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(54) **Title**: PALIPERIDONE PALMITATE PARTICLES AND COMPOSITIONS THEREOF

(57) **Abstract**: The present invention disclosed relates to Paliperidone palmitate particles, a process to manufacture the same and pharmaceutical compositions thereof. It further relates to the use of such pharmaceutical compositions in the treatment of schizophrenia, schizoaffective disorder and other related disorders.

"PALIPERIDONE PALMITATE PARTICLES AND COMPOSITIONS THEREOF"

Field of Invention:

The present invention relates to Paliperidone palmitate particles, a process to manufacture the same and pharmaceutical compositions thereof. It further relates to the use of such pharmaceutical compositions in the treatment of schizophrenia, schizoaffective disorder and other related disorders.

Background and Prior art:

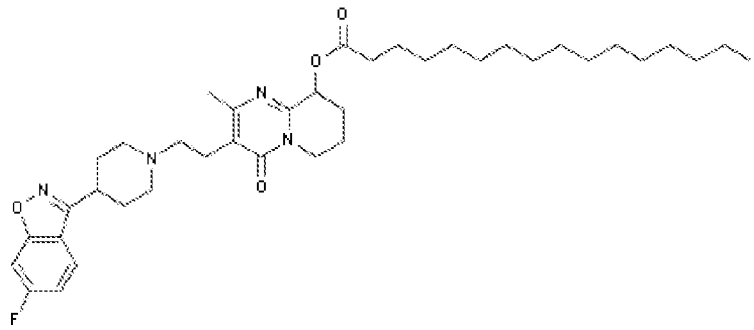
Antipsychotic medications are the most important class of drugs in the treatment of schizophrenia, schizoaffective disorder, schizophreniform disorders and the other related diseases. Conventional antipsychotics were introduced in the mid-1950s. These are the typical or first generation drugs which are usually effective in controlling the positive symptoms of schizophrenia, however are less effective in controlling the negative symptoms or the cognitive impairment associated with the disease. Atypical antipsychotics or second generation drugs, such as Risperidone and Olanzapine, were developed in the 1990s, and are generally characterized by effectiveness against both the positive and negative symptoms associated with schizophrenia. Some newer atypical antipsychotics include Amisulpride, Aripiprazole, Clozapine, Quetiapine etc.

Many patients with these mental illnesses achieve symptom stability with available oral antipsychotic medications; however, it is estimated that up to 75% have difficulty adhering to a daily oral treatment regimen, i.e. compliance problems. Problems with adherence often result in worsening of symptoms, suboptimal treatment response, frequent relapses and re-hospitalizations, and an inability to benefit from rehabilitative and psychosocial therapies.

Antipsychotic agents derived from benzioxazole include Risperidone, Iloperidone and Paliperidone. Risperidone is metabolized to 9-hydroxy-risperidone

(Paliperidone) which has a pharmacological profile and potency comparable with that of risperidone, but which has a longer elimination half-life.

Paliperidone palmitate is the palmitate ester of paliperidone (9-hydroxy-risperidone), a monoaminergic antagonist that exhibits the characteristic dopamine D_2 and serotonin (5-hydroxytryptamine type 2A) antagonism of the second-generation, atypical antipsychotic drugs. Paliperidone palmitate is hydrolyzed to Paliperidone, which is the major active metabolite of Risperidone. US6320048 is concerned with preparation of a number of novel 3-piperidinyl-1,2-benzisoxazoles having antipsychotic activity and preparation thereof. Paliperidone palmitate is the chemically known as Hexadecanoic acid 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-9-yl ester and has structure as given below.



WO94/25460 relates to a depot formulation and concerns the risperidone pamoate salt, a poorly water-soluble salt form of Risperidone, which may be suspended in a pharmaceutically acceptable carrier, such as water or an oil, and may be administered subcutaneously or intramuscularly. This salt however, has pharmacokinetic properties which are suboptimal. The release of the active ingredient from the formulations appears to be too rapid, which results in relatively high initial plasma levels and an inadequate mean duration of action, both characteristics which should be improved upon in a truly effective depot formulation.

WO95/13814 concerns sustained release formulations for parenteral

administration wherein risperidone is microencapsulated in a biocompatible, biodegradable wall-forming material (e.g. a polymer such as dl-(polylactide-co-glycolide)). The micro-encapsulated formulations have suitable pharmacokinetic properties, but require sophisticated processes of preparation in a purpose-built plant.

WO97/44039 discloses aqueous suspensions of 9-hydroxyrisperidone fatty acid esters in water, wherein the prodrug of the active ingredient is in micronized form. Unexpectedly, these formulations prove to be far too long lasting in humans to be therapeutically useful.

Extended release (ER) osmotic controlled release oral delivery (OROS) paliperidone, as a tablet formulation, is marketed in the United States (U.S.) by JANSSEN PHARMS, as Invega®, for the treatment of schizophrenia and as maintenance treatment.

Paliperidone palmitate was formulated as an aqueous nano suspension as is described in U.S. Pat. Nos. 6577545 and 6555544.

Invega Sustenna®, the innovator product of Paliperidone Palmitate marketed by Janssen Pharms is available as a white to off-white aqueous extended-release injectable suspension for intramuscular injection in dose strengths of 39 mg, 78 mg, 117 mg, 156 mg, and 234 mg paliperidone palmitate.

A 3 month long acting depot formulation, Invega Trinza® (273MG, 410MG, 546MG, and 819MG), has been recently approved by FDA. It is indicated for the treatment of the patients after they have been adequately treated with Invega Sustenna®, for at least 4 months. It is the first and only schizophrenia medication to be administered just four times a year, providing the longest dosing interval available.

EP499299 discloses nanoparticles that consist essentially of a crystalline drug substance having a surface modifier absorbed on the surface of the particles such that the effective average particle size is less than about 400 nm.

There are several methods for particle size reduction which, includes attrition, pyrolysis and hydrothermal synthesis. In attrition, macro- or micro-scale particles are ground in a ball mill, a planetary ball mill, or other size-reducing mechanism. The resulting particles are air classified to recover nanoparticles. In pyrolysis, a vaporous precursor (liquid or gas) is forced through an orifice at high pressure and are burned. The resulting solid is air classified to recover oxide particles fom by-product gases. Traditional pyrolysis often results in aggregates and agglomerates rather than single primary particles. Ultrasonic nozzle spray pyrolysis (USP) also aids in size reduction. Thus, traditionally size reduction techniques or techniques to obtain smaller particles utilize complicated processes which often are cost intensive. The use of such special machinery and other specific requirements of the process for making such particles, further add up to the cost of manufacturing the drug formulation.

Parenteral formulations are proved to be promising in the wide arena of different dosage forms. However, various attributes of the drug used and the dosage form such as particle size, cost, ease of manufacturing, sterility of the drug and the final product, patient compliance and other requirements need to be considered prior to designing a dosage form to portray it as a promising product. The technoeconomic advantage needs due consideration while manufacturing of any drug formulation.

Though many formulations are available to treat life threatening diseases such as schizophrenia, there is yet a need to develop formulations using cost effective processes, which include low cost manufacturing of the actives and involve less time consumption.

Object of the invention:

It is an object of the invention to provide a process for manufacturing Paliperidone palmitate particles.

Another object of the invention relates to a process for manufacturing Paliperidone palmitate particles, such that process results in production of sterile particles.

One another object of the invention provides a process for manufacturing Paliperidone palmitate particles, such that the process results in production of sterile particles with mean particle size less than 3000 nm.

One object of the invention relates to a process for manufacturing Paliperidone palimitate particles, which is cost effective.

Another object of the invention relates to a process for manufacturing Paliperidone palmitate particles, such that it results in generation of very low impurities.

One another object of the invention relates to a process for manufacturing Paliperidone palmitate particles, such that it results in low microbial loads.

It is an object of the invention to provide a pharmaceutical composition comprising Paliperidone Palmitate obtained by the process of the present invention.

Another object of the invention is to provide a pharmaceutical composition comprising Paliperidone palmitate obtained by the process of the present invention, optionally with one or more pharmaceutically acceptable excipients.

One another object of the invention is to provide a method of treating schizophrenia, schizoaffective disorder and other related disorders, by administering a pharmaceutical composition comprising Paliperidone Palmitate, obtained by the process of the present invention.

Another object of the present invention is to provide the use of a pharmaceutical composition comprising Paliperidone Palmitate, obtained by the process of the present invention, in the manufacture of a medicament for the treatment of schizophrenia, schizoaffective disorder and other related disorders.

One further object of the present invention is to provide a pharmaceutical composition comprising Paliperidone Palmitate obtained by the process of the present invention, for the use in treatment of schizophrenia, schizoaffective disorder and other related disorders.

Summary of the invention:

It is an aspect of the invention to provide a process for manufacturing Paliperidone palmitate particles.

Another aspect of the invention relates to a process for manufacturing Paliperidone palmitate particles, such that process results in production of sterile particles.

One aspect of the invention provides a process for manufacturing Paliperidone palmitate particles, such that the process results in production of sterile particles with mean particle size less than 3000 nm.

One aspect of the invention relates to a process for manufacturing Paliperidone palimitate particles, such that the process is cost effective.

Another aspect of the invention relates to a process for manufacturing Paliperidone palmitate particles, such that it results in generation of very low impurities.

One another aspect of the invention relates to a process for manufacturing Paliperidone palmitate particles, such that it results in low microbial loads.

It is an aspect of the invention to provide a pharmaceutical composition comprising Paliperidone Palmitate obtained by the process of the present invention.

Another aspect of the invention is to provide a pharmaceutical composition comprising Paliperidone palmitate obtained by the process of the present invention, optionally with one or more pharmaceutically acceptable excipients.

One another aspect of the invention is to provide a method of treating schizophrenia, schizoaffective disorder and other related disorders, by administering a pharmaceutical composition comprising Paliperidone Palmitate, obtained by the process of the present invention.

Another aspect of the present invention is to provide the use of a pharmaceutical composition comprising Paliperidone Palmitate, obtained by the process of the present invention, in the manufacture of a medicament for the treatment of schizophrenia, schizoaffective disorder and other related disorders.

One further aspect of the present invention is to provide a pharmaceutical composition comprising Paliperidone Palmitate obtained by the process of the present invention for the use in treatment of schizophrenia, schizoaffective disorder and other related disorders.

Brief description of the figures:

Figure 1: The figure shows the particle size distribution of the a) Paliperidone palmitate injectable suspension (Reference product) and b) the injectable suspension prepared by the process of the present invention.

Figure 2: The figure relates to the data obtained from the SEM for a) Reference product and b) Paliperidone palmitate particles obtained using the process of the invention.

Figure 3: The figure represents the XRPD of a) Paliperidone palimitate from the Reference product and b) Paliperidone palimitate prepared using the process of the present invention.

Figure 4: The figure compares the in vitro dissolution of the preparation according to the invention (Cipla) and the reference product (RLD)

Figure 5: Comparative PK profile of the formulations prepared as per the invention (T3) with that of the reference (RLD)

Detailed description of the invention:

Dosage form consideration is of utmost importance considering the mental state of the patient who suffers from psychotic disorders. To improve the patient compliance, it is also required that the medication should be affordable to the majority of the end users. Considering the cost aspect of the medication as well as the treatment, the inventors of the present invention have provided a process of manufacturing Paliperidone palmitate particles which is cost effective and can be manufactured without the requirement of any specialized equipment. The total cost of the dosage form includes the overall development cost of the product right form its inception to the distribution to the end user, which involves a number of contributory factors. Another consideration that adds up to the final cost of the product is the time required to manufacture the dosage form. More the number of

hours required to manufacture the product, more is the consumption is form of man hours, and other peripherals, resulting in the rise of the cost.

The prior art provides for preparation of depot formulations comprising Paliperidone palmitate manufactured using high energy machines such as ball milling, nano-milling, air jet milling, high pressure homogenizer and the like. There clearly exists a need to prepare these formulations using simple pharmaceutical unit operations such as mixing, filtering and filling. This invention provide a simple process for manufacturing of the drug particles and compositions thereof, such that the use of the high energy machines is not a mandate.

The present invention envisage the preparation of the Paliperidone palmitate particles which is less time consuming as compared to the prior art processes of manufacturing such particles. According to one embodiment, the invention relates to a process for manufacturing Paliperidone palmitate particles, such that process results in production of sterile particles.

The term 'sterile' with respect to the particles, as produced by the process of invention, means particles which can be formulated into an injectable or a parenteral, without any intermediate step of sterilization, such as filtration, autoclaving, radiation, or the like.

The present invention further provides a pharmaceutical composition comprising Paliperidone Palmitate obtained by the process of the present invention which would be economical, easy to manufacture, and improve patient compliance. The process of the invention encompasses the use of a solvent (s) at varying temperature. The changes is temperature of the solvent (s) result in the particle size reduction of the API.

One embodiment of the invention provides a composition comprising sterile Paliperidone palmitate particles, prepared by a process comprising the step of sudden temperature change.

'Sudden temperature change' refers to the change in the temperature of the solvent system from either hot to cold or cold to hot. According to one embodiment of the invention, the 'hot' temperature refers to a temperature above the ambient room temperature, preferably above 40 C. According to another embodiment of the invention, the 'cold' temperature refers to a temperature below the ambient room temperature up to about 60 C below freezing point of the water, i.e.; below zero degree Celsius, preferably at least 20 degrees below the freezing point of the water.

The range of the hot and cold temperature will depend upon the solvent system employed for the working of the invention.

One embodiment of the invention provides a process for manufacturing Paliperidone palmitate particles, such that the process results in production of sterile particles with mean particle size less than 3000 nm.

Another embodiment of the invention provides a composition comprising Paliperidone palmitate particles with mean particle size less than 3000 nm, made by a process comprising the steps of:

a) dissolving the drug in a warm solvent 1,
b) charging the drug solution in a another solvent 2, cooled below an appropriate temperature, and
c) filtering the particles of the drug, thus obtained,

such that the particles obtained are sterile.

The term 'mean particle size' refers to the weighted average, volume average or surfacearea average of the total representative population of the particles. The

mean particle size with reference to the instant invention can be calculated by any standard methodology. In one embodiment, the particle size determination was done using laser diffraction technique using Malvern.

The authors of the present invention, in an attempt to design a pharmaceutical composition surprisingly observed, that the particles obtained by the process as disclosed in the present invention are in form of particles within certain size limit, which is comparable to the particle size provided by the prior art processes which involve high cost, equipment and are time consuming.

The term "Paliperidone Palmitate" is used in broad sense to include its pharmaceutically acceptable derivatives thereof. Suitable pharmaceutically acceptable derivatives include pharmaceutically acceptable solvates, pharmaceutically acceptable hydrates, pharmaceutically acceptable anhydrates, pharmaceutically acceptable enantiomers, pharmaceutically acceptable esters, pharmaceutically acceptable isomers, pharmaceutically acceptable polymorphs, pharmaceutically acceptable prodrugs, pharmaceutically acceptable tautomers, pharmaceutically acceptable complexes etc.

The term "particle" used herein refers to the unit particle of Paliperidone Palmitate or granules of Paliperidone Palmitate or mixtures thereof, as obtained during the process of the present invention.One embodiment provides a process to obtain Paliperidone palmitate particles and involves the following steps:

1) Dissolving drug in a warm solvent,
2) Charging the drug solution in a another solvent, cooled below an appropriate temperature,
3) Filtering the particles of the drug, thus obtained.

Thus, this embodiment of the invention involves use of simple steps such as mixing and filtering and wherein the use of any high energy and cost intensive equipments is not a rate limiting step.

The addition of the drug solution in another solvent, according to the above process, may be done in a rate controlled manner.

Solubility of Paliperidone palmitate increases with increase in temperature of the solvent and the drug crystallizes out rapidly upon cooling.

In one embodiment, the solvent is warmed to over 40 C. Preferable temperature depends on the type of the solvent employed during the process. In one embodiment, the solvent used was warmed to 70 C- 75 C. The temperature of the solvent, which is cooled below an appropriate temperature, also depends on the type of the solvent used in the process. The solvent is preferably, cooled below the freezing point. In one embodiment of the invention, the solvent was cooled to less than 20 C below the freezing point. In another embodiment the temperature of the solvent was much lower, in the range of 20 C to 65 C, below freezing point. The cooling of the solvent may be carried out using any state of art processes.

The particle size is one of the most important parameters that need to be considered for any dosage form. The bioavailability of the drug depends on many intrinsic parameters, with particle size being one of the important ones.

The process of the invention brings about a correlation between the temperature of the solvent used and the particle size distribution of the drug

The following table 1 indicates the effect of temperature of the solvent on particle size distribution.

Table 1

Temperature (C)	**Particle size (µm)**
22-25	D10 = 7.26, D50 = 21.99, D90 = 53.22
13-15	D10 = 6.60 , D50 = 16.46 ,D90 = 35.48

0- -3	D10 = 4.96, D50 = 12.65, D90 = 28.44
-10- -35	D10 = 0.11 , D50 = 1.51 ,D90 = 3.95
-35- - 50	D10 = 0.11 , D50 = 1.50 ,D90 = 2.8

The particle size of the drug as contemplated by the present invention, also depends on the rate of cooling of the drug, as per the process of the present invention.

According to the present invention, the size of the Paliperidone palmitate particles obtained is less than 5000 nm, preferably less than 3000 nm and more preferably less than 2000 nm

The process as contemplated by the invention follows that the manufacturing of Paliperidone palmitate does not involve complicated process or costly equipment and is less time consuming.

The process of the present invention further can be carried out in reduced number of steps, enables manufacturing of the drug which is in its sterile form and further, the final dosage form in a cost effective manner.

The prior art processes need to employ sterile API, which adds up to the cost of the manufacturing of the final dosage form. The present invention, according to one of the embodiment of the invention be carried out cost effectively, using non-sterile API. The flexibility of the process of the present invention to allow the use of the non- sterile API, further reduces the cost of manufacturing the formulation, according to the invention. However, sterile API can also be used, with the process of the invention.

According to one embodiment of the invention, a process as contemplated by the invention may comprise the following steps:

a) Charging solvent (1) in a vessel,

b) Heating the solvent (1)

c) Dissolving the drug in the warm solvent (1),

d) Filtering the drug solution of the step c), through a filter,

e) Charging in another vessel, solvent (2) and cooling it,

f) Adding the filtered drug solution from the step d) to the cooled solvent of step e),

g) Filtering the precipitate drug suspension through a filter.

The solvent (1) and solvent (2) in the above process may be same or different. The solvents as used in the process as per the invention may be any polar or non-polar solvents. The polar solvents used may include but are not limited to water, ethanol, methanol, etc. or mixtures thereof. The non-polar solvents that may be used, but are not limited to benzene, toluene, hexane, pentane, octane, etc. or mixtures thereof.

The pharmacokinetic properties of the pharmaceutical compositions according to the present invention may depend to a limited extent on the physico-chemical properties of the Paliperidone palmitate particles, such as the particle size and crystal form.

The particle size for the pharmaceutical composition, according to an embodiment of the invention, is between 1- 100 um. The particle size is preferably between 1-10 um, the range of 1-5, um being the more preferred one. The pharmacokinetics properties further depend on the particle size distribution.

The following Table 2 refers to the comparison of the particle size distribution between the Reference product and one of the batches of the injectable as envisaged by the present invention, done by laser diffraction using Malvern.

Table 2

	d10 (µm)	d25 (µm)	d50 (µm)	d75 (µm)	d90 (µm)
Reference product	0.475	0.66	0.971	1.43	1.980
Batch A	0.476	0.68	1.032	1.56	2.177

The figure 1a and 1b indicates that the particle size distribution of the a) Paliperidone palmitate injectable suspension (Reference product) and b) the injectable suspension prepared by the process of the present invention are comparable.

Attributes such as the morphology and the particle size of Paliperidone palmitate obtained using the process of the present invention, were compared with that of the reference product. The figure 2a and 2b indicates these attributes are comparable.

Samples were drawn from the batches prepared according to the present invention and were tested for conversion of polymorphic form. The studies showed that the polymorphic form could be compared with that of the reference product, as seen from the figure 3a and 3b.

Further, these samples were charged on stability, to study the effect of particle size distribution.

Table 3

	D10	D25	D90
Initial	0.372	0.786	1.820
3 Days	0.375	0.787	1.790
2 weeks	0.374	0.786	1.800

Table 3 gives the particle size distribution of the Paliperidone Palmitate prepared by the process as envisaged by the present invention, charged on stability.

As per the above data there is no change in particle size distribution with reference to time. Thus, the particles obtained by the process of the invention are stable with respect to the particle size.

The term 'stable' refers to the particles obtained by the process of the invention such that there is no statistically significant change in the particle size or the particle size distribution in at least 3 days.

The term 'statistically significant' refers to the change in the particle size such that the change do not affect the dissolution or the bioavailability of the drug significantly.

The process of manufacturing of Paliperidone palmitate, as per the present invention, results in formation of low impurity levels.
The term 'low impurity levels' means that the levels of the impurities are below the detectable limits or in values comparable to that of the reference.
The following Table 4 refers to the analytical impurities comparison between the Reference product and the injectable obtained using the process of the present invention. The assay results indicates that there is no change in the purity of the drug. The profiles are comparable.

Table 4

Batch	**Related Substance (%)**							**Assay**	
	Paliperidone	Paliperidone Myristate	Paliperidone Pentadecanoate	Paliperidone Heptadecanoate	Paliperidone stearate	SMI	Total	mg	L.C. %

Reference product	BLOQ	BLOQ	BLOQ	ND	ND	BLOQ	BLOQ	154.83	99.2
Batch B	BLOQ	ND	BLOQ	BLOQ	ND	BLOQ	BLOQ	157.56	101.0

Note: LOQ is 0.1 %

BLOQ is 'Below the Limits Of Quantification'

SMI is 'Single Maximum Impurity'

Further, it has been observed that the ratio of the hot and cold solvent during the precipitation of the drug, has an impact on the particle size. In one embodiment, ethanol was used as the solvent for the preparation of the Paliperidone particles according to the invention. In general, it was found that hot: cold ethanol of 1:3 resulted in comparatively smaller particles (D90 particle size in EtOH = 2.620 µm and finished product particle size = 2.080 µm)

The following table 5 brings out the correlation between the ratio between the hot and cold ethanol used for the drug precipitation and the final particle size and particle size distribution obtained.

Table 5

Formula	**Batch Size (API)**	**Ethanol ratio**		**Total ethanol**	**Ratio of hot : Cold Ethanol**	**Temp range**	**Particle size in ethanol D(90 (µm)**	**Final formulation particle size**		
		Hot Ethanol	**Cold Ethanol**					**D(10) (µm)**	**D (50) (µm)**	**D(90) (µm)**
Reference							NA	**0.470**	**0.976**	**2.021**
A	500g	5.8 L	5.8 L	11.66 L	1:1	-61°C to -33.2°C	4.197	0.626	1.201	2.183
B	500g	2.9 L	2.9 L	5.833 L	1:1	-52°C to	4.603	0.655	1.193	2.107

						-37.2°C				
C	380g	2.2 L	6.7 L	8.86 L	1:3	-60.5°C to -39.7°C	2.620	0.492	1.013	2.080
D (Charged on stability)	79.28g	925ml	925ml	1.85 L	1:1	>-35°C to -28.3°C	3.891	0.553	1.208	2.520
E (PK batch)	79.28g	925ml	925ml	1.85 L	1:1	>-35°C to -25.9°C	3.35	0.545	1.081	2.111

The following Table 6 refers to the analytical data comparison between the Reference product and the injectable obtained using the process of the present invention, with respect to the particle size distribution and assay for the solvent content and presence of the related substances (RS). The assay results indicates the profiles are comparable.

Table 6

Batch No	**Reference**			**Test A**		
Test						
Particle size (µm)	D10	D50	D90	D10	D50	D90
PSD	0.472	0.966	1.975	0.545	1.081	2.111
ASSAY	99.2%			102.2%		
RS	BLOQ			BLOQ		
Ethanol content	ND			ND		
PEG 4000 Content mg/ml	29			30.51		

The table 7 refers to the in vitro dissolution studies conducted on the samples prepared by the process of the invention (Test) and compared with that of Reference.

Table 7

Time points (mins)	**Reference**	**Test**
1.5	15	6
5	22	13
8	25	18
10	29	21
15	34	27
20	38	32
30	46	37
45	53	48

Figure 4 compares the in vitro dissolution of the preparation according to the invention (Test) and the reference product and indicates that the values obtained are comparable.

A sample prepared according to the invention were charged on stability and the data is presented in the following table 8. The sample was found to be stable, the six month accelerated (40°C/75%RH) data showed <0.1% RS generation with assay value of 101.9%.

Table 8

Batch No.		Batch C									
API Source		Ferrer									
		Initial-reference	**Initial-Test**	**1 Month**	**3 Month**			**6 Month**			
Stability Conditions		-		40˚C/75%RH	40˚C/75%RH	30˚C/75%RH	25˚C/60%RH	40˚C/75%RH	30˚C/75%RH	25˚C/60%RH	2-8°C
Final Particle Size (µ)		1.975 µm	2.520 µm	2.939 µm	2.99 µm	3.034 µm	2.954 µm	3.013 µm	2.99 µm	2.92µm	2.92 µm
Assay		99.2%	99.5%	102%	104.6%	105.6%	103.6%	101.9%	108.2%	104.2%	103.4 %
RS		BLOQ	BLOQ	BLOQ	<0.1%	<0.1%	<0.1%	<0.1%	0.157	0.217	0.122
Dissolution	1.5 mins	15	8	6	3	4	2	5	Not Done	6	6
	5 mins	22	12	4	5	7	4	9		10	11
	8 mins	25	16	13	7	11	7	14		15	15

10 mins	29	19	15	8	14	8	17			17	18
15 mins	34	24	21	2	20	12	24			34	25
20 mins	38	28	26	15	25	16	31			29	30
30 mins	46	36	35	21	33	21	38			38	39
45 mins	53	45	43	29	43	29	48			50	52

Further, pharmacokinetic studies were conducted using the formulations made according to the invention (Test) and the data was compared with that obtained with Reference. The following table 9 gives the comparison, indicating that the values are comparable.

Table 9.

Group	T 1/2 (hr)	Tmax (hr)	Cmax (ng/ml)	AUC last (hr*µg/ml)	AUC inf (hr*µg/ml)
Reference	46.60	140.00	4638.01	796.34	816.23
Test	30.94	152.00	4086.99	715.41	723.22

Figure 5 gives the comparative PK profile of the formulations prepared as per the invention (Test) with that of the Reference. The graph indicates that the values are comparable.

Another embodiment of the invention also relates to pharmaceutical compositions comprising the Paliperidone palmitate particles manufactured using the process of the present invention.

The dosage forms envisaged under the ambit of the invention include various possible dosage forms including oral dosage forms powders for reconstitution, other dosage forms such as controlled release formulations, lyophilized formulations, modified release formulations, delayed release formulations, extended release formulations, pulsatile release formulations, dual release formulations and the like; liquid dosage form (liquids, suspensions, solutions, dispersions), transdermal preparations (ointments, creams, emulsions, microemulsions, sprays, spot-on), injection preparations etc.

The preferred dosage form of the invention is a parenteral or injection preparation.

The dosage and dosage regimen may be calculated per kg body weight. The dosage regimen may vary from a day to a month. Accordingly, the initial dosage and maintenance doses may be specified.

The route of administration may be intravenous, intramuscular or subcutaneous, or any other as per the requirement of the treatment.

Parenteral preparations may require the use of excipients such as solvents, solubility enhancers, buffering agents, tonicity adjusting agents, viscosity modifying agents, stabilizers, preservatives, etc. The selection of excipients must be such that there are added in minimum quantities and they must be compatible with the drug, i.e., they must not affect the stability, bioavailability, safety or efficacy of the active ingredients. Toxicity and undue irritation are also important factors which are to be considered.

The pharmaceutical compositions, according to the present invention, may thus further comprise a suspending agent and a wetting agent, one or more of a preservative, a buffer and an isotonizing agent. Particular ingredients may function as two or more of these agents simultaneously; e.g. behave like a preservative and a buffer, or behave like a buffer and an isotonizing agent. Suitable suspending agents for use in the aqueous suspensions according to the present invention are cellulose derivatives, e.g. methyl cellulose, sodium carboxymethyl cellulose and hydroxypropyl methyl cellulose, polyvinylpyrrolidone, alginates, chitosan, dextrans, gelatin, polyethylene glycols, polyoxyethylene- and polyoxypropylene ethers, or mixtures thereof. Suitable wetting agents for use in the aqueous suspensions according to the present invention are polyoxyethylene derivatives of sorbitan esters, e.g. polysorbate 20 and polysorbate 80, lecithin, polyoxyethylene- and polyoxypropylene ethers, sodium deoxycholate or mixtures thereof. Preservatives are antimicrobials and anti-oxidants which can be selected from the group consisting of benzoic acid, benzyl alcohol, butylated hydroxyanisole,

butylated hydroxytoluene, chlorbutol, a gallate, a hydroxybenzoate, EDTA, phenol, chlorocresol, metacresol, benzethonium chloride, myristyl-.gamma.-piccolinium chloride, phenylmercuric acetate and thimerosal. Isotonizing agents are, for example, sodium chloride, dextrose, mannitol, sorbitol, lactose, sodium sulfate. Examples of antioxidants that may also be present include, but are not limited to, acetone sodium bisulfate, ascorbate, a-tocopherol, bisulfate sodium, butylated hydroxy anisole, butylated hydroxy toluene, cystein, cysteinate HC1, dithionite sodium, gentisic acid, gentisic acid athanolamine, glutamate monosodium, formaldehyde sulfoxylate sodium, metabisulfite potassium, metabisulfite sodium, monothioglycerol, propyl gallate, sulfite sodium, tocopherol alpha, thioglycolate sodium and mixtures thereof.

Suitable buffers for use in the present invention include but are not limited to sodium phosphate, potassium phosphate, sodium hydroxide, succinate sodium, succinate disodium, sulfuric acid, tertrate sodium, tertrate acid, tromathamineor mixtures thereof.

According to another embodiment of the present invention, the pH of the formulation after reconstitution may be in the range from pH 3 to pH 8, preferably in the range from pH 5 to pH 7.5

The pharmaceutical composition, according to the present invention, comprise tonicity adjusting agents. Examples of suitable tonicity adjusting agents include, but are not limited to, magnesium sulfate, maltose, mannitol, polyethylene glycol, polylactic acid, polysorbate, potassium chloride, povidone, sodium chloride, sodium cholesteryl sulfate, sodium succinate, sodium sulfate, sorbitol, sucrose, trehalose or mixtures thereof.

Preferred according to the present invention, is the use of a mixture of disodium hydrogen phosphate (anhydrous) and sodium dihydrogen phosphate monohydrate

for rendering the solution isotonic, neutral and less prone to flocculation of the suspended ester therein.

The pharmaceutical composition, according to the present invention, may further comprise solubilizing or wetting agents at a varying concentration based on the total weight of the injectable formulation. Suitable solubilizing agents include, but are not limited to diethylene glycol monostearate, diethylene glycol monolaurate, glyceryl monostearate, polyoxyethylene sorbitol beeswax, polyethylene lauryl ether, polyoxyethylene lauryl ether, polyoxyethylene monostearate, polyoxyethylene alkyl phenol, polyethylene sorbitan monooleate, polyethylene sorbitan monolaurate, polyoxyethylene lauryl ether, potassium oleate, sorbitan tristearate, sorbitan monolaurate, sorbitan monooleate, sodium lauryl sulfate, sodium oleate, triethanolamine oleate or mixtures thereof .

The pharmaceutical composition of the present invention may optionally include one or more chelating agents. Suitable chelating agents suitable for use in the present invention include, but are not limited to calcium disodium ethylenediaminetraacetic acid (EDTA), disodium EDTA, sodium EDTA and diethylenetriaminepentaacetic acid (DTP A) etc. Citric acid, tartaric acid amino acids or mixtures thereof

Suitable viscosity modifying agents may also be included and may comprise one or more, but not limited to derivatives of sugars, such as lactose, lactose monohydrate, saccharose, hydrolyzed starch (maltodextrin) or mixtures thereof.

The pharmaceutical invention of the present invention may be formulated in exceptional circumstances as a sol-gel formulation and would comprise suitable polymer (s), as per the requirements of the formulation. The other inactives may also be included as per the requirement of the formulation.

In one embodiment of the present invention, the sol-gel formulation may include a polymer which is substantially or completely insoluble in an aqueous medium or body fluid. This thermoplastic polymer may be a homopolymer, a copolymer or a terpolymer of repeating monomelic units linked by such groups as ester, anhydride, carbonate, amide, urethane, urea, ether, esteramide, acetal, ketal, orthocarbonate and any other organic functional group that can be hydrolyzed by enzymatic or hydrolytic reaction (i.e. biodegradable by a hydrolytic reaction). The polymer may be a polyester or copolymer of hydrolytic biocompatible PEG with biodegradable polyesters, such as polylactide (PLA), polyglycolide (PGA), poly(8-caprolactone) (PCL), poly[(R)-3- hydroxybutyrate] (PHB), polyphosphazenes or block copolymers of ethylene oxide and propylene oxide polyphosphazenes, polypeptides, polysaccharides, such as chitosan, poly(trimethylene carbonate) (PTMC), acidic sulfamethazine oligomers (OSMs), basic poly(P-amino ester) (PAE), poly(amino urethane) (PAU) or poly(aminoamine) (PAA).

According to a preferred embodiment of the invention, the Paliperidone palimitate particles manufactured by the process of the invention may be used to manufacture pharmaceutical compositions that may be in powdered forms for reconstitution, in form of solutions or suspension. The powdered form obtained as per one of the embodiment of the process may be stored for reconstitution as per the requirement. It also may be dissolved in an appropriate carrier and packaged in appropriate vials.

A kit is also contemplated by this invention and the pharmaceutical composition according to the present invention may be packaged accordingly. Such a kit may comprise the powdered formulation along with a vial of appropriate carrier for reconstitution. The formulation of the invention may also be supplied as pre- filled syringes, in form of a solution/ suspension. It may also be supplied as a pre-filled syringe, wherein the powdered formulation and the carrier are filled in the syringe

but are not in direct contact with each other, until ready for use. The kit may also contain safety needles as per the requirement.

There is further provided by the present invention a method of treating schizophrenia, schizoaffective disorder and other related disorders, by administering a pharmaceutical composition comprising Paliperidone Palmitate.

The present invention further provides use of a pharmaceutical composition comprising Paliperidone Palmitate, in the manufacture of a medicament for the treatment of schizophrenia, schizoaffective disorder and other related disorders

The present invention also provides a pharmaceutical composition comprising Paliperidone Palmitate obtained by the process of the present invention for the use in treatment of schizophrenia, schizoaffective disorder and other related disorders. The following examples are intended to illustrate the invention only and is not intended in any way to construe the scope of the present invention. .

Examples:

1] Process for preparation of the particles of Paliperidone palmitate

1. Charge Ethanol into the appropriate vessel (SS vessel),
2. Heat the Ethanol to 72°-78°C,
3. Dissolve Paliperidone palmitate in the hot Ethanol solution,
4. Stir the solution of step 3 to allow for the complete dissolution of the drug,
5. Filter the drug solution of step 4 through 0.22µ PTFE filter while maintaining temperature between 72-75 degrees.
6. Separately, in another vessel charge Ethanol into the appropriate vessel (SS vessel)
7. Cool the Ethanol to -20°C - - 25°C,
8. Add filtered drug solution of step 5 to the cold ethanol of step 7 at constant flow rate and stirring,
9. Keep the temperature in the range of -20°C - - 25°C,

10. Filter the precipitate drug suspension through the 0.5 µ filter,
11. Dry the powder using nitrogen under sterile conditions.

2] Pharmaceutical composition prepared using the particles of Paliperidone palpitate manufactured according to the example 1.

Ingredients	**Range**
Paliperidone Palmitate (non- sterile API)	
Polysorbate 20	1-2.5 %
PEG 4000	1-4 %
Citric acid hydrate	0.5-1.2 %
Anhydrous disodium hydrogen phosphate	0.5- 1.2 %
Sodium dihydrogen phosphate monohydrate	0.25 -0.5 %
Sodium hydroxide	0.2-5 %
Water for Injection	q.s.

3] Pharmaceutical composition prepared using the particles of Paliperidone palmitate manufactured according to the example 1.

Ingredients	**Range**
Paliperidone Palmitate (non- sterile API)	
Polysorbate 20	1-2.5 %
Citric acid hydrate	0.5-1.2 %
Anhydrous disodium hydrogen phosphate	0.5- 1.2 %
Sodium dihydrogen phosphate monohydrate	0.25 -0.5 %
Sodium hydroxide	0.2-5 %
Water for Injection	q.s.

4] Process for preparation of the particles of Paliperidone palmitate

1. Dissolve non- sterile API and PEG 4000 in ethanol heated to 72- 75 C,
2. Filter through 0.22 u filter,
3. Add the above drug solution to ethanol cooled to -35- -50 C,
4. Filter to remove the solvents,
5. Dry the filtrate,
6. Mix the dried powder with appropriate inactive ingredients,
7. Send for PFS filling.

5] Pharmaceutical composition prepared using the particles of Paliperidone palmitate manufactured according to the example 4.

Ingredients	**Quantity (mg/mL)**
Paliperidone Palmitate	156
Polysorbate 20	12
PEG 4000	30
Citric acid monohydrate	5
Anhydrous disodium hydrogen phosphate	5
Sodium dihydrogen phosphate monohydrate	2.5
Sodium hydroxide	2.84
Water for Injection	qs

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the spirit of the invention. Thus, it should be understood that although the present invention has been specifically disclosed by the preferred embodiments and optional features, modification and variation of the concepts herein disclosed may be resorted to by those skilled in the art, and such modifications and variations are considered to be falling within the scope of the invention.

It is to be understood that the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. the use of “including,” “comprising,” or “having” and variations thereof herein is meant to encompass the items listed thereafter and equivalents thereof, as well as additional items. It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the context clearly dictates otherwise.

WE CLAIM,

1) A composition comprising Paliperidone palmitate particles with mean particle size less than 3000 nm, made by a process comprising the steps of:
   a) dissolving the drug in a warm solvent 1,
   b) charging the drug solution in a another solvent 2, cooled below an appropriate temperature, and
   c) filtering the particles of the drug, thus obtained,

such that the particles obtained are sterile.

2) The composition according to the claim 1, further comprising one or more of solvents, solubility enhancers, buffering agents, tonicity adjusting agents, viscosity modifying agents, stabilizers and preservatives.
3) A process for preparing Paliperidone particles comprising the steps of:
   a) dissolving the drug in a warm solvent 1,
   b) charging the drug solution in a another solvent 2, cooled below an appropriate temperature, and
   c) filtering the particles of the drug, thus obtained.
4) The process according to the claim 3, wherein the solvent 1 and the solvent 2 are the same.
5) The process according to the claim 3, wherein the solvent 1 and the solvent 2 are different.
6) The process according to the claim 3, wherein the solvent 1 is either polar or non-polar solvent.
7) The process according to the claim 3, wherein the solvent 2 is either polar or non-polar solvent.
8) The process according to the claims 6 and 7, wherein the polar solvents are selected from the group comprising of water, ethanol, methanol, or mixtures thereof.
9) The process according to the claims 6 and 7, wherein the non- polar solvents are selected from the group comprising of benzene, toluene, hexane, pentane, octane, or mixtures thereof.

10) A process of preparing Paliperidone particles comprising the steps of:
    a) heating ethanol to more than 70 C,
    b) dissolving Paliperidone in the warm ethanol to form a solution,
    c) filtering the drug solution through 0.22 u filter,
    d) adding the filtered drug solution to ethanol cooled to a temperature below 0 C, to obtain a suspension of the drug,
    e) filtering the precipitate.
11) The process according to the claim 10, wherein the ethanol in step a) is warmed to 72- 78 C.
12) The process according to the claim 10, wherein the ethanol in step d) is cooled to -20- -25 C.
13) The process according to the claim 10, wherein the ethanol in step d) is cooled to -35- -50 C.
14) The process according to the claim 10, wherein the Paliperidone used is sterile.
15) The process according to the claim 10, wherein the Paliperidone used is non-sterile.
16) The process according to the claim 10, wherein Paliperidone is mixed with PEG 4000, before dissolving in the warm ethanol to form a solution.
17) A composition comprising the Paliperidone particles prepared according to the claim 10, further comprising Polysorbate 20 (1-2.5 %), PEG 4000 (1-4 %), Citric acid hydrate (0.5-1.2 %), Anhydrous disodium hydrogen phosphate (0.5-1.2 %), Sodium dihydrogen phosphate monohydrate (0.25 -0.5 %), Sodium hydroxide (0.2-5 %) and water.
18) A composition comprising the Paliperidone particles prepared according to the claim 10, further comprising Polysorbate 20 (1-2.5 %), Citric acid hydrate (0.5-1.2 %), Anhydrous disodium hydrogen phosphate (0.5-1.2 %), Sodium dihydrogen phosphate monohydrate (0.25 -0.5 %), Sodium hydroxide (0.2-5 %) and water.
19) A composition prepared according to the claim 10, comprising 156 mg/ml Paliperidone Palmitate, Polysorbate 20 (12 mg/ml) PEG 4000 (30 mg/ml),

Citric acid hydrate (5 mg/ml) Anhydrous disodium hydrogen phosphate (5 mg/ml), Sodium dihydrogen phosphate monohydrate (25 mg/ml), Sodium hydroxide (2.84 mg/ml) and water.

20) The stable Paliperidone particles obtained by the process of the claim 10 having a particle size distribution

Values	**D10**	**D25**	**D90**
Particle size distribution	0.372	0.786	1.820

21) The Paliperidone particles obtained according to the claim 10, wherein the ratio of the amount of warm ethanol used in the step b) to the amount of the cold ethanol used in step d) is 1:3.

22) The Paliperidone particles obtained according to the claim 21, having D90= 2.620 µm and finished product particle size = 2.080 µm.

23) A composition comprising Paliperidone particles having low impurity levels, prepared by a process comprising the steps of:

a) heating ethanol to more than 70 C,
b) dissolving Paliperidone in the warm ethanol to form a solution,
c) filtering the drug solution through 0.22 u filter,
d) adding the filtered drug solution to ethanol cooled to a temperature below 0 C, to obtain a suspension of the drug,
e) filtering the precipitate.

24) Paliperidone particles prepared according to the claim 3 or 23, having the in vitro dissolution data as per the following table:

Time points (mins)	**Reference**	**Test**
1.5	15	6
5	22	13
8	25	18

10	29	21
15	34	27
20	38	32
30	46	37
45	53	48

25) Paliperidone particles prepared according to the claim3 or 23, having the following PK profile:

T 1/2 (hr)	**Tmax (hr)**	**Cmax (ng/ml)**	**AUC last (hr*µg/ml)**	**AUC inf (hr*µg/ml)**
30.94	152.00	4086.99	715.41	723.22

26) A compositon comprising Paliperidone particles prepared according to the claims 1, 3, 10 or 23, formulated into various possible dosage forms, including oral dosage forms powders for reconstitution, other dosage forms such as controlled release formulations, lyophilized formulations, modified release formulations, delayed release formulations, extended release formulations, pulsatile release formulations, dual release formulations and the like; liquid dosage form (liquids, suspensions, solutions, dispersions), transdermal preparations (ointments, creams, emulsions, microemulsions, sprays, spot-on), injection preparations, or sol- gel.

27) The composition according to the claim 26, wherein the dosage form is a parenteral or injection preparation.

28) The composition according to the claim 27, wherein the route of administration is intravenous, intramuscular or subcutaneous or any other as per the requirement of the treatment.

29) The composition according to the claim 28, wherein the composition further comprises one or more of solvents, solubility enhancers, buffering agents, tonicity adjusting agents, viscosity modifying agents, stabilizers and preservatives.

30) A kit comprising a composition according to the claim 29 along with a carrier for reconstitution.

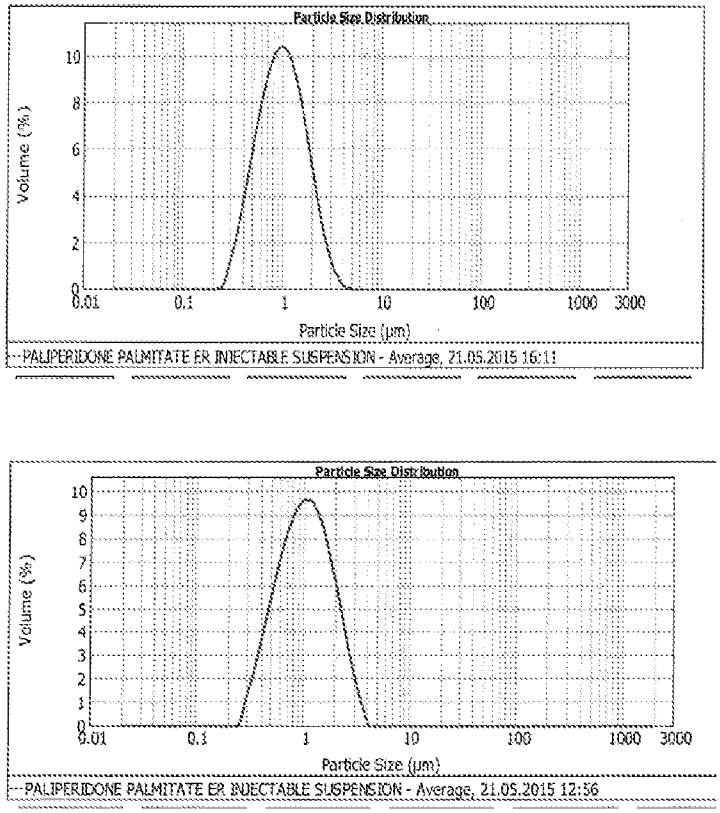
31) A kit in form of a pre-filled syringe comprising the composition according to the claim 29 in powdered form and a carrier, such that both are not in direct contact with each other.

32) A kit comprising a pre-filled syringe comprising the composition according to claim 29.

33) A composition according to the claim 29 for the treatment of schizophrenia, schizoaffective disorder and other related disorders.

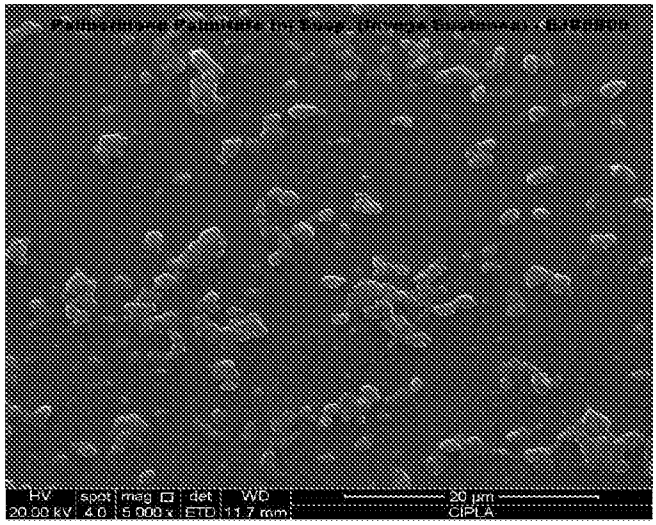
34) A process of preparing the composition according to the claim 29 for schizophrenia, schizoaffective disorder and other related disorders.

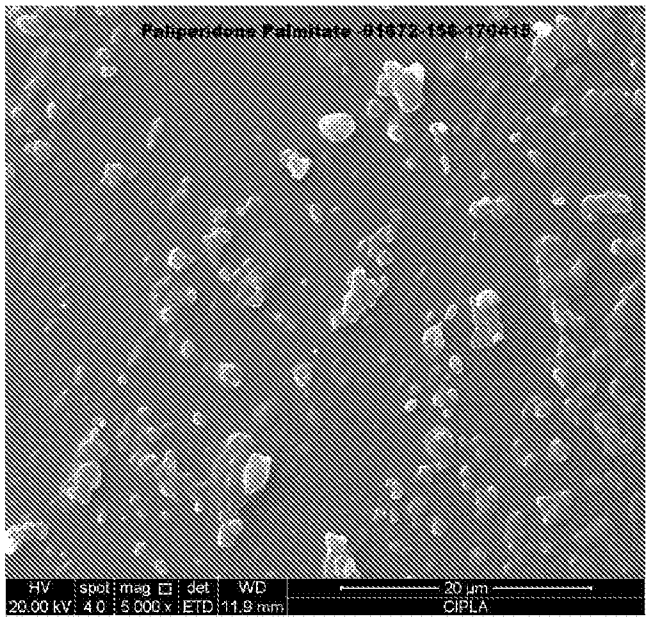
Figure 1a and 1b



The figure shows the particle size distribution of the a) Paliperidone palmitate injectable suspension (Reference product) and b) the injectable suspension prepared by the process of the present invention.

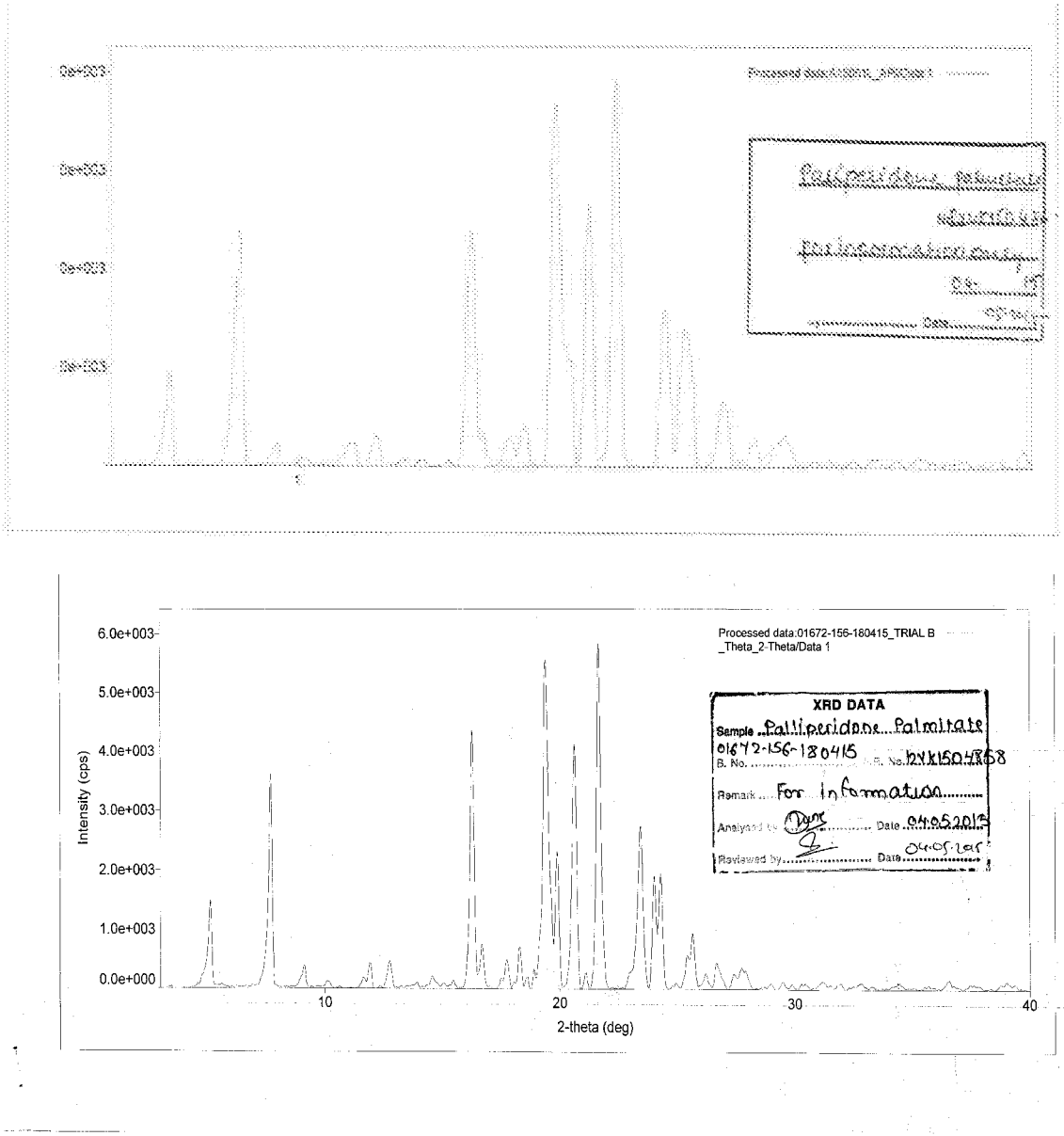
Figure 2a and 2b





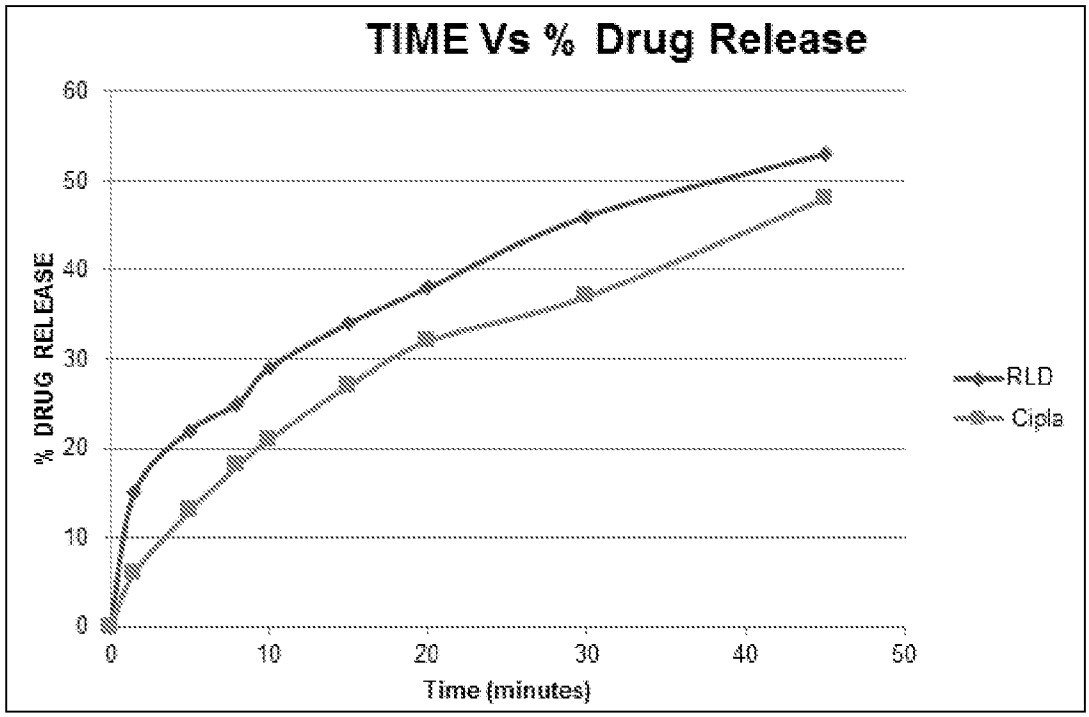
The figure relates to the data obtained from the SEM for a) Reference product and b) Paliperidone palmitate particles obtained using the process of the invention.

Figure 3a and 3b



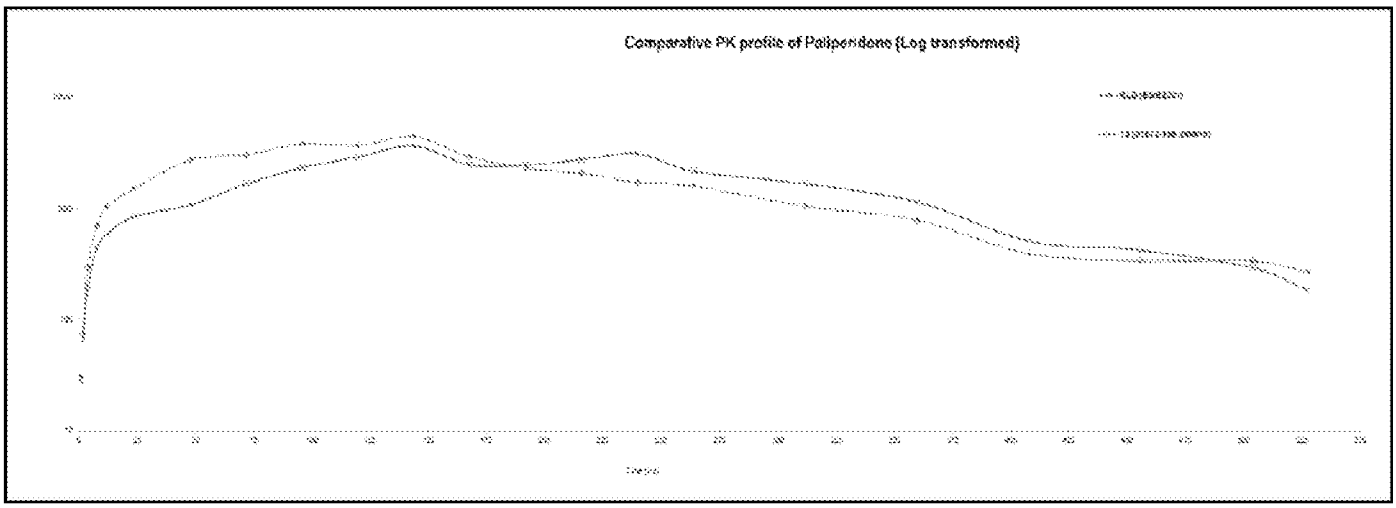
The figure represents the XRPD of a) Paliperidone palimitate from the reference product and b) Paliperidone palimitate prepared using the process of the present invention.

Figure 4



The figure compares the in vitro dissolution of the preparation according to the invention (Cipla) and the reference product (RLD)

Figure 5



Comparative PK profile of the formulations prepared as per the invention (T3) with that of the reference product (RLD).