heretofore been suitable for manufacturing of pharmaceutical formulations. Accordingly, there is a need for improvements in the design and manufacture of cryogranulation systems and methods for use in manufacturing of pharmaceutical formulations.

Summary

Embodiments of t~~T~~he present invention relates to cryogranulation systems with an improved dispenser assembly for use in manufacturing frozen pellets of pharmaceutical substances in a fluid medium. Methods of cryogranulating the pharmaceutical substance in the fluid medium are also disclosed. In particular embodiments, the dispenser assembly is used with suspensions or slurries of pharmaceutical compositions comprising biodegradable substances, such as proteins, peptides, and nucleic acids. In certain embodiments, the pharmaceutical substance can be adsorbed to any pharmaceutically acceptable carrier particles suitable for making pharmaceutical powders. In one embodiment, the pharmaceutical carrier can be, for example, diketopiperazine-based microparticles.

~~According to a first aspect of the invention, a cryogranulation system is provided. The cryogranulation system comprises at least one tray configured to carry a flow of a cooling agent; a mechanism configured to deliver the cooling agent to the at least one tray; a dispenser assembly configured to supply a pharmaceutical composition into the cooling agent, the dispenser assembly including a housing and a dispenser subassembly, the housing configured to mount the dispenser subassembly above the tray, the dispenser subassembly including an enclosure defining an interior chamber, at least one inlet port for supplying the pharmaceutical composition to the interior chamber and a plurality of dispenser ports for supplying the pharmaceutical composition to the cooling agent in the tray, the dispenser ports being configured to produce, after interaction of the pharmaceutical composition with the cooling agent, pellets of the pharmaceutical composition in a predetermined size range; and a transport assembly configured to separate the pellets from the cooling agent and to transport the pellets to a pellet receptacle.~~In a first aspect, there is provided a cryogranulation system comprising: at least one tray configured to carry a flow of a cooling agent; a mechanism configured to deliver the cooling agent to the at least one tray; a dispenser assembly configured to supply a pharmaceutical composition into the cooling agent, the dispenser assembly including a housing and a dispenser subassembly, the housing configured to mount the dispenser subassembly above the tray, the dispenser subassembly including an enclosure defining an interior chamber, at least one inlet port for supplying the pharmaceutical composition to the interior chamber and a plurality of dispenser ports for supplying the pharmaceutical composition to the cooling agent in the tray, the dispenser ports being configured to produce, after interaction of the pharmaceutical composition with the cooling agent, pellets of the pharmaceutical composition in a predetermined size range, wherein the dispenser ports of the dispenser subassembly each include an upper conduit of a first inner diameter and a lower conduit of a second inner diameter, wherein the dispenser ports of the dispenser

subassembly include first and second rows of dispenser ports, the rows being disposed perpendicularly with respect to the flow of cooling agent, wherein the first and second rows of dispenser ports are angled with respect to vertical, and wherein the dispenser ports of the first row are disposed at opposite angles with respect to the dispenser ports of the second row; and a transport assembly configured to separate the pellets from the cooling agent and to transport the pellets to a pellet receptacle.

~~According to a second aspect of the invention, a dispenser assembly is provided for supplying a pharmaceutical composition into a cooling agent in a cryogranulation system. The dispenser assembly comprises a housing and a dispenser subassembly, the housing configured to mount the dispenser subassembly above the cooling agent, the dispenser subassembly including an enclosure defining an interior chamber, at least one inlet port for supplying the pharmaceutical composition to the interior chamber and a plurality of dispenser ports for supplying the pharmaceutical composition to the cooling agent, the dispenser ports being configured to produce, after interaction of the pharmaceutical composition with the cooling agent, pellets of the pharmaceutical composition in a predetermined size range.~~In a second aspect, there is provided a dispenser assembly for supplying a pharmaceutical composition into a cooling agent in a cryogranulation system, comprising: a housing and a dispenser subassembly, the housing configured to mount the dispenser subassembly above the cooling agent, the dispenser subassembly including an enclosure defining an interior chamber, at least one inlet port for supplying the pharmaceutical composition to the interior chamber and a plurality of dispenser ports for supplying the pharmaceutical composition to the cooling agent, the dispenser ports being configured to produce, after interaction of the pharmaceutical composition with the cooling agent, pellets of the pharmaceutical composition in a predetermined size range, wherein the dispenser ports of the dispenser subassembly each include an upper conduit of a first inner diameter and a lower conduit of a second inner diameter, wherein the dispenser ports of the dispenser subassembly include first and second rows of dispenser ports, the rows being disposed perpendicularly with respect to the flow of cooling agent, wherein the first and second rows of dispenser ports are angled with respect to vertical, and wherein the dispenser ports of the first row are disposed at opposite angles with respect to the dispenser ports of the second row.

~~According to a third aspect of the invention, a method is provided for cryogranulating a pharmaceutical composition. The method comprises establishing a flow of a cooling agent; supplying a pharmaceutical composition to a dispenser assembly; dispensing the pharmaceutical composition from the dispenser assembly into the flow of cooling agent, the pharmaceutical composition being dispensed uniformly over the flow of cooling agent and with a droplet size to form pellets in a predetermined size range; and separating the pellets from the cooling agent.~~In a third aspect, there is provided a method for cryogranulating a pharmaceutical composition, comprising: establishing a flow of a cooling agent; supplying a pharmaceutical composition to a dispenser assembly; dispensing the pharmaceutical composition from the dispenser assembly into the flow of cooling agent, the pharmaceutical composition being dispensed uniformly over the flow of cooling agent and with a droplet size to form pellets in a predetermined size range, wherein dispensing the pharmaceutical composition comprises dispensing diketopiperazine-based microparticles in a fluid medium; and separating the pellets from the cooling agent.

~~According to a fourth aspect of the invention, a dispenser assembly comprises a housing having an internal volume or chamber, a cover, and a dispenser subassembly attachable to the housing. The dispenser subassembly is configured to have an outer surface and an internal surface, a top portion and bottom portion, the top portion having an inlet port configured to communicate with the internal chamber of the dispenser subassembly. The inlet port provides a conduit for delivering to the dispenser subassembly a pharmaceutical substance in a fluid medium. The dispenser subassembly is further configured with a plurality of outlet ports located at the bottom of the dispenser assembly.~~In a fourth aspect, there is provided a cryogranulation system comprising: a dispenser assembly, a reservoir for holding a source of a cooling agent, a pump assembly for delivering the pharmaceutical solution or suspension; a pump system for delivering the cooling agent, a transport system for transporting formed pellets to a receptacle and an exhaust system; wherein the dispenser assembly comprises a housing and a dispenser subassembly which comprises a first element having one or more inlet ports, a second element having a plurality of dispenser ports; and a securing mechanism for holding the first and second elements together; said dispenser subassembly adaptable to said housing and having an internal volume for receiving and dispensing a pharmaceutical suspension to be pelletized, wherein the dispenser ports of the dispenser subassembly each include an upper conduit of a first inner diameter and a lower conduit of a second inner diameter, wherein the dispenser ports of the dispenser subassembly include first and second rows of dispenser ports, the rows being disposed perpendicularly with respect to the flow of cooling agent, wherein the first and second rows of dispenser ports are angled with respect to vertical, and wherein the dispenser ports of the first row are disposed at opposite angles with respect to the dispenser ports of the second row.

~~According to a fifth aspect of the invention, a method for cryopelletizing a suspension or a slurry is provided. The method comprises pumping a pharmaceutical composition at a rate of about 0.5 to about 10 liters per minute using a peristaltic pump~~

~~through a dispenser assembly comprising a dispenser subassembly having two portions, a first element and a second element; the first element forming the top portion of the device and having one or more inlet ports for providing the liquid pharmaceutical composition and a second element forming the bottom portion of the dispenser subassembly and comprising channels which are provided with a plurality of conduits and dispensing ports; both first and second elements forming an enclosure for holding a volume of a fluid and capable of dispensing said fluid in droplet form.~~In a fifth aspect, there is provided a method for cryopelletizing a suspension or a slurry, comprising: pumping a pharmaceutical composition at a rate of about 0.5 to about 10 liters per minute using a peristaltic pump through a dispenser assembly comprising a dispenser subassembly having a housing, a first element and a second element; the first element forming the top portion of the device and having one or more inlet ports for providing the liquid pharmaceutical composition and a second element forming the bottom portion of the dispenser subassembly and comprising channels which are provided with a plurality of conduits and dispensing ports; both first and second elements forming an enclosure for holding a volume of a fluid; and dispensing said pharmaceutical suspension or slurry in droplet form into a tray of liquid nitrogen, wherein dispensing the pharmaceutical composition comprises dispensing diketopiperazine-based microparticles in a fluid medium.

Brief Description of the 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 cryogranulation system in accordance with embodiments of the invention;

FIG. 2 is a partial cross-sectional view of the cryogranulation system of FIG. 1, showing the dispenser assembly and the upper tray carrying a cooling agent;

FIG. 3 is an isometric, partially cut-away view of the dispenser assembly of FIG. 1, in accordance with embodiments of the invention;

FIG. 4 is an isometric, exploded view of the dispenser assembly of FIG. 3;

FIG. 5 is a bottom view of the dispenser assembly;

FIG. 6 is an isometric view of the dispenser subassembly shown in FIG. 4; and

FIG. 7 is a cross-sectional view of the dispenser subassembly.

Detailed Description

Cryogranulation equipment cannot be readily applied to the manufacturing of pharmaceutical compositions in the freeze-dry step of biological drug products processing without encountering many problems. Without pelletizing a pharmaceutical composition, the freezing process agglomerates the composition and leads to increased lyophilization times of the drug product. Other problems

encountered when using off the shelf cryogranulation equipment in a pharmaceutical manufacturing process, include: lack of pellet formation, streaming and freezing of the solutions and/or suspensions containing the pharmaceutical substance prior to dispensing, which leads to clogging of the dispenser apparatus, and therefore, product loss during transport due to inability to