kg/hour.

The bulk density dry powder blend had a moisture content of 2.2 percent LOD, a bulk density of 0.15 g/ml, and a tapped density of 0.25 g/ml. The wet granulation had a moisture content of 27.88 percent LOD, a bulk density of 0.45 g/ml, and a tapped density of 0.75 g/ml.

During granulation, the drug/binder blend was cured twice, once as the blend passed through the second convey section and once as it passed through the third convey section.

The wet granulation was dried in two portions, A and B, in a fluid-bed dryer with a 60° C inlet temperature at 750 cfm (ft 3/m) to a moisture level of 4 to 8 percent LOD. The final moisture level of portion A was 4.81 percent LOD, and that of portion B was below the target level at 3.7 percent LOD. Although both dried portions were carried forward for processing, portion B was only used for compaction studies.

The dried granulations were passed through a Quadro Comil 197S equipped with a 0.032-in. screen and a 0.150-in. screen with a 2300 rpm impeller speed.

The milled granulation was blended with external excipients in a 250-liter bin blender, first with crospovidone for 15 minutes and then with a previously blended and delumped mixture of colloidal silicon dioxide and magnesium stearate for an additional 10 minutes. The amounts of crospovidone, silicon dioxide, and magnesium stearate used were, respectively, 16.44 percent, 0.23 percent, and 0.94 percent based on the total weight of the final tablet formulations.

The final blend was compressed in a 19-station Kikusui Virgo tablet press using 0.750 x 0.425 inch (19.1 x 10.8 mm) oval, deep concave punches. The press was run at the minimum press speed of 22 rpm and the paddle feeder at 55 rpm. Pre-compression was 0.90 tons (818 kg), and the main compression was 1.0 ton (909 kg).

Ten-kilogram batches of tablet cores were coated with Opadry clear film in an Accela Cota coating system using a 24-in. perforated pan to a theoretical weight gain of 2 percent. Pan speed was maintained at 10 rpm with a spray rate of between 20 and 40 ml/minute. As a result of a loss of moisture by the cores during coating, no weight gain was observed.

The dissolution profile of the 625-mg tablets obtained was compared with that of 250-mg commercial tablets. The 17.1-minute disintegration time of the 625-mg tablets is several-fold longer than the 1.75-minute time of the 250-mg tablets. However, within 15 minutes, the dissolution of the 625-mg tablets in simulated gastric fluid without pepsin was 68 percent compared to 78 percent for the 250-mg tablets, and within 45 minutes, the 88 percent dissolution of the 625-mg tablets compared to the 89 percent dissolution of the 250-mg tablets.

This invention is not limited by the embodiments disclosed herein. It is intended that the appended claims cover all such modifications and embodiments that fall within the true spirit and scope of the present invention.

CLAIMS:

1. A tablet comprising a nelfinavir compound and a binder wherein the nelfinavir compound to binder weight ratio is 4 to 1, and wherein the nelfinavir compound is present in an amount sufficient to provide a nelfinavir dosage equivalent to 625 mg of nelfinavir free base.

2. A tablet according to claim 1, wherein the nelfinavir compound is nelfinavir mesylate, and is present in an amount of 730 mg.

3. A tablet according to claim 1, further comprising at least one excipient.

4. A tablet according to claim 1, further comprising at least one of from 15 to 20 weight percent crospovidone, from 0.1 to 0.5 weight percent silicon dioxide, from 0.5 to 1.5 weight percent magnesium stearate, wherein said weight percent is based on total tablet weight, and a coating.

5. A method of making a high dosage nelfinavir tablet, the high dosage nelfinavir tablet containing an amount of a nelfinavir compound equivalent to 625 mg of nelfinavir free base, the method comprising the steps of:

forming a granulated mixture of the nelfinavir compound and a binder in a granulating process; and

processing the granulated mixture to form a high-dosage nelfinavir tablet,

wherein the granulating process comprises:

adding moisture and applying mechanical energy to the granulated mixture; and

curing the granulated mixture in at least one curing step in which no moisture is added and no mechanical energy is applied to the mixture.

6. The method of claim 5, wherein the at least one curing step is for a cure time of at least 1 minute.

7. The method of claim 5, wherein the at least one curing step is for a cure time of at least 1 minute to 30 minutes.

8. The method of claim 5, wherein the at least one curing step is for a cure time of at least 10 minutes to 15 minutes.

9. The method of claim 5, further comprising dry blending the nelfinavir compound and a binder before granulating the mixture.

10. The method of claim 5, wherein the weight ratio of nelfinavir compound to binder in the mixture is from 3:1 to 5:1.

11. The method of claim 10, wherein the weight ratio of nelfinavir compound to binder is more than 3.5:1.

12. The method of claim 10, wherein the weight ration of nelfinavir compound to binder is 4:1.

13. The method of claim 5, wherein the nelfinavir compound is nelfinavir mesylate.

14. The method of claim 5, wherein the binder is calcium silicate.

15. The method of claim 5, further comprising drying the granulated mixture at a temperature of from 60°C to up to 80°C.

16. The method of claim 5, further comprising milling the granulated mixture.

18. The method of claim 5, further comprising milling the granulated mixture with a round-hole screen having a hole size of from 0.610 mm (0.024 inch) to 1.143 mm (0.045 inch).

19. The method of claim 5, further comprising blending the granulated mixture with at least one excipient.

20. The method of claim 5, further comprising blending the granulated mixture with at least one excipient selected from the group consisting of magnesium stearate, crospovidone, and colloidal silicon dioxide.

21. The method of claim 5, wherein the granulated mixture comprises 730 mg of nelfinavir mesylate as the nelfinavir compound.