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(54) **Title**: ASEPTIC WET MILLING PROCESS FOR PALIPERIDONE PALMITATE

(57) **Abstract**: An aseptic wet milling process for preparing a pharmaceutical composition comprising micronized paliperidone palmitate by using two types of milling beads is disclosed. In particular, the aseptic wet milling process uses two types of milling beads sequentially in a single equipment to obtain particles of micronized paliperidone palmitate with desired size ranges and having uniform size distribution.

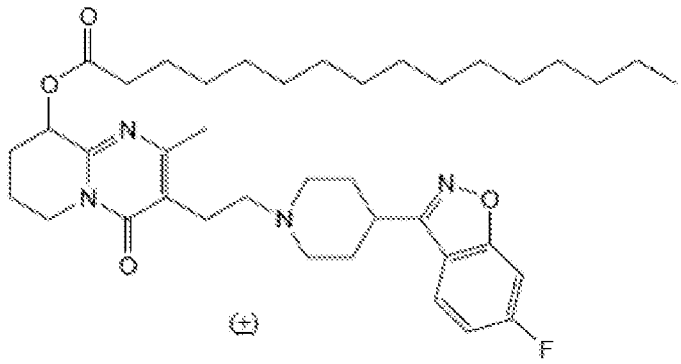
Aseptic Wet Milling Process for Paliperidone Palmitate

FIELD OF THE INVENTION

The invention relates to a process for micronizing paliperidone palmitate aseptically using wet milling. In particular, the aseptic wet milling process uses two types of milling beads sequentially in single equipment to obtain particles of micronized paliperidone palmitate with desired size ranges and having uniform size distribution.

BACKGROUND OF THE INVENTION

Paliperidone palmitate is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives with the chemical name (9RS)-3-[2-[4(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4Hpyrido[1,2-a]pyrimadin-9-yl hexadecanoate. Its molecular formula is C39H57FN4O4 and its molecular weight is 664.89. The structural formula is:



The injection composition of paliperidone palmitate is available commercially and marketed under the brand name of Invega Sustena® in US market. It is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 25 mg, 50 mg, 75 mg, 100 mg, and 150 mg of paliperidone. The composition is provided in a prefilled syringe (cyclic-olefin-copolymer) with a plunger stopper and tip cap (bromobutyl rubber).

Generally, sterile micronization of active ingredient is carried out in air-jet mills fitted in isolators. Jet mills can be operated in sterile conditions by integrating the mill in an isolator or a restricted access barrier system (RABS). Thus, micronizing an API aseptically by air-jet milling is expensive and requires sophisticated equipments.

US patent publication nos. 2008/0214808 and 2009/0163519 disclose micronization of paliperidone palmitate ester by wet milling process.

US Patent No. 6,555,544 discloses a process for preparing submicron particles of an antipsychotic agent.

There still exists an enduring need to develop an alternate, economically less expensive, and robust method for preparing sterile composition comprising paliperidone palmitate with an effective average particle size of less than 3 µm.

The inventors of the invention surprisingly found that the sterile micronization of paliperidone palmitate by air-jet milling can be avoided and instead as an alternative, less expensive wet media milling can be used to produce particles with desired size range in a single equipment. In addition, the inventors of the invention unexpectedly found that the processing time for reducing the particle size of paliperidone palmitate was reduced significantly by utilizing two types of milling beads sequentially.

The invention uses wet milling process in such a way that it produces particles of micronized paliperidone palmitate having an effective average particle size of less than 3 µm and having narrow size distribution range. Moreover, the wet milling process may reduce the time to achieve desired particle size.

SUMMARY OF THE INVENTION

In one aspect, there is provided a process for micronizing paliperidone palmitate aseptically using wet milling, said process comprising the steps of:

(a) mixing crystalline paliperidone palmitate having effective average particle size in the range of about 40 µm to about 300 µm in a sterile vehicle to form a premix;

(b) subjecting the premix of step (a) to wet milling in the presence of first milling beads having size of about 1.5 mm to obtain a suspension of paliperidone palmitate with reduced effective average particle size; and

(c) subjecting the suspension formed in step (b) to wet milling in the presence of second milling beads having size of about 0.3 mm to obtain suspension of micronized paliperidone palmitate having effective average particle size of less than 3 µm,

wherein the total process is carried out in single equipment aseptically.

In an embodiment, the process is carried out as a batch processing.

In another aspect, there is provided a process wherein the processing with first milling beads is effected for the $1/4^{th}$ to $3/4^{th}$ of the total processing time.

In another aspect, there is provided a process wherein the processing with second milling beads is effected for the $1/4^{th}$ to $3/4^{th}$ of the total processing time.

In another aspect, there is provided a process wherein the processing with first milling beads is effected for half of the total processing time and the processing with second milling beads is effected remaining half of the total processing time.

In another aspect, the process of wet milling for micronizing paliperidone palmitate wherein the first milling beads reduce the particle size of paliperidone palmitate to an effective average particle size of less than about 40 µm. Preferably, the particle size is reduced to an effective average particle size of less than about 30 µm, more preferably less than about 20 µm and yet more preferably less than about 10 µm.

In another embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the size of first type of milling beads ranges from 0.5 mm to 2.5 mm.

In another embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the size of second type of milling beads ranges from 0.15 mm to 0.45 mm.

In another embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the milling beads are made up of material selected from zirconium oxide, yttrium-stabilized zirconium oxide, steel, ceramic material, copper, silicon carbide, porcelain, quartz, aluminum oxide, non-ferrous metal or in special cases of plastics material.

In another aspect, a process for micronizing paliperidone palmitate aseptically using wet milling, said process comprising steps of:

(a) mixing particles of paliperidone palmitate with effective average size in the range of about 40 to about 100 µm in a sterile vehicle to form a premix;
(b) subjecting the premix of step (a) to wet milling in the presence of first milling beads to obtain a suspension of paliperidone palmitate particles with reduced effective average size in the range of about 10 to about 39 µm; and
(c) subjecting the suspension formed in step (b) to wet milling in the presence of second milling beads to obtain particles of paliperidone palmitate with effective average size of less than 3 µm,

wherein the total process is carried out in single equipment aseptically.

In another general embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the $1/4^{th}$ particle size reduction takes place in

2/3rd of the total processing time when compared to wet media milling by single type of milling beads as against two types of milling beads.

In another embodiment, the process of wet milling for micronizing paliperidone palmitate wherein the second milling beads reduce the particle size of paliperidone palmitate to an effective average particle size of less than 3 µm. Preferably, having effective average particle size below 2.9 µm, more preferably 2.7 µm, more preferably 2.5 µm, more preferably 2.3 µm, yet more preferably 2.1 µm and yet more preferably about 2.0 µm.

In another embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the polydispersity index of the particles of paliperidone palmitate obtained is below 2.0. Preferably, the polydispersity index of the particles of paliperidone palmitate obtained is below 1.9, more preferably below 1.8, more preferably below 1.7, more preferably below 1.6 and yet more preferably about 1.5.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

The term "effective average particle size" refers to average particle size by volume and it is also shown with d_{90} in short. In this sense, the term d_{90} signifies that 10% of the said substance by volume has a particle size over the value stated with d_{90} and the other 90% of the substance by volume has a particle size below the value stated with d_{90}. D_{90} value can be measured by one of the known measuring devices, for instance by a device which measures particle distribution by laser diffraction, for instance, by Malvern Mastersizer.

The term "polydispersity index (PDI)" refers to a measure of the distribution of particle sizes for a collection of particles. PDI can be measured by one of the known measuring devices, for instance by a device which measures particle distribution by laser diffraction, for instance, by Malvern Mastersizer.

The term "wet milling" as used herein is intended to mean the grinding of materials with a sufficient quantity of a liquid to form a slurry. The process of wet milling and apparatus therefore are conventionally known in the art and do not form a critical feature of the invention.

The “milling beads” in the method of the invention, preferably are chemically inert and rigid. The term “chemically-inert”, as used herein, means that the milling beads do not react chemically with the biologically active compound or the grinding compound. The milling beads are essentially resistant to fracture and erosion in the milling process. The milling beads are desirably provided in the form of beads which have smooth ovoid or spherical shapes. Preferably, the milling beads are provided in the form of one or more of beads, balls or spheres.

The milling beads may be made for example of zirconium oxide, yttrium-stabilized zirconium oxide, steel, ceramic material, copper, silicon carbide, porcelain, quartz, aluminum oxide, non-ferrous metal or in special cases of plastics material.

The term “aseptic” is used interchangeably with the word “sterile”. In some embodiments, the aseptic processing or fabrication complies with GMP (Good Manufacturing Practice) industry guidelines such as those associated with Guidance for Industry—Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice, U.S. Department of Health and Human Services Food and Drug Administration, September 2004.

In one aspect, a process of wet milling for micronizing paliperidone palmitate which process employs two types of milling beads namely first type of milling beads and second type of milling beads.

In another embodiment, the process of wet milling for micronizing paliperidone palmitate, said process is carried out as a batch processing employing two types of milling beads sequentially.

In another embodiment, the process of wet milling for micronizing paliperidone palmitate comprises first milling beads, wherein the size of first type of milling beads ranges from about 0.5 mm to about 2.5 mm.

In another embodiment, the process of wet milling for micronizing paliperidone palmitate comprises second milling beads, wherein the size of second type of milling beads ranges from about 150 µm to about 450 µm.

In another embodiment, the process of micronizing paliperidone palmitate aseptically using wet milling, wherein the milling process is carried out at 50-3000 rpm.

In another aspect, there is provided a process of micronizing paliperidone palmitate aseptically using wet milling, said process comprising the steps of:

(a) mixing crystalline paliperidone palmitate having effective average particle size in the range of about 40 µm to about 300 µm in a sterile vehicle to form a premix;
(b) subjecting the premix of step (a) to wet milling in the presence of first milling beads to obtain a suspension of paliperidone palmitate with reduced effective average particle size; and
(c) subjecting the suspension formed in step (b) to wet milling in the presence of second milling beads to obtain suspension of paliperidone palmitate having effective average particle size of less than 3 µm,

wherein the total process is carried out in a single equipment aseptically.

In another general embodiment, the process of wet milling for micronizing paliperidone palmitate wherein the micronized paliperidone palmitate particles

have effective average particle size of less than 3 µm. Preferably, having effective average particle size less than 2.9 µm, more preferably less than 2.7 µm, more preferably less than 2.5 µm, more preferably less than 2.3 µm, yet more preferably less than 2.1 µm and yet more preferably about 2.0 µm.

In another general embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the processing with first milling beads and second milling beads constitute less than 4 hr. Preferably, processing with first milling beads and second milling beads constitute less than 3.5 hr, more preferably, less than 3 hr and yet more preferably less than 2 hr.

In another general embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the processing with first milling beads and second milling beads constitute about 2 hr.

In another general embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the processing with first milling beads is effected for the $1/4^{th}$ to $3/4^{th}$ of the total processing time.

In another general embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the processing with second milling beads is effected for the $1/4^{th}$ to $3/4^{th}$ of the total processing time.

In another general embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the processing with first milling beads is effected for about 30 min and processing with second milling beads is effected for about 1 hr and 30 min.

In another general embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the processing with first milling beads is effected

for about 1 hr and processing with second milling beads is effected for about 1 hr.

In another general embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the processing with first milling beads is effected for about 1 hr 30 min and processing with second milling beads is effected for about 30 min.

In another general embodiment, the the process of wet milling for micronizing paliperidone palmitate, wherein the $1/4^{th}$ particle size reduction takes place in $2/3^{rd}$ of the total processing time when compared to wet media milling by single type of milling beads as against two types of milling beads, sequentially.

In another general aspect, there is provided a process of wet milling for micronizing paliperidone palmitate, wherein the polydispersity index of the micronized paliperidone palmitate is below 2.0. Preferably, the polydispersity index of the micronized paliperidone palmitate particles is below 1.9, more preferably below 1.8, more preferably below 1.7, more preferably below 1.6 and yet more preferably about 1.5.

In another general embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the size of first type of milling beads ranges from 0.5 mm to 2.5 mm.

In another general embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the size of second type of milling beads ranges from 0.15 mm to 0.45 mm.

In another general embodiment, the process of wet milling for micronizing paliperidone palmitate, wherein the milling beads are made up of material selected from the group consisting of zirconium oxide, yttrium-stabilized zirconium oxide, steel, ceramic material, copper, silicon carbide, porcelain,

quartz, aluminum oxide, non-ferrous metal or in special cases of plastics material.

In another aspect, there is provided a process micronizing paliperidone palmitate aseptically using wet milling, said process comprising the steps of:

(a) mixing crystalline paliperidone palmitate having effective average particle size in the range of about 40 µm to about 100 µm in a sterile vehicle to form a premix;

(b) subjecting the premix of step (a) to wet milling in the presence of first milling beads having size of about 1.5 mm to obtain a suspension of paliperidone palmitate with reduced effective average particle size range of about 10 µm to 39 µm; and

(c) subjecting the suspension formed in step (b) to wet milling in the presence of second milling beads having size of about 0.3 mm to obtain suspension of micronized paliperidone palmitate having effective average particle size of less than 3 µm,

wherein the total process is carried out in single equipment aseptically.

In another aspect, there is provided a process for micronizing paliperidone palmitate aseptically using wet milling, said process comprising the steps of:

(a) mixing crystalline paliperidone palmitate having effective average particle size in the range of about 40 µm to about 100 µm in a sterile vehicle to form a premix;

(b) subjecting the premix of step (a) to wet milling in the presence of first milling beads having size of about 1.5 mm to obtain a suspension of paliperidone palmitate with reduced effective average particle size range of about 10 µm to 39 µm; and

(c) subjecting the suspension formed in step (b) to wet milling in the presence of second milling beads having size of about 0.3 mm to obtain suspension of paliperidone palmitate having effective average particle size of about 2 µm,

wherein the total process is carried out in single equipment aseptically.

In another embodiment, the process of wet milling for micronizing paliperidone palmitate wherein the first milling beads reduce the particle size of paliperidone palmitate to an effective average particle size of less than 39 µm. Preferably, the particle size is reduced to an effective average particle size of less than 30 µm, more preferably less than 20 µm, more preferably less than 15 µm and yet more preferably less than 10 µm.

In another general embodiment, the process of wet milling for aseptically micronizing paliperidone palmitate, wherein the obtained particles are having average particle size below 3.0 µm. Preferably, having effective average particle size below 2.9 µm, more preferably 2.7 µm, more preferably 2.5 µm, more preferably 2.3 µm, yet more preferably 2.1 µm and yet more preferably about 2.0 µm.

In another general embodiment, the process of wet milling for aseptically micronizing paliperidone palmitate, wherein the particles having average particle size below 1.2 µm are obtained after 4 hr of batch processing. Preferably, after 3.5 hr of batch processing, more preferably, after 3.0 hr of batch processing and yet more preferably after 2.0 hr of batch processing.

In another general embodiment, the process of wet milling for aseptically micronizing paliperidone palmitate, wherein the particles having average particle size of about 2.0 µm are obtained after about 2 hr of batch processing.

In another general embodiment, the process of wet milling for aseptically micronizing paliperidone palmitate, wherein the particles having average particle size of about 2.0 µm are obtained after 2 hr of batch processing in which processing with first milling beads is effected for about 30 min and processing with second milling beads is effected for about 1 hr and 30 min.

In another general embodiment, the process of wet milling for aseptically micronizing paliperidone palmitate, wherein the particles having average particle size of about 2.0 µm are obtained after 2 hr of batch processing in which processing with first milling beads is effected for about 1 hr 30 min and processing with second milling beads is effected for about 30 min.

In another general aspect, there is provided a process of wet milling for aseptically preparing a composition comprising micronized paliperidone palmitate and at least one pharmaceutically acceptable excipient.

In another embodiment, the process of wet milling for aseptically preparing a composition comprising micronized paliperidone palmitate, a surfactant and at least one pharmaceutically acceptable excipient.

In another embodiment, the process of wet milling for aseptically preparing a composition comprising micronized paliperidone palmitate, polysorbate 20, citric acid monohydrate, disodium hydrogen phosphate anhydrous, polyethylene glycol 4000, sodium dihydrogen phosphate monohydrate, sodium hydroxide, and water for injection.

In another embodiment, the process of wet milling for aseptically preparing a composition comprising:

(a) 10 to 20% of micronized paliperidone palmitate,
(b) 0.5 to 5.0 % of polysorbate 20,
(c) 0.1 to 1.0 % of citric acid monohydrate,
(d) 0.1 to 1.0 % of disodium hydrogen phosphate anhydrous,
(e) 0.5 to 5.0 % of polyethylene glycol 4000,
(f) 0.1 to 1.0 % of sodium dihydrogen phosphate monohydrate,
(g) 0.1 to 1.0 % of sodium hydroxide, and
(h) q.s. of water for injection

In another embodiment, the process of wet milling for aseptically preparing a composition comprising:

(a) 15.07% of micronized paliperidone palmitate,
(b) 1.16 % of polysorbate 20,
(c) 0.48 % of citric acid monohydrate,
(d) 0.48 % of disodium hydrogen phosphate anhydrous,
(e) 2.90 % of polyethylene glycol 4000,
(f) 0.24 % of sodium dihydrogen phosphate monohydrate,
(g) 0.27 % of sodium hydroxide, and
(h) q.s. of water for injection

In another embodiment, the process of wet milling for aseptically preparing a composition comprising:

(a) 10 to 20% of micronized paliperidone palmitate,
(b) 0.5 to 5.0 % of polysorbate 20,
(c) 0.1 to 1.0 % ethylenediaminetetraacetic acid (EDTA),
(d) 0.1 to 1.0 % of disodium hydrogen phosphate anhydrous,
(e) 0.5 to 5.0 % of polyethylene glycol 4000,
(f) 0.1 to 1.0 % of sodium dihydrogen phosphate monohydrate,
(g) 0.1 to 1.0 % of sodium hydroxide, and
(h) q.s. of water for injection

In another embodiment, the process of wet milling for aseptically preparing a composition comprising:

(a) 15.07% of micronized paliperidone palmitate,
(b) 1.93 % of polysorbate 20,
(c) 0.50 % of ethylenediaminetetraacetic acid (EDTA),
(d) 0.48 % of disodium hydrogen phosphate anhydrous,
(e) 2.90 % of polyethylene glycol 4000,
(f) 0.24 % of sodium dihydrogen phosphate monohydrate,
(g) 0.27 % of sodium hydroxide, and

(h) q.s. of water for injection

In another aspect, there is provided a composition comprising micronized paliperidone palmitate obtained by a process comprising steps of:

(a) mixing crystalline paliperidone palmitate having effective average particle size in the range of about 40 µm to about 100 µm in a sterile vehicle to form a premix;

(b) subjecting the premix of step (a) to mechanical means in the presence of first milling beads to obtain a suspension of paliperidone palmitate with reduced effective average particle size range of about 10 µm to 39 µm; and

(c) subjecting the suspension formed in step (b) to mechanical means in the presence of second milling beads to obtain suspension of paliperidone palmitate having effective average particle size of about 2 µm,

wherein the total process is carried out in single equipment aseptically.

The invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the invention.

The invention now will be described in particularity with the following illustrative examples; however, the scope of the invention is not intended to be, and shall not be, limited to the exemplified embodiments below.

EXAMPLES

Comparative Example A:

Table 1

Sr. No.	Ingredients	Quantity (% w/w)
1	Paliperidone Palmitate	15.07
2	Polysorbate 20	1.16

3	Citric acid monohydrate	0.48
4	Disodium hydrogen phosphate anhydrous	0.48
5	Polyethylene glycol 4000	2.90
6	Sodium dihydrogen phosphate monohydrate	0.24
7	Sodium hydroxide	0.27
8	Water for injection	Qs

Manufacturing Process:

Unmicronized Paliperidone palmitate (sterile grade) was dispersed into the polysorbate solution. The suspension was milled aseptically in the grinding chamber using Yttrium stabilized zirconium beads (1.5mm) till required particle size was reached. The suspension was filtered aseptically through a 40 micron filter into a sterilized SS container. Water for injections was transferred into a separate SS container, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, polyethylene glycol 4000 were added and mixed until dissolved. This solution was sterilized by filtration through sterile 0.22 micron filter and transferred aseptically into milled suspension. The final suspension was mixed until homogeneous. The suspension was filled aseptically into sterile syringes.

Comparative Example B:

Table 2

Sr. No.	**Ingredients**	**Quantity (% w/w)**
1	Paliperidone Palmitate	15.07
2	Polysorbate 20	1.16
3	Citric acid monohydrate	0.48
4	Disodium hydrogen phosphate	0.48

	anhydrous	
5	Polyethylene glycol 4000	2.90
6	Sodium dihydrogen phosphate monohydrate	0.24
7	Sodium hydroxide	0.27
8	Water for injection	Qs

Manufacturing Process:

Micronized Paliperidone palmitate (sterile grade) was dispersed into the polysorbate solution. The suspension was milled aseptically in the grinding chamber using Yttrium stabilized zirconium beads (1.5mm) till required particle size was reached. The suspension was filtered aseptically through a 40 micron filter into a sterilized SS container. Water for injections was transferred into a separate SS container, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, polyethylene glycol 4000 were added and mixed until dissolved. This solution was sterilized by filtration through sterile 0.22 micron filter and transferred aseptically into milled suspension. The final suspension was mixed until homogeneous. The suspension was filled aseptically into sterile syringes.

Comparative Example C:

Table 3

Sr. No.	**Ingredients**	**Quantity (% w/w)**
1	Paliperidone Palmitate	15.07
2	Polysorbate 20	1.16
3	Citric acid monohydrate	0.48
4	Disodium hydrogen phosphate anhydrous	0.48
5	Polyethylene glycol 4000	2.90

6	Sodium dihydrogen phosphate monohydrate	0.24
7	Sodium hydroxide	0.27
8	Water for injection	Qs

Manufacturing Process:

Micronized Paliperidone palmitate (sterile grade) having was dispersed into the polysorbate solution. The suspension was milled aseptically in the grinding chamber using Yttrium stabilized zirconium beads (0.3mm) till required particle size was reached. The suspension was filtered aseptically through a 40 micron filter into a sterilized SS container. Water for injections was transferred into a separate SS container, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, polyethylene glycol 4000 were added and mixed until dissolved. This solution was sterilized by filtration through sterile 0.22 micron filter and transferred aseptically into milled suspension. The final suspension was mixed until homogeneous. The suspension was filled aseptically into sterile syringes.

Example 1:

Table 4

Sr. No.	**Ingredients**	**Quantity (% w/w)**
1	Paliperidone Palmitate	15.07
2	Polysorbate 20	1.16
3	Citric acid monohydrate	0.48
4	Disodium hydrogen phosphate anhydrous	0.48
5	Polyethylene glycol 4000	2.90
6	Sodium dihydrogen phosphate monohydrate	0.24
7	Sodium hydroxide	0.27
8	Water for Injection	Qs

Manufacturing Process:

Unmicronized Paliperidone palmitate (sterile grade) was dispersed into the polysorbate solution. The suspension was milled aseptically in the grinding chamber using first milling beads (Yttrium stabilized zirconium beads) till required particle size was reached. Then the first milling beads were removed from the grinding chamber and second milling beads (Yttrium stabilized zirconium beads) were introduced. The suspension was milled aseptically in the grinding chamber using second milling beads till required particle size was reached. The suspension was filtered aseptically through a 40 micron filter into a sterilized SS container. Water for injections was transferred into a separate SS container, citric acid monohydrate, disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, polyethylene glycol 4000 were added and mixed until dissolved. This solution was sterilized by filtration through sterile 0.22 micron filter and transferred aseptically into milled suspension. The final suspension was mixed until homogeneous. The suspension was filled aseptically into sterile syringes.

Example 2:

Table 5

Sr. No.	Ingredients	Quantity (% w/w)
1	Paliperidone Palmitate	15.07
2	Polysorbate 20	1.16
3	Ethylenediaminetetraacetic acid (EDTA)	0.50
4	Disodium hydrogen phosphate anhydrous	0.48
5	Polyethylene glycol 4000	2.90
6	Sodium dihydrogen phosphate monohydrate	0.24
7	Sodium hydroxide	0.27
8	Water for Injection	Qs

Manufacturing Process:

Unmicronized Paliperidone palmitate (sterile grade) was dispersed into the polysorbate solution. The suspension was milled aseptically in the grinding chamber using first milling beads (Yttrium stabilized zirconium beads) till required particle size was reached. Then the first milling beads were removed from the grinding chamber and second milling beads (Yttrium stabilized zirconium beads) were introduced. The suspension was milled aseptically in the grinding chamber using second milling beads till required particle size was reached. The suspension was filtered aseptically through a 40 micron filter into a sterilized SS container. Water for injections was transferred into a separate SS container, ethylenediaminetetraacetic acid (EDTA), disodium hydrogen phosphate anhydrous, sodium dihydrogen phosphate monohydrate, sodium hydroxide, polyethylene glycol 4000 were added and mixed until dissolved. This solution was sterilized by filtration through sterile 0.22 micron filter and transferred aseptically into milled suspension. The final suspension was mixed until homogeneous. The suspension was filled aseptically into sterile syringes.

Example 3:

Table 6

Sr. No.	Ingredients	Quantity (% w/w)
1	Paliperidone Palmitate	15.07
2	Polysorbate 20	1.93
3	Ethylenediaminetetraacetic acid (EDTA)	0.50
4	Disodium hydrogen phosphate anhydrous	0.48
5	Polyethylene glycol 4000	2.90
6	Sodium dihydrogen phosphate monohydrate	0.24
7	Sodium hydroxide	0.27
8	Water for Injection	Qs

Manufacturing Process:

As described in Example 2.

Particle Size Data: The results for processing time and particle size as obtained are mentioned in table 7. All batches were having batch size of 160 ml.

Table 7

Feeding Material	Beads								
	Comparative Example A (1.5 mm)			0.3 mm			Example 1 (1.5 mı followed by 0.3 mı		
	Time (hr)	Size (D_{90}) in µm	polydispersity index (PDI)	Time (hr)	Size (D_{90}) in µm	polydispersity index (PDI)	Time (hr)	Size (D_{90}) in µm	polydisp index (
Unmiconized paliperidone palmitate (40 µm)	3	8	3.5	-	-	-	2	2	1.5
	Comparative Example B (1.5 mm)			Comparative Example C (0.3 mm)					
Micronized Paliperidone palmitate (6 µm)	3	6	2	1.15	2	1.5	-	-	-

CLAIMS

We claim:

1. A process for micronizing paliperidone palmitate aseptically using wet milling, said process comprising the steps of:
   a) mixing crystalline paliperidone palmitate having effective average particle size in the range of about 40 µm to about 300 µm in a sterile vehicle to form a premix;
   b) subjecting the premix of step (a) to wet milling in the presence of first milling beads having size about 1.5 mm to obtain a suspension of paliperidone palmitate with reduced effective average particle size; and
   c) subjecting the suspension formed in step (b) to wet milling in the presence of second milling beads having size about 0.3 mm to obtain suspension of micronized paliperidone palmitate having effective average particle size of less than 3 µm,
   wherein the total process is carried out in a single equipment aseptically.

2. The process of claim 1, wherein the process is carried out as a batch processing.

3. The process of claim 1, wherein the processing with first milling beads is effected for the $1/4^{th}$ to $3/4^{th}$ of the total processing time.

4. The process of claim 1, wherein the processing with second milling beads is effected for the $1/4^{th}$ to $3/4^{th}$ of the total processing time.

5. The process of claim 1, wherein the polydispersity index of the micronized paliperidone palmitate particles is below 2.5.

6. The process of claim 1, wherein the polydispersity index of the micronized paliperidone palmitate particles is below 1.8.

7. The process of claim 1, wherein the polydispersity index of the micronized paliperidone palmitate particles is about 1.5.

8. The process of claim 1, wherein the first and second milling beads are made up of material selected from zirconium oxide, yttrium-stabilized zirconium oxide, steel, ceramic material, copper, silicon carbide, porcelain, quartz, aluminum oxide, non-ferrous metal or in special cases of plastics material.

9. A process for micronizing paliperidone palmitate aseptically using wet milling, said process comprising the steps of:
a) mixing particles of paliperidone palmitate with effective average size in the range of about 40 µm to about 100 µm in a sterile vehicle to form a premix;
b) subjecting the premix of step (a) to wet milling in the presence of first milling beads having size of about 1.5 mm to obtain a suspension of paliperidone palmitate particles with reduced effective average size in the range of about 10 µm to about 39 µm; and
c) subjecting the suspension formed in step (b) to wet milling in the presence of second milling beads having size of about 0.3 mm to obtain particles of micronized paliperidone palmitate with effective average particle size of less than 3 µm,
wherein the total process is carried out in a single equipment aseptically.

10. The process of claim 1 or 9, wherein the micronized paliperidone palmitate particles have effective average particle size of less than 2.5 µm.

11. The process of claim 1 or 9, wherein the micronized paliperidone palmitate particles have effective average size is about 2.0 µm.

12. The process of claim 1 or 9, wherein the polydispersity index of the micronized paliperidone palmitate particles is below 2.0

13. The process of claim 1 or 9, wherein the polydispersity index of the micronized paliperidone palmitate particles is about 1.5.

14. The process of claim 1 or 9, wherein the 1/4th particle size reduction takes place in 2/3rd of the total processing time when compared to wet media milling by single type of milling beads as against two types of milling beads.

15. A pharmaceutical composition comprising micronized paliperidone palmitate particles having effective average particle size of less than 3 µm prepared by a process of claim 1 or 9.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/051734

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/02 A61K47/10 A61K47/12 A61K47/18
A61K47/26 A61K9/14 A61K31/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, EMBASE, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 99/30687 A1 (SMITHKLINE BEECHAM PLC [GB]; DUMPLETON DAVID ROBERT [GB]; HOLLAND SIMO) 24 June 1999 (1999-06-24) page 10, lines 15-24 page 11, lines 27-36 page 12, line 25 - page 16, line 18	1-14
X	US 2009/163519 A1 (VERMEULEN AN [BE] ET AL) 25 June 2009 (2009-06-25) cited in the application	15
Y	paragraph [0031]; example 1	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 June 2016	27/06/2016

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