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(54) Title: PALIPERIDONE COMPOSITION COMPRISING SOLID MATRIX PARTICLES

(57) Abstract: The present invention provides for a solid pharmaceutical composition comprising at least one solid matrix particle comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance and wherein said solid pharmaceutical composition provides for prolonged release of said active substance.

PALIPERIDONE COMPOSITION COMPRISING SOLID MATRIX PARTICLES

Field of the Invention

The present invention provides for a solid pharmaceutical composition comprising at least one solid matrix particle comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance and wherein said solid pharmaceutical composition provides for prolonged release of said active substance. The invention further relates to a process of making said solid pharmaceutical composition. Furthermore, the invention particularly relates to suitable oral formulations comprising the active substance paliperidone, using such a technology.

Background of the Invention

Schizophrenia is a chronic, severe, and disabling psychotic disorder characterized by extreme disturbances of cognition and thought, affecting language, perception and sense of self. It is a mental illness with a lifetime estimated risk of 1%.

Schizophrenia is characterized by positive symptoms (auditory hallucinations, disorganized or bizarre thoughts, delusions and irrational fears) and negative symptoms of social withdrawal, poor motivation, poverty of speech, apathy and lack of energy.

One of the key issues in schizophrenia management is adherence with treatment. It is estimated that nearly half of outpatients with schizophrenia are noncompliant or only partially compliant with their therapy during the first year after hospital discharge. The consequences of non-adherence or partial adherence in the majority of cases include relapse and re-hospitalization. Medication non-adherence is especially difficult in this population because of both behavioral (e.g., denial of disease) and cognitive (e.g., forgetting to take medication) issues.

The treatment of schizophrenia is multifactorial, with antipsychotic medications comprising a major part of treatment.

Chlorpromazine and other first-generation antipsychotics (or typical antipsychotics) antagonize the dopamine D_2-like class of receptors. Although effective against psychosis, they do not improve and may even exacerbate the negative symptoms of

schizophrenia and are associated with dose-limiting extrapyramidal symptoms (EPS). The second-generation dual-action dopamine and serotonine D_2/5-HT_{2A} receptor blockers (or atypical antipsychotics) retain the antipsychotic effect of the typical antipsychotics, but show a much reduced propensity to cause EPS, and also may improve negative symptoms of schizophrenia.

Paliperidone represents the most recent atypical antipsychotic indicated for the short- and long-term treatment of schizophrenia.

Paliperidone, a benzisoxazole derivative and the principal active metabolite of risperidone, is commonly referred to as 9-hydroxyrisperidone.

Paliperidone, the chemical name of which is (±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*pyrido[1,2-a]pyrimidin-4-one, was first disclosed in EP 0 368 388 B1.

Prolonged release formulations offer the possibility of reducing dosage regimes for drugs, especially for those drugs administered orally to patients, by prolonging the time period during which pharmacologically effective levels of the active substance are present in the body. Prolonged release formulations thereby result in a better assurance of compliance, reduction of severity and frequency of side effects, since the drug level in the blood is more constant, and drug level fluctuations associated with conventional immediate release formulations administered several times a day are avoided.

The following documents are directed to osmotic-controlled release dosage forms (formulated by using OROS drug delivery technology) that in general utilize osmotic pressure to generate a driving force for imbibing fluid into a compartment formed, at least in part, by a semipermeable membrane that permits free diffusion of fluid but not drug or osmotic agent(s), if present.

WO 2004/010981 relates to dosage forms and methods for providing a substantially ascending rate of release of paliperidone. Moreover, the patent is concerned with a dosage form comprising a capsule shaped tablet core containing a plurality of layers wherein the paliperidone is contained in at least one layer and at least one other layer

comprises a suitable fluid-expandable polymer; (b) a semipermeable membrane surrounding the capsule shaped tablet core to form a compartment having an osmotic gradient to drive fluid from an external fluid environment contacting the semipermeable membrane into the compartment; and (c) an orifice formed through the semipermeable membrane and into the capsule shaped tablet core to permit paliperidone to be released from within the compartment into the external fluid environment.

OROS dosage forms are further disclosed in the following documents WO 2005/048952, WO 2006/085856, WO 2006/101815, WO 2007/016388, WO 2007/081736, WO 2007/044234.

Disadvantages to osmotic pump dosage forms include complex manufacture and the use of harsh solvents in their preparation.

Robert Conley, et al. (Clinical spectrum of the osmotic-controlled release oral delivery system (OROS), an advanced oral delivery form, *Current medical research and opinion* 2006, *22*(10), pp. 1879-1892) describe that the OROS tablet is excreted in the faeces and this may be problematic in some patient groups, for example, schizophrenia patients, where the excretion of foreign bodies may be disturbing. Some patients, as with any oral medication, may have difficulty swallowing the tablet and this may limit its utility in this population of patients.

Summary of the Invention

An object underlying the present invention is to provide a further simplified and thus inexpensive solid pharmaceutical formulation that provides for prolonged release of the active substance paliperidone.

In contrast to the pharmaceutical formulations according to the prior art described above, the present invention relates to a solid pharmaceutical composition comprising at least one solid matrix particle comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance and wherein said solid pharmaceutical composition provides for prolonged release of said active substance. Such solid dosage forms offer the advantage of an easier scale-up, better cost-effectiveness due to lower cost of

production, no need for sophisticated equipment and less time-consuming production processes. The particles according to the present invention can be prepared by direct compression or by wet/dry/melt granulation (fluid bed or high shear granulator) which represents a very simple and easy method. Such solid dosage forms can optionally be coated.

Thus, in one aspect, the present invention provides for a solid pharmaceutical composition comprising at least one solid matrix particle comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance and wherein said solid pharmaceutical composition provides for prolonged release of said active substance.

In a second aspect, the present invention provides for a monolithic matrix system (MMS) comprising one solid matrix particle and comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance wherein the solid pharmaceutical composition provides for prolonged release of said active substance.

In a third aspect, the present invention provides for a multi particulate matrix system (MPMS) comprising at least two solid matrix particles each comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance wherein the solid pharmaceutical composition provides for prolonged release of said active substance.

In a further aspect, the present invention is directed to a process for the manufacture of a solid pharmaceutical composition comprising at least one solid matrix particle. The solid pharmaceutical composition according to the present invention is prepared by a process comprising steps selected from sieving and mixing powder ingredients, granulation of powder mixture such as dry, wet and melt granulation, compression such as direct compression of mixture of ingredients in powder form and compression of pregranulated ingredients, coating of solid matrix particles such as film and sugar coating, mixing of the respective separately obtained solid matrix particles, filling into hard capsules or sachets, film coating of capsules filled with solid matrix particles. The present invention includes any combination of the above processes.

In a further aspect the present invention relates to a process for forming a solid pharmaceutical composition comprising the step of melt granulation of a mixture

containing at least the active substance, one or more matrix forming agents and a low melting binder to obtain granules, followed by either directly incorporation of these granules into capsules or sachets, or by compressing them into tablets.

In a further aspect, the present invention provides for a solid pharmaceutical composition comprising at least one solid matrix particle comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance and wherein said solid pharmaceutical composition provides for prolonged release of said active substance, for use in the treatment of schizophrenia.

Description of the Figure

Figure 1 shows in vitro dissolution profiles of the composition of example 9 at different pH.

Detailed Description

"Active substance" in the context of this invention means paliperidone or a pharmaceutically acceptable salt thereof.

"Prolonged release" in the context of this invention means that the formulation exhibits a dissolution profile such that after 2 hours less than 30% of the active substance originally contained in a particle type is released, after 12 hours 30 to 70% of the active substance contained in a particle type is released, and after 24 hours more than 70% of the active substance contained in a particle type is released after dissolving the dosage formulation in 500 ml USP buffer pH 6.8 at 37°C in an Apparatus 2 (Ph.Eur. or USP, paddles, 50 rpm). Unless stated otherwise, all percentages given herein are by weight.

"One type of solid matrix particles" in the context of this invention means that the solid matrix particles have the same composition and approximately the same size and shape, manufacturing process and release kinetics, e.g. 2, 3 or more micro or mini tablets can be produced by the same process.

In one aspect, the present invention provides for a solid pharmaceutical composition comprising at least one solid matrix particle comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance and wherein said solid pharmaceutical composition provides for prolonged release of said active substance.

More particularly, when the solid pharmaceutical composition according to the present invention comprises one solid matrix particle said composition is named monolithic matrix system (MMS) and when the solid pharmaceutical composition according to the present invention comprises at least two solid matrix particles said composition is named multi particulate matrix system (MPMS).

In a second aspect, the present invention provides for a monolithic matrix system (MMS) comprising one solid matrix particle comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance wherein the solid pharmaceutical composition provides for prolonged release of said active substance.

The monolithic matrix system according to the present invention is in the form of a tablet wherein the tablet can be coated or uncoated. The tablet can have a diameter of 5 mm to 20 mm, preferably of 6 mm to 15 mm, more preferably of 7 mm to 13 mm. The height of this tablet is typically 1 to 15 mm, preferably 2 to 12 mm, more preferably 3 to 10 mm. The shape of such tablet can be round, oblong capsule-like, wherein the ratio of minimal to maximal diameter of such tablet is in the range of 1:2 to 1:10. The ratio between surface area and volume of the solid matrix particle is very important and is crucial for active substance release kinetics behaviour. This ratio is preferably in the range 0.2 to 5 cm^2/cm^3, more preferably 0.5 to 4 cm^2/cm^3.

In third aspect, the present invention provides for a multi particulate matrix system (MPMS) comprising at least two solid matrix particles each comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance wherein the solid pharmaceutical composition provides for prolonged release of said active substance.
At least two solid matrix particles can be the same or different in respect to size, shape, composition, manufacturing process and/or release kinetics of active substance wherein at least one type of solid matrix particles provides for prolonged release of said active substance, and wherein the solid matrix particles present in the MPMS are coated or

uncoated. The MPMS according to the present invention can be in the form of a capsule or a sachet.

The MPMS of the present invention may contain one, two, three, four or more types of solid matrix particles that differ in their compositions so as to provide for different release kinetics of the active substance and optionally other characteristics. The MPMS of the present invention may differ either in the amount of active substance contained in the respective solid matrix particle types or the types and/or amounts of excipients in the respective solid matrix particle types and/or manufacturing process used in production of such solid matrix particles types.

In a further aspect of the present invention, the two, three or more solid matrix particle types respectively differ in the amount of active substance and/or the amount of excipients contained therein, shape and/or size and/or manufacturing process used.

The kinetics of active substance release from solid matrix particle types of the MPMS can be the same or different. At least one type of solid matrix particles in the MPMS according to the present invention provides for a prolonged release of the active substance. Preferably, said at least one type of solid matrix particles providing for prolonged release is combined with other types of solid matrix particles such that the entire MPMS exhibits prolonged release.

The solid matrix particles of the MPMS of the present invention may for example be present in the form of micro or mini tablets having a diameter of 1.5 mm to 12 mm, preferably of 2 mm to 10 mm, more preferably of 3 mm to 8 mm and having the thickness of 2 mm to 10 mm, preferably 2 to 8 mm.

The number of solid matrix particles which are contained in the MPMS depends on the strength of the dosage unit and the desired particle size. The number of said solid matrix coated or uncoated particles depends on the strength of the dosage unit. This means that the size of a capsule can, within certain limits, be selected independent from the strength and number of solid matrix coated or uncoated particles contained therein, as long as the capsule can host the number of the solid matrix particles needed to provide a

certain dose. Preferably, the MPMS contains between 2 and 50 particles, more preferably between 2 and 40 particles.

In both the MMS embodiment and the MPMS embodiment of the present invention, the solid matrix particles preferably contain 0.5 to 30 w/w%, more preferably 0,8 to 15 w/w% and most preferably 1 to 8 w/w% of active substance (calculated as paliperidone).

The solid matrix particles may have the following characteristics:

Hardness:	minimal 25 N, preferably more than 30 N, more preferably more than 35 N, wherein hardness is preferably tested with a radial hardness tester Erweka MultiCheck laboratory hardness tester .
Shape:	round, oval, with or without bevelled edges, with or without imprint
Face surface:	flat or convex
Colour:	any colour is suitable, white is preferred

Preferably, the solid matrix particles consist only of the matrix containing active substance, matrix forming agent and optionally other components, and optionally one or more coatings. Preferably, the solid matrix particles are covered by a single coating layer.

Solid matrix particles of the present invention provide for the prolonged release of the active substance which is controlled by the type and the amount of the matrix forming agent. The prolonged release can be obtained according to the following principles or combinations of them:

1) by incorporation of the active substance in an insoluble and nonswelling matrix based on one or more pharmaceutically acceptable excipients insoluble and/or nonswellable in physiological fluids optionally admixed with other excipients such

as fillers, binders, disintegrating agents, water penetration enhancers, surfactants, glidants and/or lubricants.

2) by incorporation of the active substance in a swelling matrix based on one or more pharmaceutically acceptable excipients insoluble but swellable in physiological fluids optionally admixed with other excipients such as fillers, binders, disintegrating agents, water penetration enhancers, surfactants, glidants and/or lubricants.

The gastrointestinal fluid penetrates into the matrix according to the point 1 or 2 above, the active substance is dissolved and the dissolved active substance diffuses out of the matrix and is absorbed. The driving force for diffusion is the concentration of the active substance in the aqueous solution created by the penetrating GI fluid. If the matrix is the swelling matrix, e.g. crosslinked (ionic) polymer with entrapped solid active substance, the swelling kinetics of the matrix, the dissolution rate of the active substance, and the diffusion of the active substance will all contribute to the overall release rate.

3) by formulation of the active substance in a swellable and eroding matrix, based on e.g. a soluble polymer. The rate with which the active substance will be available at the absorption site is for these matrices a combination of the swelling and erosion rates of the matrix, and the dissolution and diffusion rates of the active substance.

4) release controlled by osmotic pressure, whereby a semipermeable membrane is placed around a tablet or an active substance containing particle which allows transport of water into the formulation by osmosis. In this embodiment, it is preferred that the formulation does not comprise an orifice formed through the semipermeable membrane. The "semipermeable membrane" is preferably placed around a part of a tablet, such that the tablet actually has a partial coating, with one side of the tablet not being coated but still differing from inlay tablets.

According to another aspect of the invention, the prolonged release can be obtained according to the following principles or combinations of them:

1') by incorporation of the active substance in an insoluble lipohilic matrix based on one or more pharmaceutically acceptable excipients insoluble in physiological

fluids optionally admixed with other excipients such as fillers, binders, disintegrating agents, water penetration enhancers, surfactants, glidants and/or lubricants;

2') by incorporation of the active substance in a hydrophilic matrix based on one or more pharmaceutically acceptable hydrophilic polymers capable of swelling in water and/or physiological fluids in the larger extent than microcrystalline cellulose such as Avicel type PH101, optionally admixed with other excipients such as fillers, binders, disintegrating agents, water penetration enhancers, surfactants, glidants and/or lubricants.

The gastrointestinal fluid penetrates into the matrix according to the point 1' or 2' above, the active substance is dissolved and the dissolved active substance diffuses with a controlled rate out of the matrix and is absorbed. The driving force for diffusion is the concentration of the active substance in the aqueous solution created by the penetrating GI fluid. If the matrix is the swelling matrix, e.g. crosslinked (ionic) polymer with entrapped solid active substance, the swelling kinetics of the matrix, the dissolution rate of the active substance, and the diffusion of the active substance will all contribute to the overall release rate.

The solid matrix particles can be based on hydrophilic and/or hydrophobic matrix forming agents.

In a preferred embodiment the matrix forming agent can be selected from the group consisting of excipients which swell upon contact with physiological fluids, non-swellable polymers, insoluble excipients and any combination thereof.

In a preferred embodiment, said matrix forming agent is present in an amount of 40 to 99.5 w/w%, more preferably in an amount of 60 to 98 w/w% of the matrix particles.

The excipients which swell upon contact with physiological fluids can be selected from hydroxypropylmethylcellulose of different viscosity and/or substitution grades having a viscosity of 2% solution in water (determined according to USP method) in the range of 50 to 250,000 mPas and having methoxyl group content preferably in the range of 16 to 32 w/w%, more preferably in the range of 19-32 w/w% and most preferably in the range of 19-30 w/w% and hydroxypropyl group content preferably in the range of 4 to 32

w/w%, more preferably in the range of 7-12 w/w%, hydroxypropyl cellulose e.g. Klucel HF, HXF, EF or MF types having a viscosity of 1% aqueous solution in the range of 1,000 to 4,000 mPas, hydroxypropylmethylcellulose phthalate, poly(ethyleneoxide) of molecular weight in the range of 1,000,000 to 7,000,000 e.g. Polyox WSR303), polylactic acid, xanthan gum, alginates, sodium and calcium carboxymethylcellulose, carrageenan (Carrageenan Iota, Kappa, Lambda), carbomer, carbopol (different product types e.g. Carbopol 971P, Carbopol 71G), methacrylic ester copolymers sold as Eudragit® NE, methylhydroxyethylcellulose, propylhydroxyethylcellulose, polyHEMA, methylcellulose, and other swellable polymers.

A combination of above mentioned polymers can also be used. It is for instance preferred to use hydroxypropylmethylcellulose in combination with another matrix forming agent. A preferred combination is a combination of a neutral swelling polymer with a ionic swelling polymer such as a combination of hydroxypropylmethylcellulose or hydroxypropylmethylcellulose phthalate or poly(ethyleneoxide) with an anionic polymer such as carrageenan. Such a combination of polymers can be used to achieve pH independent solubility of the active substance paliperidone, which per se (tested as pure substance) shows pH dependent solubility.

The non-swellable polymer can be selected from the group consisting of water insoluble polymers such as for example ethyl cellulose of different viscosity types having the viscosity of 5w/vol% solution in mixture of toluene and alcohol in the range of 3-100 mPas (Ethocel), cellulose acetate propionate, cellulose acetate, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1, sold as Eudragit® RS 100, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2 copolymer, commercially available as Eudragit® RL, polyvinylpyrrolidone acetate, Eudragit® RS PO, polyvinyl chloride, polyvinyl acetate, mixture of polyvinyl acetate and polyvinylpyrrolidone, commercially available as Kollidon SR or Kollicoat SR and polyethylene. It is preferred to use the above-mentioned non-swellable polymers in combination with another matrix forming agent. For polyvinylpyrrolidone combinations with matrix forming agents other than hydroxypropylmethylcellulose are particularly preferred.

The insoluble excipient is a lipidic substance and can be selected from the group consisting of fatty alcohols with 10-18 C atoms such as stearol, and palmitol, esters and ethers of fatty acids with alcohols such as glycerol, sucrose, or fatty alcohols with 10-18 C atoms in the fatty acid residue such as sucrose stearate/palmitate with HLB value of less than 6, glyceryl behenate, glyceryl tristearate or laurylstearate, waxes. It is preferred to use the insoluble excipient in combination with another matrix forming agent. In the context of the present invention, the term "insoluble" preferably refers to substances, which according to USP/ Ph. Eur. General Notice/ Solubility; are insoluble or practically insoluble, namely having a solubility of 1g substance or less in 10.000 ml of fluid. The fluid is preferably water (unless specified otherwise).

In another aspect of the invention, it is possible to use a hydrophilic matrix comprising one or more hydrophilic polymers. Preferably, the hydrophilic polymer or polymers is/are present in an amount of 40 to 99.5 w/w%, more preferably in an amount of 60 to 98 w/w% of the matrix particles.

Hydrophilic polymers can be selected from non-ionic or ionic hydrophilic polymers. Non-ionic hydrophilic polymers can be linear or crosslinked polymers having no functional groups capable of ionization at physiological pH, i.e. in the pH range 1 to 8. Nonlimiting examples of non-ionic hydrophilic polymers are hydroxypropylmethylcellulose of different viscosity and/or substitution grades having a viscosity of 2% solution in water (determined according to USP method) in the range of 50 to 250,000 mPas and having methoxyl group content preferably in the range of 16 to 32 w/w%, more preferably in the range of 19-32 w/w% and most preferably in the range of 19-30 w/w% and hydroxypropyl group content preferably in the range of 4 to 32 w/w%, more preferably in the range of 7-12 w/w%, hydroxypropyl cellulose e.g. Klucel HF, HXF, EF or MF types having a viscosity of 1% aqueous solution in the range of 1,000 to 4,000 mPas, hydroxypropylmethylcellulose phthalate, poly(ethyleneoxide) of molecular weight in the range of 1,000,000 to 7,000,000 e.g. Polyox WSR303), methacrylic ester copolymers sold as Eudragit® NE, methylhydroxyethylcellulose, propylhydroxyethylcellulose, methylcellulose, and other swellable polymers. Ionic hydrophilic polymers can be selected from anionc and/or cationic hydrophilic polymes. Nonlimiting examples of anionic hydrophilic polymers are polylactic acid, xanthan gum, alginates, sodium and calcium carboxymethylcellulose, carrageenan (Carrageenan Iota, Kappa, Lambda),

carbomer, polyHEMA, carbopol (different product types e.g. Carbopol 971P, Carbopol 71G), Example of cationic hydrophilic polymer is chitosan.

A combination of above mentioned hydrophilic polymers can also be used. It is for instance preferred to use a combination of non-ionc hydrophilic polymer such as hydroxypropylmethylcellulose or poly(ethyleneoxide) with aniononic hydrophilic polymer such as carrageenan or hydroxypropylmethylcellulose phthalate. Such a combination of polymers can be used to achieve pH independent solubility of the active substance paliperidone, which per se (tested as pure substance) shows pH dependent solubility.

In another aspect of the invention, an insoluble matrix comprising an insoluble excipient is used. Said excipient is preferably present in an amount of 40 to 99.5 w/w%, more preferably in an amount of 60 to 98 w/w% of the matrix particles.

The insoluble lipophilic matrix can be based on insoluble small molecule having molecular weigh of less than 10,000 g/mole and/or insoluble polymer or the mixture thereof. Insoluble polymer can be selected from the group consisting of water insoluble polymers such as for example ethyl cellulose of different viscosity types having the viscosity of 5w/vol% solution in mixture of toluene and alcohol in the range of 3-100 mPas (Ethocel), cellulose acetate propionate, cellulose acetate, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride)1:2:0.1, sold as Eudragit® RS 100, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2 copolymer, commercially available as Eudragit® RL, polyvinylpyrrolidone acetate, Eudragit® RS PO, polyvinyl chloride, polyvinyl acetate, mixture of polyvinyl acetate and polyvinylpyrrolidone, commercially available as Kollidon SR or Kollicoat SR and polyethylene. It is preferred to use the above-mentioned non-swellable polymers in combination with another matrix forming agent. For polyvinylpyrrolidone combinations with matrix forming agents other than hydroxypropylmethylcellulose are particularly preferred. Insoluble small molecule can be selected form esters and/or ethers of glycerole with fatty acids having 8 to 24 carbon atoms such as glyceryl behenate or glyceryl stearate, waxes such as palmitylstearate, sucrose esters with fatty acids having 8 to 24 carbon atoms and having HLB value below 6, fatty alcohols with 10 to 24 carbon atoms such as palmitol, stearol. It is preferred to

use the insoluble small molecule and/or insoluble polymer in combination with another matrix forming agent such as hydrophilic polymer.

The release rate can be additionally slowed by coating the above described solid matrix particles with modified release coating.

In a special aspect of the present invention at least one solid matrix particle can be coated with a coating having only minor effect on the release rate of an active substance from the solid matrix particle but affecting the other properties of solid matrix particles such as taste, colour, protection against water vapour sorption, protection against oxidation by oxygen from the air, easier swallowing of the solid matrix particle or the like.

Prolonged release solid matrix particles can be coated by film coatings which are in one aspect of the present invention soluble in water and are applied onto the solid matrix particles in order to improve the physical appearance of the particles such as colour, taste or smell, ease the swallowing of the particles, improve physical and chemical stability of the ingredients in the particles especially the active substance paliperidone by diminishing the permeation of water vapour and or oxygen into the core resulting in chemical degradation of ingredients especially active substance. Water soluble film coatings are applied by the processes and equipment known from the state of the art such as for example coating in perforated coating pans, Wurster fluid bed equipment by spraying the dispersion of appropriate water soluble polymer and other inactive ingredients such as pigments, plasticizers, glidants, antitacking agents in water, water miscible organic solvents, such as alcohols or ketones or mixtures thereof. Appropriate polymers can be selected from soluble viscosity types of hydroxypropylmethyl cellulose, methyl cellulose, polyvinyl alcohol, aminoalkyl methacrylate copolymers (Eudragit EPO), sodium carboxymethylcellulose or the like. Pigments can be selected from metal oxides such iron oxides, titanium oxide. The coating thickness can be in the range of 5 to 70 µm, preferably 10 to 50 µm.

In another aspect of the present invention a film coating can be applied onto the solid matrix particles in order to achieve a lag time before the start of dissolution of active substance from the solid matrix particles. Proper adjustment of lag time allows to optimize active substance absorption and consequently its plasma profile. As usual, the

term "lag time" means the time period during which less than 5% of active substance is released from the composition. The lag time is preferably determined in vitro using 500 ml of 0.1M HCl at 37°C in an Apparatus 1 – basket (Ph. Eur. or USP, 100 rpm), of the composition of the present invention. It is preferably in the range of 0.5 to 7 hours, more preferably 1 to 6 hours and most preferably 1.5 to 5 hours. Polymers for achieving lag time in dissolution can be selected from those used for gastro-resistant coatings such as hydroxypropylmethyl cellulose acetate succinate, methacrylic acid ethylacrylate copolymer, hydroxypropylmethyl cellulose acetate phthalate or the like.

Lag time can also be achieved by film coating of the solid matrix particles with polymers that swell upon contact with water and form a gel barrier that slowly erodes from the surface. Such polymers can be selected from the group consisting of methyl cellulose, hydroxypropylmethyl cellulose, methylhydroxyethyl cellulose, propylhydroxyethyl cellulose, polyethyleneoxides and other swellable polymers of higher viscosity grades. To achieve desired lag time, mixtures of different grades of polymers can be used.

Active substance release from the solid matrix particles can be further decreased by applying a prolonged release film coating based on water insoluble polymers such as ethyl cellulose, polyvinylacetate, ammonio methacrylate copolymers (Eudragit RS and/or Eudragit RL), methacrylic ester copolymers (Eudragit NE), methylmetacrylate ethylmetacrylate copolymer (Kollicoat EMM) onto solid matrix particles. Further excipients selected from plasticizers, antitacking agents, pore formers, glidants, pigments can be used in the coating. Pore formers are selected from water soluble substances having molecular weight of less than 10,000 and having solubility at least 1 g in 10 ml of water and from hydrophilic polymers such as low viscosity types of hydroxypropylmethyl cellulose (HPMC) or hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), povidone with K values of less than 50, copovidone. Plasticizers can be selected from substances capable of decreasing the glass transition point (Tg) of the water insoluble polymer such as alkyl esters of citric acid (e.g. triethylcitrate, tributylcitrate, acetildibutylcitrate), phtalates such as diethylphtalate, dibuthylphtalate, esters of glycerol with monocarboxylic acid such as triacetine, dibutylsebacate or the like. Magnesium stearate, partial esters of glycerol with fatty acids with 10 to 18 carbon atoms such as glyceryl monostearate (GMS) or talc can be selected as anti tacking

agents. Colloidal silicone dioxide can be used as glidant. The thickness of such coating can be in the range of 5 to 70 µm, preferably 10 to 50 µm.

As regards the above indications, the viscosity of ethylcellulose is measured preferably at 25°C using 5% w/v ethylcellulose dissolved in a solvent blend of 80% toluene : 20% alcohol (w/w); the viscosity of hydroxypropyl methylcellulose is preferably measured at 20°C using 2% w/w aqueous solution of hydroxypropyl methylcellulose according to the USP measuring method; and the viscosity of hydroxypropyl cellulose is preferably measured at 25°C using 1% w/w aqueous solution of hydroxypropyl cellulose. As usual, when referring to the molecular weight of a substance, the present application refers to the weight-average molecular weight, unless specified otherwise.

The active substance contained in the solid matrix particles of the MMS or the MPMS may be present in an unionized form or in the form of a salt, hydrate or solvate thereof. It may further be present in a crystalline or non-crystalline form such as a polymorphic, pseudopolymorphic or amorphous form. The term "active substance" should be understood to include any such salt, in crystalline or noncrystalline form including all polymorphic and/or solvated forms of the respective active substance. Preferably, the active substance is not microencapsulated.

The active substance paliperidone can generally be prepared by any known process such as the processes described in EP 0 368 388 B1, WO 2008/024415, WO 2008/021345.

Paliperidone used in the present invention can be in any crystalline or noncrystalline form such as for example disclosed in WO 2008/021342 and IPCOM000167996D.

As paliperidone belongs to the group of low solubility active substances, it is important that the particle size, particle shape and specific surface area of active substance are controlled. Average particle diameter of paliperidone of the present invention is in the range of 1 to 250 µm, preferably 5 to 150 µm.

The average particle diameter is determined by laser light scattering method using e.g. a Malvern-Mastersizer Apparatus MS 2000 with Isopar L as dilution medium. The average

particle diameter is determined by measuring the angular distribution of laser light scattered by a homogeneous suspension of particles.

The amount of the active substance present in the MMS or the MPMS can be 1-50 mg, preferably 1.5-30 mg and more preferably 1.5-15 mg per dosage unit.

The solid pharmaceutical composition according to the present invention can further contain any other active substance in a combination with paliperidone. Another active substance can preferably be selected from risperidone, olanzapine, venlafaxine, fluoxetine and paroxetine.
The solid matrix particle according to the present invention may, in addition to the active substance and one or more matrix forming agents, further comprise one or more pharmaceutically acceptable excipient(s). Suitable excipients are selected from the group consisting of a diluent, a binder, a disintegrant, a water penetration enhancer, a surfactant, a lubricant, a glidant and an antioxidant.

The physical characteristics of particles of incorporated excipients may have an important role in order to achieve the optimal release kinetics and processibility of the composition, especially in case of using direct compression as manufacturing method. Preferably, the incorporated excipients have an average particle size in the range of from 10 to 350 µm, more preferably from 20 to 300 µm.

In a preferred aspect the diluent can be selected from the group consisting of microcrystalline cellulose, powdered cellulose, composite materials combining crystalline cellulose with lactose (Cellactose, Tablettose), guar gum (Avicel CE15) or silicified cellulose (Prosolv), calcium hydrogen phosphate in anhydrous and hydrated form, various types of sugars such as lactose (anhydrous and monohydrate), compressible sugar, fructose, dextrates, sugar alcohols such as mannitol, sorbitol, maltitol, xylitol, lactitol, or other sugars such as saccharose, raffinose, trehalose, fructose or mixture thereof, calcium carbonate, calcium lactate or mixture thereof.

In a preferred aspect the binder can be selected from the group consisting of polyvinylpyrrolidone, microcrystalline cellulose, cellulose ether, hydroxyethylcellulose,

hydroxypropylcellulose, hydroxypropylmethylcellulose of different grades (i.e. viscosity), starch, pregelatinised starch, or polymethacrylate, or mixtures thereof.

In a preferred aspect the disintegrant can be selected from the group consisting of crospovidone, starch, pregelatinised starch, sodium starch glycollate, microcrystalline cellulose, carboxymethylcellulose sodium (CMC-Na) or calcium (CMC-Ca), cross-linked CMC-Na, polacrilin potassium, low-substituted hydroxypropylcellulose or mixtures thereof.

In a preferred aspect the water penetration enhancer can be selected from excipients soluble in physiological fluids or water characterized in that the solubility of such excipient in water at 25°C is at least 1g in 10 ml of water, preferably 1g in 5 ml of water such as carbohydrates selected from sucrose, mannitol, sorbitol, dextran, hydrophilic polymers selected from water soluble hydroxypropylmethyl cellulose (HPMC) types having the viscosity of 2% aqueous solution in the range 1 to 20 mPas, preferably 2 to 15 mPas, low viscosity types of hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), povidone and copovidone, polyvinyl alcohol, polyethyleneglycols, anorganic soluble salts such as sodium chloride characterized in that 1 g of salt is dissolved in less than 10 ml of water at 20°C.

The surfactant, if present, can be selected from the group consisting of anionic surfactants, ampholytic surfactants, nonionic surfactants and cationic surfactants.

In a preferred aspect the anionic surfactant can be selected from the group consisting of organic sulphonates (RSO_3^-) or sulphates ($ROSO_3^-$), wherein R preferably represents alkyls from C_8H_{17} to $C_{22}H_{45}$ or aromatic substituents; alkali metal or earth alkali metal sulphonates or sulphates, potassium laurate, $CH_3(CH_2)_{10}COO^-K^+$, and sodium lauryl sulphate, $CH_3(CH_2)_{11}SO_4^-Na^+$. The most preferred anionic surfactant can be sodium lauryl sulphate.

In a preferred aspect the cationic surfactant can be selected from the group consisting of organic quaternary ammonium halides, $R_4N^+Cl^-$ with R preferably representing alkyl

trimethyl ammonium chloride, wherein R preferably represents alkyls from C_8H_{17} to $C_{18}H_{37}$, e.g. dodecyl trimethyl ammoniumchloride, $C_{12}H_{25}(CH_3)_3NCl$, cetrimide, a mixture consisting of tetradecyl (about 68%), dodecyl (about 22%), and hexadecyltrimethylammonium bromides (about 7%), as well as benzalkonium chloride, a mixture of alkylbenzyldimethylammonium chlorides of the general formula $[C_6H_5CH_2N^+(CH_3)_2R]Cl^-$, wherein R represents a mixture of alkyls from C_8H_{17} to $C_{18}H_{37}$; imidazolines such as ditallow derivative quaternized with dimethyl sulphate; dialkyl dimethyl ammoniumchlorides with the alkyl groups having a chain length of 8–18 C atoms. Cationic surfactants modified by incorporating poly(ethylene oxide) chains, e.g. dodecyl methyl poly(ethylene oxide) ammonium chloride can also be used.

In a preferred aspect the ampholytic surfactant can be selected from sulfobetaines, $RN^+(CH_3)_2CH_2CH_2SO_3^-$), wherein R preferably represents alkyl groups having a chain length of 8–24C atoms, N-Dodecyl-N,N-Dimethylbetaine, $C_{12}H_{25}N^+(CH_3)_2CH_2COO^-$ or N-alkyl amino propionates having the structure $R\text{-}NHCH_2CH_2COOH$,

In a preferred aspect the nonionic surfactant can be selected from the surfactants containing hydroxyl or polyoxyethylene $(\text{-}O\text{-}CH_2CH_2\text{-})_n$ groups, and more preferably it can be selected from polyoxyethylated glycol monoethers, cetomacrogol, sorbitan esters (Spans) and polysorbates (Tweens), or from polyoxyethylene-polyoxypropylene copolymers (poloxamers), or from the group of esters such as dioctyl sulphosuccinate and/or sucrose esters with fatty acids such as sucrose stearate or the like.

In a preferred aspect the lubricant and the glidants can be selected from the group consisting of stearic acid, magnesium stearate, magnesium palmitate, magnesium oleate, hydrogenated vegetable oil, hydrogenated castor oil, talc, sodium stearyl fumarate, macrogols or mixtures thereof. A particularly preferred member of this group can be magnesium stearate.

The composition according to the present invention may further comprise one or more antioxidants selected from the group consisting of alkyl gallates (e.g. dodecyl-, ethyl-, octyl-, propyl-gallate), butylated hydroxyanisole, butylated hydroxytoluene, tocopherols

(e.g. alpha tocopherol), ascorbic acid palmitate, ascorbic acid, sodium ascorbate, potassium and sodium salts of sulphurous acid (e.g. bisulphites, metabisulphites, sulphites), flavonoides (rutin, quercetin, caffeic acid).

In a further aspect, the present invention is directed to a process for the manufacture of a solid pharmaceutical composition comprising at least one solid matrix particle as defined above. The solid pharmaceutical composition according to the present invention is prepared by a process comprising steps selected from sieving and mixing powder ingredients, granulation of powder mixture such as dry, wet and melt granulation, compression such as direct compression of mixture of ingredients in powder form and compression of pregranulated ingredients, coating of solid matrix particles such as film and sugar coating, mixing of the respective separately obtained solid matrix particles, filling into hard capsules or sachets, film coating of capsules filled with solid matrix particles. The present invention includes any combination of the above processes. In a preferred embodiment the solid pharmaceutical composition of the present invention is prepared by a process comprising steps of sieving (optionally), mixing the powdered ingredients, compression thereof to form solid matrix particles, and optionally coating of the solid matrix particles. More preferably, compression is effected in the form of direct compression. Similarly, it is more preferred to apply a film or sugar coating to the solid matrix particles. Alternatively to direct compression, the process can involve wet or dry granulation, hot melt granulation or hot melt extrusion, followed by either direct incorporation of these granules into capsules or sachets, or by compression.

"Dry granulation" means that powder components are mixed in an appropriate blender. The obtained homogenous mixture is agglomerated by roller compaction or slugging. The obtained compacts are crushed into granulate and if necessary sieved. Appropriate particle size fractions are used for manufacturing the solid pharmaceutical composition according to the present invention.

"Wet granulation" means that the powder obtained following the initial mixing of the components is granulated using proper quantities of granulation liquid. A drying step to remove the granulation liquid is necessary.

"Melt granulation" means a granulation process by which granules are obtained through the addition of either a molten binder or a solid binder which melts during the process. In the latter case the plastic properties of the binder are used. After the granulation the binder solidifies at room temperature. The obtained agglomerates can be milled and/or sieved to obtain the required particle size of granulate.

"Direct compression" involves the direct mixing of the dry components of the desired formulation, followed by a compression step to manufacture mini or micro tablets. The process does not involve the use of any liquid which may be the primary cause of instability of dosage forms and moreover requires an additional drying step to remove the granulation liquid in order to give the final dosage form. Therefore and also in view of cost aspects, direct compression is particularly preferred in this invention.

The step of direct compression, which is a preferred embodiment, includes the direct mixing of the dry components of the desired particle type, followed by a compression step to form a compact. A compact is to be understood as meaning solid matrix particle in form of a tablet having a diameter of 1 mm to 20 mm.

In a further aspect the present invention relates to a process for forming a solid pharmaceutical composition as defined above comprising the step of melt granulation of a mixture containing at least the active substance, one or more matrix forming agent and a low melting binder to obtain granules, followed by either directly incorporation of these granules into capsules or sachets, or by compressing them into tablets. Preferably, the low melting binder has a melting or softening point determined by hot stage microscopy below 150°C, preferably below 120°C and most preferably below 100°C. Preferred examples of the low melting binder include complex glycerides like Gelucire, poloxameres, sugar esters, polyethylene glycols having an average molecular weight in the range of from 1.500 to 10.000, preferably from 3.000 to 8.000, partial or full esters of fatty acids with 8 to 24 carbon atoms with mono, di or poly alcohols such as fatty alcohols with 8 to 24 carbon atoms, ethylene glycole, propylene glycole, glycerol and the like.
Further excipients selected from the group of diluent, glidants, lubricants can be used in manufacturing of granulate. The coating process of solid matrix particles is optional.

Low gas permeable primary packaging materials such as aluminium or polychloro-3-fluoroethylene homopolymer/PVC laminate can be used with the thickness in the range 10 to 40 µm in case of Al/Al blisters and 10 to 110 µm in case of Al-polychloro-3-fluoroethylene homopolymer/PVC laminate blisters. Optionally, dosage forms containing paliperidone can be packed into primary packaging with desiccant. Desiccant can be placed inside the packaging unit together with dosage units such as for example tablets and/or in the closure system or can be incorporated into the walls of the primary packaging unit.

To avoid the potential oxidative degradation of incorporated active substance and inactive ingredients susceptible to oxidative degradation, the final dosage form can be packed in primary packaging under inert atmosphere such as for example nitrogen, argon or xenon resulting in decreased concentration of oxygen in the atmosphere surrounding the dosage form in primary packaging such as for example blisters, strips, plastic or glass containers. Decreased concentration of oxygen means, that the concentration of residual oxygen in the atmosphere surrounding the individual dosage form such as for example tablet or capsule is below 10 vol/vol%, preferably below 7.5 vol/vol%, more preferably below 5 vol/vol% and most preferably below 2.5 vol/vol%.

In a further aspect, the present invention provides for a solid pharmaceutical composition comprising at least one solid matrix particle comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance and wherein said solid pharmaceutical composition provides for prolonged release of said active substance, for use in the treatment of schizophrenia and also related cns disorders such as bipolar mania, autism, insomnia, and obsessive compulsive disorder.

The following examples are to further illustrate preferred aspects of the invention without limiting it thereto.

Examples

Examples 1A/B

Manufacturing method 1A and 1B: Matrix polymers (HPMC K4M, HPMC K100LV) are mixed with paliperidone. Magnesium stearate is added and additionally mixed. Prepared tabletting mixture is tableted on tabletting machine.

Example 1A

	Amount (g)
HPMC K4M	30,71
HPMC K100LV	174,04
Paliperidone	3,15
Mg stearate	2,1
Total weight	210

Example 1B

	Amount (g)
HPMC K4M	51,19
HPMC K100LV	153,56
Paliperidone	3,15
Mg stearate	2,1
Total weight	210

Examples 2A/B

Manufacturing method 2A and 2B: Matrix polymers (HPMC K4M, HPMC K100LV) and micrcrystaline cellulose (MCC) are mixed with paliperidone. Magnesium stearate is added and additionally mixed. Prepared tabletting mixture is tableted on tabletting machine.

Example 2A

	Amount (g)
HPMC K4M	30,71
HPMC K100LV	81,9
MCC	92,13
Paliperidone	3,15
Mg stearate	2,1
Total weight	210

Example 2B

	Amount (g)
HPMC K4M	30,71
HPMC K100LV	133,09
MCC	40,95
Paliperidone	3,15
Mg stearate	2,1
Total weight	210

Examples 3A/B

Manufacturing method 3A and 3B: Matrix polymers (Xanthan, HPMC K100LV) are mixed with paliperidone. Magnesium stearate is added and additionally mixed. Prepared tabletting mixture is tableted on tabletting machine.

Example 3A

	Amount (g)
Xanthan gum	30,71
HPMC K100LV	174,04
Paliperidone	3,15
Mg stearate	2,1
Total weight	210

Example 3B

	Amount (g)
Xanthan gum	51,19
HPMC K100LV	153,56
Paliperidone	3,15
Mg stearate	2,1
Total weight	210

Example 4A/B

Manufacturing method 4A and 4B: Matrix polymers (Carrageenan iota, HPMC K4M) are mixed with paliperidone. Magnesium stearate is added and additionally mixed. Prepared tabletting mixture is tableted on tabletting machine.

Example 4A

	Amount (g)
HPMC K 4M	102,38
Carrageenan iota	102,37
Paliperidone	3,15
Mg stearate	2,1
Total weight	210

Example 4B

	Amount (g)
HPMC K 4M	153,56
Carrageenan iota	51,19
Paliperidone	3,15
Mg stearate	2,1
Total weight	210

Example 5A/B

Manufacturing method 5A and 5B: Matrix polymers (Carrageenan iota, HPMC K 100 LV) are mixed with paliperidone. Magnesium stearate is added and additionally mixed. Prepared tabletting mixture is tableted on tabletting machine.

Example 5A

	Amount (g)
HPMC K 100 LV	153,56
Carrageenan iota	51,19
Paliperidone	3,15
Mg stearate	2,1
Total weight	210

Example 5B

	Amount (g)
Xanthan	153,56
Carrageenan iota	51,19
Paliperidone	3,15
Mg stearate	2,1
Total weight	210

Example 6A

Paliperidone, Sodium Lauryl Sulphate, Eudragit RS PO, HPMC K4M, Kollidon SR, Klucel EF, Magnesium stearate and Talc in the amounts as indicated below were sieved through a 20 mesh sieve and mixed for an appropriate time period until a uniform mixture was formed. The resulting mixture was compressed using a rotary tabletting machine to give mini tablets (5 mm punches were used). For administration, these 2 mini tablets of 50 mg were filled into gelatine capsules of size 2.

	Amount (g)
Carbopol 971P	20,0
Sodium Laurylsulphate	12,8
Eudragit RS PO	39,5
HPMC K4M	115,3
Klucel EF	6,0
Paliperidone	6,3
Mg stearate	2,1
Talc	8,0
Total weight	210

Example 6B

Paliperidone, Sodium Lauryl Sulphate, PEG6000, Polyox WSR303, BHT, Klucel EF, Magnesium stearate and Talc in the amounts as indicated below were sieved through a 20 mesh sieve and mixed for an appropriate time period until a uniform mixture was formed. The resulting mixture was compressed using a rotary tabletting machine to give mini tablets (5 mm punches were used). For administration, these 2 mini tablets of 50 mg were filled into gelatine capsules of size 2.

	Amount (g)
Polyox WSR 303	163,8
Sodium Laurylsulphate	12,8
PEG 6000	10,0
BHT	1,0
Klucel EF	6,0
Paliperidone	6,3
Mg stearate	2,1

Talc	8,0
Total weight	210

Example 7

Solid matrix particle	
	Amount(mg)
Paliperidone	3
HPMC K 100 LV	100
HPMC K 100 M	45,5
Carrageenan lambda (GP-209 NF)	48,5
MCC (Avicel PH 200)	49,25
Magnesium stearate	3,75
Modified release coating	
Methylcellulose	30
PEG 6000	4,5
Talc	30
Purified water	qs

Solid matrix particle

1. Paliperidone is mixed with a part of HPMC. Other ingredients are added and mixed.
2. Obtained mixture is compressed on a rotary tablet press to obtain tablet cores.

Modified release coating

1. Methyl Cellulose (MC) is dissolved in a part of purified water.
2. Talc is suspended in a part of purified water.
3. Talc suspension is added to the suspension of MC.
4. Suspension obtained in Step 3 is sprayed onto tablet cores in a pan coater.

Example 8

Solid matrix particle	
	Amount(mg)
Paliperidone	3
Polyox WSR 303 (Poly Ethyleneoxide	182,75
Carrageenan lambda (GP-209 NF)	48,5
MCC (Avicel PH 200)	12,0
Magnesium stearate	3,75
Modified release coating	
Methylcellulose	30
PEG 6000	4,5
Talc	30
Purified water	qs

Solid matrix particle

1. Paliperidone is mixed with Carrageenan. Other ingredients are added and mixed.
2. Obtained mixture is compressed on a rotary tablet press to obtain tablet cores.

Modified release coating

1. Methyl Cellulose (MC) is dissolved in a part of purified water.
2. Talc is suspended in a part of purified water.
3. Talc suspension is added to the suspension of MC.
4. Suspension obtained in Step 3 is sprayed onto tablet cores in a pan coater.

Example 9

Solid matrix particle	
	Amount(mg)
Paliperidone	3
Polyox WSR 303 (Poly Ethyleneoxide	193,19
Carrageenan lambda (GP-209 NF)	50,0
Butylhydroxytoluene	0,1
Magnesium stearate	3,75
Modified release coating	
Methylcellulose	30
PEG 6000	4,5
Talc	30
Purified water	qs

Solid matrix particle

1. Paliperidone is mixed with Carrageenan. Other ingredients are added and mixed.
2. Obtained mixture is compressed on a rotary tablet press to obtain tablet cores.

Modified release coating

1. Methyl Cellulose (MC) is dissolved in a part of purified water.
2. Talc is suspended in a part of purified water.
3. Talc suspension is added to the suspension of MC.
4. Suspension obtained in Step 3 is sprayed onto tablet cores in a pan coater.

The in vitro dissolution profile of the sample obtained according to this example is determined at varying pH. The results of these dissolution studies are shown in Figure 1. The pharmaceutical composition of Example 9 exhibits similar in vitro dissolution profiles obtained after being submerged in different pH media (pH 1.0, pH 2.0, pH 3.0, pH 5.5, pH 6.0) at 37°C in an Apparatus 1 – basket (Ph. Eur. or USP, 100 rpm, 500 mL).

The drug release is pH independent if dissolution profiles in media with different pH values do not differ more than 20% in each time point, which is shown in Figure 1 for the pH range of 1.2-6.0.

Claims

1. A solid pharmaceutical composition comprising at least one solid matrix particle comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance and wherein said solid pharmaceutical composition provides for prolonged release of said active substance.

2. A pharmaceutical composition, which is a monolithic matrix system (MMS), comprising one solid matrix particle and comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance wherein the solid pharmaceutical composition provides for prolonged release of said active substance.

3. A pharmaceutical composition, which is a multi particulate matrix system (MPMS), comprising at least two solid matrix particles each comprising paliperidone or a pharmaceutically acceptable salt thereof as an active substance wherein the solid pharmaceutical composition provides for prolonged release of said active substance.

4. The solid pharmaceutical composition according to claims 1 to 3, characterized in that solid matrix particle comprises an active substance and one or more matrix forming agents selected from the group consisting of excipients which swell upon contact with physiological fluids, non-swellable polymers, insoluble excipients and any combinations thereof.

5. The solid pharmaceutical composition according to claim 4, characterized in that the active substance is paliperidone.

6. The pharmaceutical composition according to any one of claims 1 to 5, wherein the pharmaceutical composition comprises a matrix forming agent selected from hydroxypropylmethylcellulose, preferably having viscosity and/or substitution grades such that viscosity of 2% solution in water (determined according to USP method) is in the range of 50 to 250,000 mPas and having methoxyl group content preferably in the range of 16 to 32 w/w%, hydroxypropyl cellulose, hydroxypropylmethylcellulose phthalate, poly(ethyleneoxide) preferably of molecular weight in the range of 1,000,000 to 7,000,000 e.g. Polyox WSR303), polylactic acid, xanthan gum, alginates, sodium and

calcium carboxymethylcellulose, carrageenan (Carrageenan Iota, Kappa, Lambda), carbomer, carbopol, methacrylic ester copolymers sold as Eudragit® NE, methylhydroxyethylcellulose, propylhydroxyethylcellulose, polyHEMA, methylcellulose, ethyl cellulose, preferably of a viscosity of 5w/vol% solution in mixture of toluene and alcohol in the range of 3-100 mPas (Ethocel), cellulose acetate propionate, cellulose acetate, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1, sold as Eudragit® RS 100, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2 copolymer, commercially available as Eudragit® RL, polyvinylpyrrolidone acetate, Eudragit® RS PO, polyvinyl chloride, polyvinyl acetate, mixture of polyvinyl acetate and polyvinylpyrrolidone, commercially available as Kollidon SR or Kollicoat SR, polyethylene, fatty alcohols with 10-18 C atoms, esters and ethers of fatty acids with alcohols such as glycerol, sucrose, or fatty alcohols with 10-18 C atoms in the fatty acid residue, waxes.

7. The pharmaceutical composition according to claim 6, wherein the matrix forming agent is selected from HPMC, carrageenan, and polyethylene oxide.

8. The pharmaceutical composition according to any one of claims 1 to 5, wherein the pharmaceutical composition comprises a matrix forming agent selected from methyl acrylate, methyl methacrylate and methacrylic acid, commercially available as Eudragit FS; copolymers based on methacrylic acid and methyl methacrylate, commercially available as Eudragit S and Eudragit L, carbomer, carbopol (different product types e.g. Carbopol 971P, Carbopol 71G), hydroxypropylmethyl cellulose acetate phtalate, hydroxypropylmethyl cellulose acetate succinate, Carmellose sodium, xanthane, carrageenan, alginates, and polyvinyl acetate phthalate.

9. The pharmaceutical composition according to claim 8, wherein the matrix forming agent furthermore comprises a polymer that does not carry ionic charges, such that the matrix forming agent is preferably a combination of hydroxypropylmethylcellulose or poly(ethyleneoxide) with an anionic polymer such as carrageenan or hydroxypropylmethylcellulose phthalate.

10. The pharmaceutical composition according to any one of claims 1 to 5, wherein the solid matrix particle comprises a hydrophilic matrix comprising one or more hydrophilic polymers.

11. The pharmaceutical composition according to claim 10, wherein the hydrophilic polymers are selected from non-ionic or ionic hydrophilic polymers, wherein the non-ionic hydrophilic polymers can be linear or crosslinked polymers having no functional groups capable of ionization at physiological pH, i.e. in the pH range 1 to 8, such as hydroxypropylmethylcellulose, preferably having a viscosity of 2% solution in water (determined according to USP method) in the range of 50 to 250,000 mPas and having methoxyl group content preferably in the range of 16 to 32 w/w%, hydroxypropyl cellulose preferably having a viscosity of 1% aqueous solution in the range of 1,000 to 4,000 mPas, hydroxypropylmethylcellulose phthalate, poly(ethyleneoxide) of molecular. weight in the range of 1,000,000 to 7,000,000 (e.g. Polyox WSR303), methacrylic ester copolymers sold as Eudragit® NE, methylhydroxyethylcellulose, propylhydroxyethylcellulose, methylcellulose, and other swellable polymers, and wherein the ionic hydrophilic polymers can be selected from anionic and/or cationic hydrophilic polymers such as polylactic acid, xanthan gum, alginates, sodium and calcium carboxymethylcellulose, carrageenan (Carrageenan Iota, Kappa, Lambda), carbomer, polyHEMA, carbopol (different product types e.g. Carbopol 971P, Carbopol 71G) and chitosan.

12. The pharmaceutical composition according to claim 11, wherein the hydrophilic matrix is preferably a combination of non-ionc hydrophilic polymer such as hydroxypropylmethylcellulose or poly(ethyleneoxide) with anionononic hydrophilic polymer such as carrageenan or hydroxypropylmethylcellulose phthalate.

13. The pharmaceutical composition according to any one of claims 1 to 5, wherein the pharmaceutical composition comprises an insoluble matrix comprising an insoluble excipient

14. The pharmaceutical composition according to claim 13, wherein the insoluble matrix comprises one or more insoluble small molecules having molecular weight of less than 10,000 g/mole and/or one or more insoluble polymers or a mixture thereof.

15. The pharmaceutical composition according to any one of claims 13 and 14, wherein the insoluble polymer is selected from the group consisting of water insoluble polymers such as for example ethyl cellulose of different viscosity types preferably having the viscosity of 5 w/vol% solution in mixture of toluene and alcohol in the range of 3-100 mPas (Ethocel), cellulose acetate propionate, cellulose acetate, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1, sold as Eudragit® RS 100, poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2 copolymer, commercially available as Eudragit® RL, polyvinylpyrrolidone acetate, Eudragit® RS PO, polyvinyl chloride, polyvinyl acetate, mixture of polyvinyl acetate and polyvinylpyrrolidone, commercially available as Kollidon SR or Kollicoat SR and polyethylene.

16. The pharmaceutical composition according to any one of claims 13 to 15, wherein the insoluble small molecule is selected form esters and/or ethers of glycerol with fatty acids having 8 to 24 carbon atoms such as glyceryl behenate or glyceryl stearate, waxes such as palmitylstearate, sucrose esters with fatty acids having 8 to 24 carbon atoms and having HLB value below 6, fatty alcohols with 10 to 24 carbon atoms such as palmitol, stearol.

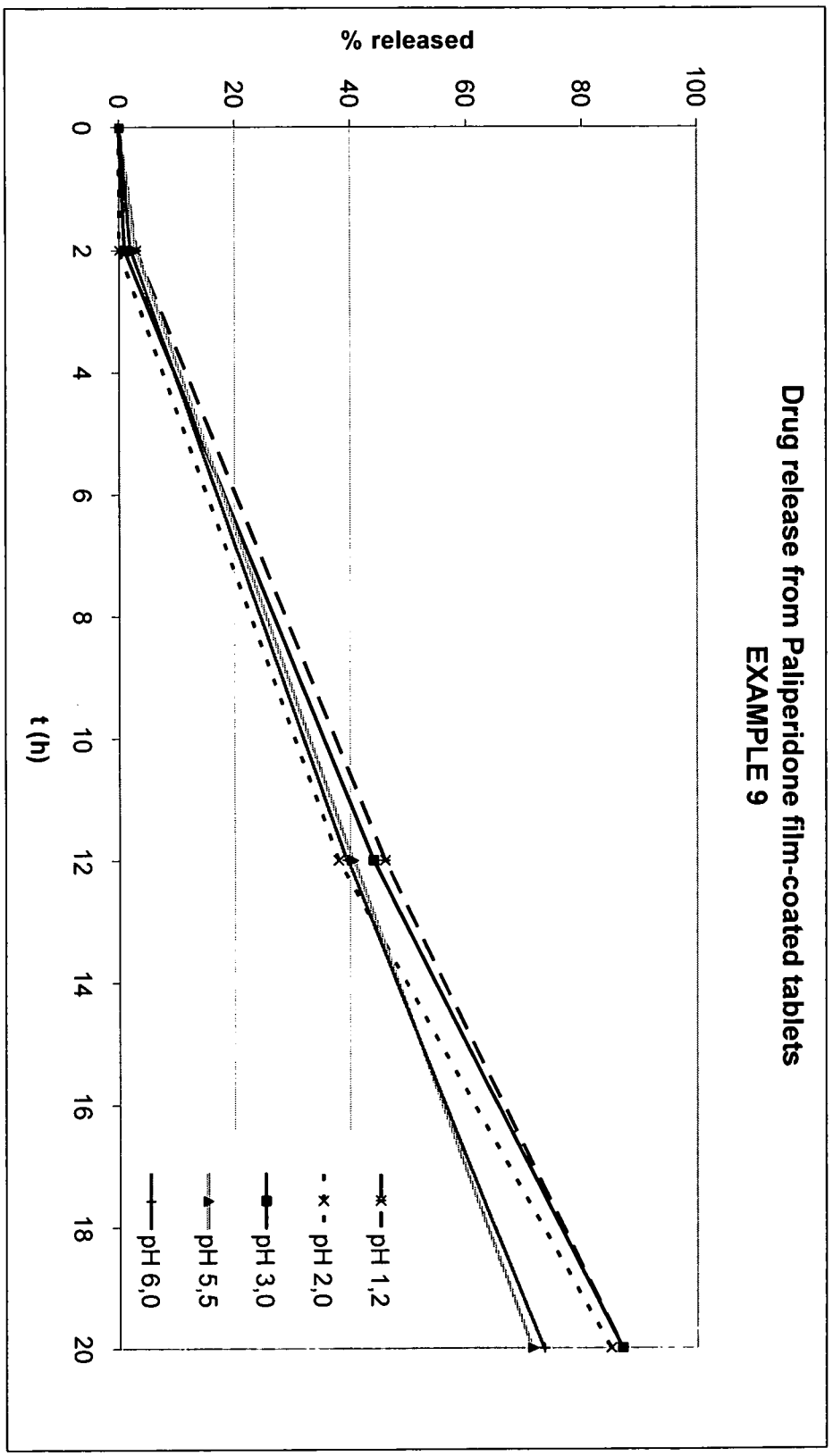
17. The pharmaceutical composition according to any one of claims 13 to 16, wherein the insoluble polymers and/or insoluble small molecule are present in combination with another matrix forming agent, such as polyvinylpyrrolidone in combination with a matrix forming agent such as hydrophilic polymer, preferably other than hydroxypropylmethylcellulose.

18. A process for the manufacture of a solid pharmaceutical composition according to claims 1-17, characterized in that said process comprises steps selected from sieving and mixing powder ingredients, granulation of powder mixture, compression, coating of solid matrix particles, mixing of the respective separately obtained solid matrix particles, filling into hard capsules or sachets, film coating of capsules filled with solid matrix particles and any combinations thereof.

19. A process for forming a solid pharmaceutical composition according to claims 1-17, comprising the steps of melt granulation of a mixture containing at least an active substance, one or more matrix forming agents and a low melting binder to obtain granules, followed by either direct incorporation of the granules into capsules or sachets, or by compressing them into tablets.

20. The solid pharmaceutical composition according to claims 1-17 for use in the treatment of schizophrenia.

Figure 1


Drug release from Paliperidone film-coated tablets
EXAMPLE 9
% released
0
20
40
60
80
100
t (h)
0
2
4
6
8
10
12
14
16
18
20
pH 1,2
pH 2,0
pH 3,0
pH 5,5
pH 6,0

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/005427

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/22 A61K9/28 A61K9/48 A61K31/517

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 practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 2006/189635 A1 (KRAMER MICHELLE [US] ET AL) 24 August 2006 (2006-08-24) examples 6-10,17-19	1-20
X	US 2006/034927 A1 (CASADEVALL GEMMA [ES] ET AL) 16 February 2006 (2006-02-16) example 3	1-20
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 November 2009	17/11/2009

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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