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(54) Title: FINE PARTICLES OF CILOSTAZOL AND PROCESSES FOR PRODUCTION THEREOF

(57) Abstract: The present invention relates to fine particles of cilostazol and processes for production thereof.

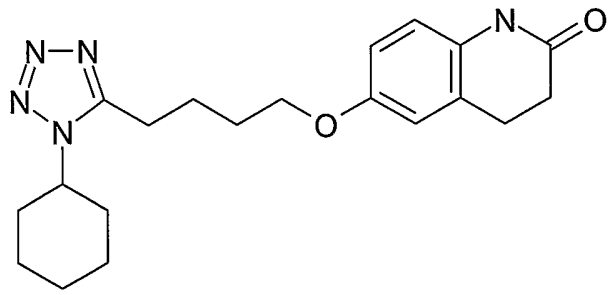
FINE PARTICLES OF CILOSTAZOL AND PROCESSES FOR PRODUCTION THEREOF

Field of the Invention

The present invention relates to fine particles of cilostazol and processes for their production.

Background of the Invention

Cilostazol (Formula I) is a quinolone derivative having cellular phosphodiesterase inhibitory activity. Particularly, cilostazol has an inhibitory activity on the cellular phosphodiesterase III enzyme. It is indicated for the reduction of symptoms of intermittent claudication (thrombosis). Cilostazol is poorly soluble in water which necessitates special formulation procedures for achieving a desired pharmacokinetic profile.



FORMULA I

U.S. Patent No. 4,277,429 discloses a process for the preparation of cilostazol in crystalline form, wherein 90% of particles have a diameter of 100 to 130 microns. This bulk powder is mixed with pharmaceutically acceptable excipients and the entire mass is passed through 200-mesh sieve (about 73 microns). The granules obtained were compressed to get tablet dosage form.

Japanese Patent Publication No. 07-291869 discloses that the bioavailability of cilostazol is remarkably increased by forming a phosphonic acid diester derivative into a fine powder (average particle diameter of not more than about 10 microns).

U.S. Patent No. 5,145,684 discloses particles of a crystalline drug substance having a surface modifier absorbed on the surface in an amount sufficient to maintain an effective

average particle size of less than about 400 nm. This arrangement is described as providing an increase in the bioavailability.

WO 96/21448 discloses a resin particle having a particle size of not greater than 2,000 microns. The resin particles include an ethylene vinyl alcohol copolymer and 5 to 10% by weight of cilostazol incorporated therein.

Japanese Patent Publication No. 10-67657 discloses a multiple-unit type sustained release preparation containing two sustained release small tablets prepared by incorporating hydroxypropylmethylcellulose as a sustained release material into cilostazol having an average particle diameter of about 20 micron.

WO 00/57881 discloses a cilostazol preparation that is described as having the function of dissolving cilostazol even at the lower portion of the digestive tract. The preparation incorporates a fine powder of cilostazol as an active ingredient into a dispersing and/or solubilizing agent. The average particle diameter of the fine powder of cilostazol is about 10 microns or less.

U.S. Patent Application No. 20030166937 discloses micronization of cilostazol using a pin mill or air jet mill to get a particle size wherein 90% of the particles have a diameter of about 60 microns or 15 microns.

Summary of the Invention

In one general aspect there is provided a process for the preparation of cilostazol. The process includes suspending cilostazol in an organic solvent; heating the mixture to get a clear solution; optionally filtering the clear solution; cooling the clear solution to crystallize cilostazol; and isolating cilostazol having a particle size wherein 90% of particles have a diameter of about 70 microns or less and 80% of particles have diameter of about 60 microns or less.

Embodiments of the present invention may include one or more of the following features. For example, the organic solvent may include an alkanol. Suitable alkanols include one or more of methanol, ethanol, n-propanol, isopropanol, n-butanol, tert-butanol or mixtures thereof.

The heating of the mixture may include heating to reflux. The cooling of the solution may include cooling to about 25°C and/or cooling under stirring. Isolating the cilostazol particles may include drying the cilostazol in a vacuum oven.

In another general aspect there is provided a process for the preparation of cilostazol. The process includes suspending cilostazol in an organic solvent; heating the mixture to get a clear solution; optionally filtering the clear solution; adding water at higher temperature to the clear solution; cooling the resultant mass to crystallize cilostazol; and isolating the cilostazol wherein 90% of particles have a diameter of about 45 microns or less and the average particle diameter is greater than 20 microns.

Embodiments of the present invention may include one or more of the following features. For example, the organic solvent may include an alkanol. Suitable alkanols include one or more of methanol, ethanol, n-propanol, isopropanol, n-butanol, tert-butanol or mixtures thereof.

The heating of the mixture may include heating to reflux. The cooling of the solution may include cooling to about 25°C and/or cooling under stirring. Isolating the cilostazol particles may include drying the cilostazol in a vacuum oven.

In another general aspect there is provided cilostazol particles, wherein 90% of particles have a diameter of about 70 microns or less and 80% of particles have a diameter of about 60 microns or less.

Embodiments of the present invention may include one or more of the following features. For example, the cilostazol particles may have a particle size wherein 90% of particles have a diameter of about 45 microns or less and an average particle diameter greater than 20 microns.

In yet another general aspect, there is provided a pharmaceutical composition comprising cilostazol particles, wherein 90% of particles have a diameter of about 70 microns or less and 80% of particles have a diameter of about 60 microns or less, and one or more pharmaceutically acceptable excipients.

Embodiments of the present invention may include one or more of the following features. For example, 90% of the cilostazol particles may have a diameter of about 45 microns or less and an average particle diameter greater than 20 microns.

In another general aspect there is provided a method of inhibiting cellular phosphodiesterase enzyme in a mammal in need thereof. The method includes administering a pharmaceutical composition comprising an effective amount of cilostazol particles, wherein 90% of particles have a diameter of about 70 microns or less and 80% of particles have a diameter of about 60 microns or less, and one or more pharmaceutically acceptable excipients.

Embodiments of the present invention may include one or more of the following eatures. For example, 90% of the cilostazol particles may have a diameter of about 45 microns and an average particle diameter greater than 20 microns.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

Detailed Description of the Invention

The present inventors have now found that cilostazol can be micronized more cost efficiently by using crystallization instead of milling. By using crystallization and optimizing the crystallization conditions, it is possible to get cilostazol particles in which (a) 90% of particles have a diameter of about 70 microns or less and 80% of particles have a diameter of about 60 microns or less, or (b) 90% of particles have a diameter of about 45 microns or less and an average particle diameter greater than 20 microns.

The present invention provides a process for the preparation of cilostazol in which 90% of particles have a diameter of about 70 microns or less and 80% of particles have a diameter of about 60 microns or less. The process for making cilostazol particles having these characteristics includes suspending cilostazol in an organic solvent comprising an alkanol; heating the mixture to get a clear solution; optionally filtering the clear solution; cooling the clear solution to crystallize cilostazol; and isolating the cilostazol. As a result of this process, 90% of the particles have a diameter of about 70 microns or less and 80% of particles have a diameter of about 60 microns or less.

More specifically to get these particle size characteristics, cilostazol bulk powder is suspended in an organic solvent which includes an alkanol. The alkanol may include one or more of methanol, ethanol, n-propanol, isopropanol, n-butanol, tert-butanol or mixtures thereof. The resultant mass is heated at a temperature of about 40°C to the reflux temperature to get a clear solution of cilostazol in the organic solvent. The resultant solution may be optionally filtered through a celite bed or charcoal bed to remove foreign extraneous particulate contamination. The clear filtrate is then cooled to a temperature of about 0°C to about 55°C under stirring to initiate the crystallization of cilostazol. After complete crystallization, the slurry is filtered and the solids obtained are washed. The product is dried under a vacuum to get cilostazol particles. The resulting cilastazol

particles have 90% of particles with a diameter of about 70 microns or less and 80% of particles with a diameter of about 60 microns or less.

Also provided is a process for the preparation of cilostazol particles in which 90% of particles have a diameter of about 45 microns and an average particle diameter greater than 20 microns. The process includes suspending cilostazol in an organic solvent comprising an alkanol; heating the mixture to get a clear solution; optionally filtering the clear solution; adding water at a higher temperature to the clear solution; cooling the resultant mass to crystallize cilostazol; and isolating the cilostazol particles. The resulting, isolated cilastazol particles have 90% of particles with a diameter of about 45 microns or less and an average particle greater than 20 microns.

More specifically, to get particles with this particle size characteristics, cilostazol bulk powder is suspended in an organic solvent which includes an alkanol. The alkanol may be one or more of methanol, ethanol, n-propanol, isopropanol, n-butanol, tert-butanol or mixtures thereof. The resultant mass is heated at a temperature of about 40°C to the reflux temperature to get a clear solution of cilostazol in the organic solvent. The resultant solution may be optionally filtered through a celite bed or charcoal bed to remove foreign extraneous particulate contamination. To the clear filtrate water is added at a higher temperature and the resultant mass is cooled to a temperature of about 0°C to about 55°C under stirring to initiate the crystallization of cilostazol. After complete crystallization, the slurry is filtered and the solids obtained are washed. The product is dried under vacuum to get cilostazol particles in which 90% of particles have a diameter of about 45 microns or less and the average particle diameter is greater than about 20 microns.

The present invention also provides for (a) cilostazol particles in which 90% of particles have a diameter of about 70 microns or less and 80% of particles have a diameter of about 60 microns or less and (b) cilostazol particles in which 90% of particles have a diameter of less than about 45 microns and an average particle diameter greater than 20 microns.

The cilostazol particles may be formulated into pharmaceutical compositions that includes cilostazol particles and one or more pharmaceutically acceptable excipients. The cilostazol in the pharmaceutical compositions may have a particle size in which (a) 90% of particles have a diameter of about 70 microns or less and 80% of particles have a diameter

of about 60 microns or less or (b) 90% of the particles have a diameter of less than about 45 microns and the average particle diameter is greater than 20 microns and one or more pharmaceutically acceptable excipients.

Some suitable pharmaceutically acceptable excipients which may be included in the pharmaceutical composition include one or more of diluents, binders, lubricants and colorants. Other types of pharmaceutically acceptable excipients may be used as needed.

Also provided is a method for the inhibition of cellular phosphodiesterase. The method includes administering a pharmaceutical composition which includes a therapeutically effective amount of cilostazol in which (a) 90% of particles have diameter of about 70 microns or less and 80% of particles have diameter of about 60 microns or less or (b) 90% of particles have diameter of about 45 microns or less and an average particle diameter greater than 20 microns.

Particle size measurements were successfully carried out with a Malvern Mastersizer 2000 equipped with a Hydro 2000S (A), a flow cell, Fourier lenses and a multi-element detector. The technique used is the wet method, which includes a dispersion media of 0.06% w/v solution of Tween 20 in distilled water.

The following examples are provided merely to exemplify the inventions and not to limit the inventions.

EXAMPLE 1

A mixture of cilostazol (25 g) in methanol (375 ml) was heated to reflux to dissolve the solids. The hot solution was filtered through a celite bed and the clear filtrate was cooled to about 25°C under stirring. After stirring for six more hours, the mass was filtered and the product was dried in a vacuum oven to get cilostazol having the following particle size characteristics.

Particle size:	D(v,0.8)	D(v,0.9)
Mean	35.65	65.45
Relative Standard Deviation %	0.14	0.16

EXAMPLE 2

A mixture of cilostazol (25 g) in methanol (375 ml) was heated to reflux to dissolve the solids. At the same temperature, water (375 ml) of a higher temperature was added to the clear solution. The resultant mass was cooled to about 25°C under stirring. After stirring for six more hours, the mass was filtered and the product was dried in a vacuum oven to get cilostazol having the following particle size characteristics.

Particle size:	D(v,0.9)	Average Particle Diameter
Mean	32.65	28.45
Relative Standard Deviation %	0.14	0.11

While several particular forms of the inventions have been described, it will be apparent that various modifications and combinations of the inventions detailed in the text can be made without departing from the spirit and scope of the inventions. Accordingly, it is not intended that the inventions be limited, except as by the appended claims.

We claim:

1. A process for the preparation of cilostazol, the process comprising:

a) suspending cilostazol in an organic solvent;

b) heating the mixture to get a clear solution;

c) optionally filtering the clear solution;

d) cooling the clear solution to crystallize cilostazol; and

e) isolating cilostazol,

wherein 90% of particles have a diameter of about 70 microns or less and 80% of particles have diameter of about 60 microns or less.

2. The process of claim 1, wherein the organic solvent comprises an alkanol.

3. The process of claim 2, wherein the alkanol comprises methanol, ethanol, n-propanol, isopropanol, n-butanol, tert-butanol or mixtures thereof.

4. The process of claim 1, wherein the mixture of step b) is heated to reflux.

5. The process of claim 1, wherein the solution of step d) is cooled to about 25°C.

6. The process of claim 1, wherein the solution of step d) is cooled under stirring.

7. The process of claim 1, wherein isolating cilostazol particles comprises drying the cilostazol in a vacuum oven.

8. A process for the preparation of cilostazol, the process comprising:

a) suspending cilostazol in an organic solvent;

b) heating the mixture to get a clear solution;

c) optionally filtering the clear solution;

d) adding water at a higher temperature to the clear solution;

e) cooling the resultant mass to crystallize cilostazol; and

f) isolating the cilostazol,

wherein 90% of particles have a diameter of about 45 microns or less and the average particle diameter is greater than 20 microns.

9. The process of claim 8, wherein the organic solvent comprises an alkanol.

10. The process according to claim 9, wherein the alkanol comprises methanol, ethanol, n-propanol, isopropanol, n-butanol, tert-butanol or mixtures thereof.

11. The process of claim 8, wherein the mixture of step b) is heated to reflux.

12. The process of claim 8, wherein the solution of step e) is cooled to about 25°C.

13. The process of claim 8, wherein the solution of step e) is cooled under stirring.

14. The process of claim 8, wherein isolating cilostazol particles comprises drying the cilostazol in a vacuum oven.

15. Cilostazol having a particle size wherein 90% of particles have a diameter of about 70 microns or less and 80% of particles have a diameter of about 60 microns or less.

16. The cilostazol particles of claim 15, wherein 90% of particles have a diameter of about 45 microns or less and an average particle diameter greater than 20 microns.

17. A pharmaceutical composition comprising cilostazol particles, wherein 90% of particles have a diameter of about 70 microns or less and 80% of particles have a diameter of about 60 microns or less, and one or more pharmaceutically acceptable excipients.

18. The pharmaceutical composition of claim 17, wherein 90% of the cilostazol particles have a diameter of about 45 microns or less and an average particle diameter greater than 20 microns.

19. A method of inhibiting cellular phosphodiesterase enzyme in a mammal in need thereof, the method comprising administering a pharmaceutical composition comprising an effective amount of cilostazol particles, wherein 90% of particles have a diameter of about 70 microns or less and 80% of particles have a diameter of about 60 microns or less, and one or more pharmaceutically acceptable excipients.

20. The method of claim 19, wherein 90% of the cilostazol particles have a diameter of about 45 microns and an average particle diameter greater than 20 microns.