REACTOR FOR PRODUCING PHARMACEUTICAL PARTICLES IN A PRECIPITATION PROCESS

Cross Reference to Related Application

This application claims priority based on Provisional Application Serial No. 61/257,311, filed November 2, 2009, and Provisional Application Serial No. 61/384,662, filed September 20, 2010, which are hereby incorporated by reference in their entirety.

Technical Field

This invention relates to reactors, reactor systems and methods for producing pharmaceutical particles in a precipitation process during the manufacturing of a drug product. In some embodiments, the reactors, reactor systems and methods are utilized in a process for manufacturing pharmaceutical products for pulmonary delivery.

Background

U.S. Patent No. 6,071,497, issued June 6, 2000 to Steiner et al., describes methods to manufacture microparticles of a diketopiperazine that involves a precipitation of the microparticles. The method described in Patent No. 6,071,497, however, is a process in which a drug is incorporated in the microparticles as they form. Alternatively, U.S. Patent No. 6,444,226 discloses a method for making a formulation using preformed diketopiperazine microparticles by forming a complex of the microparticles with an active agent. Such microparticle suspensions can be further processed to produce dry powder that can be administered to a patient by inhalation for therapeutic purposes. In all of the described methods, precipitation reactions involving diketopiperizine are extremely fast, with a reaction half-time in the order of 0.5 second, and the precipitated suspension is a non-Newtonian fluid.

A precipitation process is typically used to produce small particles, as the crystal formation in the precipitation takes place very rapidly. Conditions used during the precipitation process define the particle size and the structure of the particles. The process involves bringing dissolved solid mixtures to supersaturation while mixing. The mixing rate and level of supersaturation play an important role in particle size formation. Prior art mixing apparatus includes impinging jet mixers, high pressure homogenizers and static mixing followed by spray drying. None of these devices can be used in a continuous process, if the precipitation process is extremely fast and the resulting suspension is a non-Newtonian fluid. The non-Newtonian nature of the fluid causes precipitated particles to stick to the wall of the

precipitation device if velocity gradients are small in the exit stream. Thus, clogging of the mixing apparatus can occur.

Accordingly, there is a need for improved reactors, reactor systems and methods for producing particles in a continuous precipitation process.

Summary of Invention

Embodiments of the present invention provide reactors, reactor systems and methods for producing pharmaceutical particles in a precipitation process during the manufacturing of a drug product. Embodiments of the invention are particularly useful for precipitation reactions that occur in a very short time and may cause clogging of a reactor. Embodiments of the invention involve supplying a first reactant material and a second reactant material to the reaction chamber at first and second inlets, respectively. The second inlet may be downstream of the first inlet in the reaction chamber. The first reactant material is increased in speed and is reduced to small droplets and then reacts with the second reactant material downstream of the second inlet to provide at an outlet of the reaction chamber particles formed by reaction of first and second reactant materials.

According to an aspect of the present invention, there is provided a process for manufacturing microparticles of a compound having the formula 3,6-bis(N-fumary1-4-aminobuty1)-2,5-diketopiperazine, including: providing a reactor having a reaction chamber and including a stator assembly having two or more stators and a rotor assembly having two or more rotors; rotating the rotor assembly about an axis of rotation relative to the stator assembly; supplying a first reactant material comprising an acetic acid solution to the reaction chamber at a first radial location; and supplying a second reactant material comprising 3,6-bis(N-fumaryl-4-aminobutyl)-2,5-diketopiperazine dissolved in a basic solution to the reaction chamber through openings in a second stator of the two or more stators at a second radial location different from the first radial location, wherein the first and second reactant materials react to produce precipitation of the microparticles in the reaction chamber, wherein the second stator includes a plurality of circumferentially spaced teeth, and wherein the openings in the second stator are located radially inwardly of the teeth of the second stator and are in radial alignment with the teeth of the second stator.

Disclosed herein is a reactor for producing particles in a precipitation process. The reactor comprises a housing defining a reaction chamber; a stator assembly including two or

more stators in the reaction chamber; a rotor assembly including two or more rotors in the reaction chamber, the rotor assembly configured for rotation about an axis of rotation relative to the stator assembly; a first inlet to supply a first reactant material to the reaction chamber at a first radial location; a second inlet to supply a second reactant material to the reaction chamber at a second radial location different from the first radial location, wherein the first and second reactant materials react to produce precipitation of particles in the reaction chamber; and an outlet to supply the particles formed in the reaction chamber.

Disclosed herein is a reactor for producing particles in a precipitation process. The reactor comprises a housing enclosing a reaction chamber; a stator assembly including at least a first stator and a second stator in the reaction chamber; a rotor assembly including at least a first rotor, second rotor and a third rotor in the reaction chamber; a first inlet to supply a first reactant material to the reaction chamber upstream of the first rotor; a second inlet to supply a second reactant material to the reaction chamber in a region of the second stator; and an outlet to provide particles formed by reaction of the first and second reactant materials, wherein the first reactant material is increased in speed by the first rotor and is reduced to small droplets by the first stator and the second rotor, and wherein the first reactant material reacts with the second reactant material downstream of the second inlet.

Disclosed herein is a reactor system for producing particles in a precipitation process. The reactor system comprises a reactor including a housing enclosing a reaction chamber, a stator assembly including at least a first stator and a second stator in the reaction chamber, a rotor assembly including at least a first rotor, a second rotor and a third rotor in the reaction chamber, a first inlet coupled to the reaction chamber upstream of the first rotor, a second inlet coupled to the reaction chamber in a region of the second stator, and an outlet of the reaction chamber; a drive mechanism configured to rotate the rotor assembly relative to the stator assembly in the reaction chamber; a first source configured to supply a first reactant material to the first inlet of the reactor; and a second source configured to supply a second reactant material to the second inlet of the reactor, wherein the first reactant material is increased in speed by the first rotor and is reduced to small droplets by the first stator and the second rotor, and wherein the first reactant material reacts with the second reactant material downstream of the second inlet to provide, at the outlet of the reaction chamber, particles formed by reaction of the first and second reactant materials.

Disclosed herein is a method for producing particles in a precipitation process. The method comprises providing a reactor having a reaction chamber and including a stator assembly including at least a first stator and a second stator in the reaction chamber and a rotor assembly including at least a first rotor, a second rotor and a third rotor in the reaction chamber; rotating the rotor assembly relative to the stator assembly in the reaction chamber; supplying a first reactant material to the reaction chamber upstream of the first rotor; and supplying a second reactant material to the reaction chamber in a region of the second stator, wherein the first reactant material is increased in speed by the first rotor and is reduced to small droplets by the first stator and the second rotor, wherein the first reactant material reacts with the second reactant material downstream of the second inlet to provide at an outlet of the reaction chamber particles formed by reaction of the first and second reactant materials.

Disclosed herein is a method for producing particles in a precipitation process. The method comprises providing a reactor having a reaction chamber and including a stator assembly having two or more stators and a rotor assembly having two or more rotors; rotating the rotor assembly about an axis of rotation relative to the stator assembly; supplying a first reactant material to the reaction chamber at a first radial location; and supplying a second reactant material to the reaction chamber at a second radial location different from the first radial location, wherein the first and second reactant materials react to produce precipitation of particles in the reaction chamber.

Brief Description of Drawings

For a better understanding of the present invention, reference is made to the accompanying drawings, which are incorporated herein by reference and in which:

FIG. 1 is a schematic block diagram of a reactor system in accordance with embodiments of the invention;

FIG. 2 is a simplified cross-sectional diagram of a reactor in accordance with embodiments of the invention;

FIG. 3 is a schematic view of a rotor assembly used in a reactor in accordance with embodiments of the invention;

FIG. 4 is a schematic view of a first embodiment of a stator assembly used in a reactor in accordance with embodiments of the invention;

FIG. 5 is a fragmentary cross-sectional schematic view of the stator assembly of FIG. 4;

CLAIMS

1. A process for manufacturing microparticles of a compound having the formula 3,6-bis(N-fumaryl-4-aminobutyl)-2,5-diketopiperazine, comprising:

providing a reactor having a reaction chamber and including a stator assembly having two or more stators and a rotor assembly having two or more rotors;

rotating the rotor assembly about an axis of rotation relative to the stator assembly;

supplying a first reactant material comprising an acetic acid solution to the reaction chamber at a first radial location; and

supplying a second reactant material comprising 3,6-bis(N-fumaryl-4-aminobutyl)-2,5-diketopiperazine dissolved in a basic solution to the reaction chamber through openings in a second stator of the two or more stators at a second radial location different from the first radial location, wherein the first and second reactant materials react to produce precipitation of the microparticles in the reaction chamber, wherein the second stator includes a plurality of circumferentially spaced teeth, and wherein the openings in the second stator are located radially inwardly of the teeth of the second stator and are in radial alignment with the teeth of the second stator.

2. The process of claim 1, wherein the reactor further comprises an outlet port for allowing communication with another vessel.

3. The process of claim 1, wherein precipitation of the microparticles produced in the reaction chamber occurs at a temperature range of from about 10 °C to about 30 °C.

4. The process of claim 1, wherein precipitation of the microparticles produced in the reaction chamber occurs at a temperature range of from about 15 °C to about 20 °C.

5. The process of claim 1, wherein an acid to basic solution ratio of the reaction ranges from 0.8 to about 1.2.

6. The process of claim 1, wherein the basic solution has a pH value greater than 10.

7. The process of claim 6, wherein the basic solution comprises ammonium hydroxide, sodium hydroxide, or potassium hydroxide or mixtures thereof.

8. The process of claim 1, wherein precipitation of the microparticles produced in the reaction chamber occurs at a pressure from about 15 psig to about 2000 psig.

9. The process of claim 8, wherein the solutions are fed into the reaction chamber at a flow rate of about 10 kg/min to about 100 kg/min.

10. The process of claim 1, wherein a ratio of the acetic acid solution to the basic solution in the reaction is about 0.8 to about 1.2 (w/w).

11. The process of claim 1, wherein the acetic acid solution comprises 1% to about 4% (w/w) of the reaction.

12. The process of claim 1, further comprising a surfactant in a range of from about 0.01% to about 5% (v/v).