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(54) **Title:** PHARMACEUTICAL COMPOSITIONS

(57) **Abstract:** There are provided pharmaceutically-acceptable compositions suitable for peroral administration to the gastrointestinal tract, in which an antipsychotic, or a pharmaceutically-acceptable salt thereof, is dissolved and/or dispersed in at least one $C_{8-22}$ fatty acid, such as oleic acid or myristic acid. The dosage forms are useful in the treatment of a variety of psychotic conditions, such as schizophrenia, bipolar disorder and ADHD.

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# PHARMACEUTICAL COMPOSITIONS

This invention relates to new pharmaceutical compositions containing antipsychotics, also known as neuroleptics or major tranquilizers that are useful in the treatment of *inter alia* psychoses including but not limited to delusions, hallucinations, paranoia or disordered thought in, for instance, schizophrenia or bipolar disorder, which compositions may be abuse-resistant.

## Prior Art and Background

The listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or common general knowledge.

Antipsychotics are often classified as "first-generation" and "second-generation" antipsychotics. The original classification of antipsychotics according to their chemical structure is still used for first-generation antipsychotics. Second-generation are often further classified according to their pharmacodynamic properties, which reflect their affinities for specific receptors.

First-generation antipsychotics are also called "typical" antipsychotics (TAAs) or conventional antipsychotics. In particular, when referring to TAAs as first-generation antipsychotics there is a further classification of "low potency" first-generation antipsychotics and "high potency" antipsychotics. Low potency first-generation antipsychotics include substances such as chlorpromazine, prochlorperazine, thioridazine and the like. Often TAAs such as haloperidol, loxapine, thioridazine or perphenazine and the like have a high risk of side effects. Common side effects include but are not limited to dry mouth, muscle stiffness, muscle cramping, tremors, extrapyramidal symptoms (EPS) and weight gain. EPS, also known as extrapyramidal side effects (EPSE), are drug-induced movement disorders that include acute and tardive symptoms. These symptoms comprise dystonia, akathisia, parkinsonism, bradykinesiam, tremor and tardive dyskinesia (TD). The occurrence of orthostatic hypotension in patients taking anti-psychotic drugs is also common. These side effects are believed to be caused by blockage of the dopaminergic neurotransmission by the administered neuroleptics.

First-generation antipsychotics block dopamine 2 (D2) receptors. There are four dopamine pathways in the brain, namely the mesocorticol pathway, the mesolimbic

pathway, the nigrostriatal pathway and the tuberoinfundibular pathways. When postsynaptic dopamine 2 receptors are blocked by D2 antagonists acting in the mesocorticol dopamine pathway, this can cause emotional blunting and cognitive problems that mimic the negative symptoms of schizophrenia such as blunting of affect, poverty of speech and thought, apathy, anhedonia, reduced social drive, loss of motivation, lack of social interest, and inattention to social or cognitive input. When postsynaptic dopamine 2 receptors are blocked by D2 antagonists acting in the nigrostriatal pathway, it produces disorders of movement, which can appear very much like those in Parkinson's disease. When postsynaptic dopamine 2 receptors are blocked by D2 antagonists acting in the tuberoinfundibular pathway, prolactin levels rise, sometimes so much so that women may begin lactating inappropriately, a condition known as galactorrhea.

The therapeutic actions of first-generation are due to blockage of dopamine 2 (D2) receptors specifically in the mesolimbic dopamine pathway. This has the effect of reducing hyperactivity in this pathway that is postulated to cause the positive symptoms of psychosis such as delusions, hallucinations and disorganized speech or behaviour. A problem associated with first-generation antipsychotics is that they often block all four pathways.

In addition to blocking D2 receptors in all four dopamine pathways, first-generation antipsychotics may also block muscarinic cholinergic receptors. Dopamine normally suppresses acetylcholine activity; if dopamine receptors are blocked, acetylcholine becomes overly active. Thus, first-generation antipsychotics that cause fewer EPS generally have stronger anticholinergic properties.

Second-generation antipsychotic drugs are also known as "atypical" antipsychotics (AAAs) and generally have a lower incidence of side effects compared to typical antipsychotics. Examples of atypical antipsychotic drugs are clozapine, asenapine, olanzapine, quetiapine, paliperidone, risperidone, fluphenazine, haloperidol, pimozide, thiothixene and the like. AAAs generally possess a therapeutic profile exhibiting greatly reduced Parkinson-like side effects.

There are at least four different classes of atypical antipsychotics based on their pharmacodynamic properties. Serotonin-dopamine antagonists (SDA) are atypical antipsychotics with a high selectivity for serotonin 5-$HT_{2A}$ receptors and dopamine $D_2$ receptors (and also $\alpha_1$-adrenoceptors). Multi-acting receptor-targeted antipsychotics (MARTA) comprise drugs showing an affinity for 5-$HT_{2A}$, $D_2$ and receptors of other

systems (cholinergic, histaminergic, 5-$HT_{1A}$, 5-$HT_{2c}$ and others). $D_2/D_3$ receptors comprise drugs that preferentially block $D_2$ and $D_3$ subtypes of the $D_2$-like receptors. Yet another class are partial dopamine receptor agonists comprising partial agonist at dopamine $D_2$ receptors acting as a functional antagonist in the mesolimbic dopamine pathway, but showing functional agonist activity in the mesocortical pathway, optionally also avoiding the complete blockade of the nigrostriatal or tuberoinfundibular pathways, associated with extrapyramidal symptoms (EPS) and elevated prolactin levels, respectively.

Schizophrenia and bipolar disorder are generally treated by the administration antipsychotic drugs, including both typical antipsychotics and atypical antipsychotics. Patients suffering from attention deficit hyperactivity disorder (ADHD) are often prescribed atypical antipsychotics. Risperidone, which is a SDA, has been reported in connection with ADHD.

Treatment of psychosis is very difficult. Patients cannot in general be relied upon to follow dosing instructions. It has also that the risk for relapse can substantially increase with noncompliant patients. Therefore, less complicated dosing and less frequent dosing is advantageous. Long-acting medications, e.g., antipsychotic medications, have several advantages over short- acting oral tablets or IM agents when administered, e.g., for the treatment of chronic schizophrenia and/or bipolar disorder, e.g., assurance of compliance resulting in fewer relapses and re-hospitalizations. By contrast, some of the current long-acting products (e.g., Risperdal Consta® long-acting injection) requires supplementation, e.g. with oral risperidone, both at the initiation of intramuscular dosing and in the event of a missed dose, due to a 3-week lag between the time of dose administration and initiation of drug release.

All currently approved or development-stage, long-acting injections of antipsychotic drugs are administered intramuscularly, which is associated with the disadvantages of injection site pain and, for this class of drug, the more significant potential safety issue of inadvertent vascular contact resulting in systemic exposure of toxic levels of drug. This issue was most recently manifest during the development of Zyprexa® (olanzapine) long-acting-injection in which excessive sedation and even incidences of coma have been observed post injection. In contrast, dosage forms that have the potential for subcutaneous (SC) administration mitigate this potential safety issue.

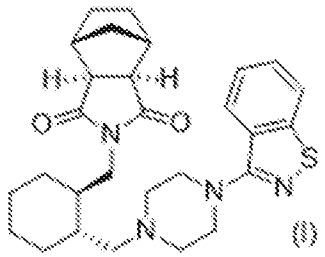
Compositions that provide controlled delivery of pharmaceutical active agent offer several advantages. For instance, controlled delivery can reduce or obviate the need

for repeated dosing. Further, biodegradable matrices for drug delivery are useful because they obviate the need to remove a drug-depleted device.

Psychoactive substances often bring about subjective (although these may be objectively observed) changes in consciousness and mood that the user may find rewarding and pleasant (e.g., euphoria or a sense of relaxation) or advantageous (e.g. increased alertness) and are thus reinforcing. Substances which are both rewarding and positively reinforcing have the potential to induce a state of addiction; compulsive drug use despite negative consequences.

Psychoactive drug misuse, dependence and addiction have resulted in legal measures and moral debate. Governmental controls on manufacture, supply and prescription attempt to reduce problematic medical drug use. Ethical concerns have also been raised about over-use of these drugs clinically, and about their marketing by manufacturers.

Lurasidone (chemical name: (3aR,4S,7R,7aS)-2-[[(1R,2R)-2-[[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]methyl]cyclohexyl]methyl]hexahydro-4,7-methano-1H-isoindole-1,3(2H)-dione) of the following formula I is a compound having a pharmacological activity as an antipsychotic agent, which is characteristic of a high affinity for dopamine $D_2$, serotonin 5-$HT_{1A}$, 5-$HT_{2A}$, 5-$HT_7$, and noradrenaline $\alpha_{2C}$ receptors, and characteristic of minimal to no affinity for histamine $H_1$ and muscarinic $M_1$ receptors.

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In currently approved drug products, the hydrochloride salt of lurasidone is used. Lurasidone possesses antipsychotic effects, antidepressant- and anxiolytic-like effects, and pharmacological profiles with potentially-reduced liability for extrapyramidal and CNS depressant side effects, which is expected to be used for the treatment of schizophrenia and/or bipolar disorder. Further studies have shown that Lurasidone may improve cognitive function.

Lurasidone hydrochloride has a low aqueous solubility (0.224 mg/mL in water) and when used in micronized form, the active pharmaceutical ingredient is difficult to process due to sticky nature. Lurasidone hydrochloride is very slightly soluble in water, and practically insoluble in 0.1 N HCl (Khan *et al* (*IJLSR,* 2016, p.17-22); Cruz, M. P. (*PT*, 2011, p.489-492)), hence having poor oral bioavailability of less than 12%. It should be taken with food (at least 350 calories) to increase absorption. For development of pharmaceutical formulations, particularly oral dosage forms, therefore, the active ingredient must have sufficient oral bioavailability, if possible, without the need to take with a meal.

Methods for improving the solubility and oral bioavailability of lurasidone or lurasidone hydrochloride have been described, for example, using self-emulsifying drug delivery systems, wherein lurasidone (Miao, *et al* (*Drug Dev. Ind. Pharm.*, 2016, p.1234-1240) and Dondapati *et al* (*TACL*, 2016, p.86-97)) or lurasidone hydrochloride (CN 107875122) is mixed with oils and surfactants, using nanocrystal drug delivery systems, wherein lurasidone hydrochloride is mixed with zirconium oxide beads (Shah *et al* (*Pharm. Sci. Tech.*, 2016, p.1150-1158)), in oil-in-water nano-emulsions, wherein pharmaceutically active ingredients are in combination with fatty acids or non-ionic surfactants (US 2017/0143627), or in solid dispersions, wherein lurasidone is mixed with a carrier and a plasticizer (WO 2019/128991).

WO 2010/032140 and US 2017/0312226 describe particulate and/or multi-particulate pharmaceutical compositions, which are produced by lyophilization or by granulation, and comprise fatty acids to improve adsorption of the active ingredient in, for example, the gastrointestinal tract.

Enhancing bioavailability of poorly absorbed therapeutic agents, to permit release at a preferred site in, for example, the gastrointestinal tract, *via* oral administration has been described using bioadhesive polymers and impermeable or semi-permeable layers (US 2011/0142889), using coating with redox-sensitive materials, such as azopolymers or disulphide polymers (WO 97/05903), using pH-dependent or anionic copolymer coatings (WO 2016/120378), and using acid labile and alkalinizing coatings (US 2016/0022590).

There is a demand in the art for new antipsychotic formulations and particularly new lurasidone formulations, which would be more soluble, stable with acceptable pharmacokinetic properties and more suitable for technological processing.

There is also a need for effective, preferably abuse-resistant, products for use in treatment of psychosis. It would also be preferred if it were capable of being administered perorally (i.e. to be swallowed and ingested within the gastrointestinal tract).

In developing a solid oral dosage forms comprising antipsychotics such as lurasidone as an active ingredient, it is desirable to develop a formulation having a good disintegration and dissolution profile.

Abuse-deterrent oral formulations for delivering drugs, such as opioids, to the gastrointestinal tract in the form of fatty acid salts in the presence of various carriers, such as waxes, is described in inter alia WO 2005/123039 and WO 2017/222575. See also WO 2005/009409.

US 2008/0286373 describes a formulation of the antipsychotic agent ziprasidone in combination with PEG esters of $C_{12-24}$ fatty acids.

We have now unexpectedly found that antipsychotics, and in particular lurasidone, can be solubilised at very high concentrations in fatty acids when formulated in accordance with the invention.

**Disclosure of the Invention**

According to a first aspect of the invention, there is provided a pharmaceutically-acceptable composition, in which an antipsychotic drug is dissolved and/or dispersed in a $C_{8-22}$ fatty acid, which compositions are referred to hereinafter as "the compositions of the invention".

Compositions of the invention are suitable for peroral administration and delivery to the gastrointestinal tract. This means that a composition of the invention, and/or dosage forms including them, should preferably be suitable for swallowing as a whole, complete composition/dosage form for subsequent consumption and/or ingestion within the gastrointestinal tract, and, in use, is swallowed and then consumed and/or ingested within that tract.

Compositions of the invention may thus be suitable for direct administration to subjects, or may be contained within pharmaceutically-acceptable dosage forms. Dosage forms that comprise compositions of the invention should preferably be

designed to deliver that composition to the gastrointestinal tract, such as the stomach, and/or any part of the small intestine (including the duodenum, the jejunum and the ileum, including the terminal ileum), and/or the large intestine or colon. In this respect, suitable dosage forms may also comprise a pharmaceutically-acceptable carrier, which carrier is capable of releasing the composition of the invention within the gastrointestinal tract (such as within the stomach and/or small intestine and/or colon).

Appropriate pharmaceutically-acceptable carriers include appropriate dosing means known to the skilled person. For example, the compositions of the invention may, along with further ingredients or excipients, be compressed into a tablet, granulated into a pellet or a pill, or, preferably, may be filled into a capsule, such as a soft-shell or a hard-shell capsule, which can be made from gelatin, cellulose polymers, e.g. hydroxypropyl methylcellulose (HPMC or hypromellose), hypromellose acetate succinate (HPMCAS), starch polymers, pullulan or other suitable materials, for example by way of standard capsule filling processes.

Suitable fatty acids for use in compositions of the invention include those that contain one or more carboxylic acid (-$CO_2H$) groups, and one or more aliphatic hydrocarbon chains, in which the total number of carbon atoms in the fatty acid molecule is between 8 (e.g. 12 and 22 (e.g. 20), preferably between 12 (e.g. 14) and 18, in number). Hydrocarbon chains may be linear or branched, saturated or unsaturated (if/as appropriate), straight-chain, cyclic or part-cyclic as appropriate, largely depending on the form of the composition of the invention.

Compositions of the invention may be in the form of a solid or a liquid. When the composition is in the form of a liquid it preferably comprises a $C_{8-20}$ fatty acid that is a liquid at about 40°C. When the composition is in the form of a solid it preferably comprises a $C_{12-22}$ fatty acid that is a solid at about the same temperature, such as about 37°C.

Liquid $C_{8-20}$ fatty acids that may be employed in compositions of the invention (i.e. as solvents for the antipsychotic drug) are liquid at about 40°C. By "liquid at about 40°C", we mean that the $C_{8-20}$ fatty acid has a melting point that is below about 40°C, such as below about body temperature (i.e. 37°C) under normal atmospheric conditions, such as pressure and humidity. Preferred liquid fatty acids include caprylic acid, capric acid, oleic acid and linoleic acid. Particularly preferred liquid fatty acids include oleic acid.

Solid $C_{12-22}$ fatty acids that may be employed in compositions of the invention (i.e. as solvents for the antipsychotic drug) are preferably solid at about body temperature (i.e. 37°C). By "solid at about 37°C", we mean that the $C_{12-22}$ fatty acid has a melting point that is above about 37°C i.e. it is solid at that temperature and below (and potentially at certain temperatures above that temperature) under normal atmospheric conditions, such as pressure and humidity. Preferred solid fatty acids include lauric acid, palmitic acid, stearic acid, arachidic acid and behenic acid. Particularly preferred solid fatty acids include myristic acid.

The term "solid" will be well understood by those skilled in the art as comprising matter that retains its shape and density when not confined, in which molecules are generally compressed as tightly as the repulsive forces among them will allow. The term "liquid" will conversely be well understood by those skilled in the art as comprising matter that conforms to the shape of a container in which it is held, and which acquires a defined surface in the presence of gravity.

Antipsychotic drugs (also referred to herein simply as "antipsychotics") that may be employed in compositions of the invention include first-generation or second-generation antipsychotic drugs.

First-generation antipsychotics that may be employed in compositions of the invention include phenothiazines such as acepromazine, chlorpromazine, cyamemazine, dixyrazine, fluphenazine, levomepromazine, mesoridazine, perazine, periciazine, perphenazine, pipotiazine, prochlorperazine, promazine, promethazine, prothipendyl, thioproperazine, thioridazine, trifluoperazine or triflupromazine; thioxanthenes such as chlorprothixene, clopenthixol, flupentixol, thiothixene, zuclopenthixol; butyrophenones such as benperidol, bromperidol, droperidol, haloperidol, moperone, pipamperone or timiperone; dihydroindolone derivatives such as dihydroindolon or molindolone; dibenzepine; diphenylbutylpiperidines such as fluspirilene, penfluridol, or pimozide; dibenzodiazapines such as clorazepate, diazepam, flurazepam, halazepam, prazepam, chlordiazepoxide, lorazepam, lormetazepam, oxazepam, temazepam, clonazepam, flunitrazepam, nimetazepam, nitrazepam, adinazolam, alprazolam, estazolam, triazolam, climazolam, loprazolam, or midazolam; thiodiazepines such as bentazepam, clotiazepam, etizolam, metizolam, or deschloroetizolam; dibenzothiazepines such as quetiapine, tianepine or metiapine; perathiepine, chlorotepine, metitepine; tricyclics carpipramine, clocapramine, clorotepine, clotiapine, loxapine or mosapramine; molindone or substituted benzamides such as sulpiride, sultopride, or veralipride.

Preferred phenozthiazines have a substituent at position 10 such as chlorpromazine, mesoridazine, pipotazine, perphenazine or trifluoperazine. Preferred substituents at position 10 are aliphatic hydrocarbons, piperidine or piperazine.

First-generation antipsychotics that may be employed in compositions of the invention include substances that block D2 receptors and/or block muscarin cholingeric receptors.

Preferred first-generation antipsychotics that may be employed in compositions of the invention block D2 receptors in the mesolimbic pathway and/or block muscarin cholingeric receptors.

Second-generation antipsychotics that may be employed in compositions of the invention include benzamides such as amisulpride, nemonapride, remoxipride sultopride, sulpiride or veralipride; benzisoxazoles/benzisothiazoles such as iloperidone, lurasidone, paliperidone, paliperidone palmitate, perospirone, risperidone or ziprasidone; butyrophenones such as melperone; phenylpiperazines/quinolinones such as aripiprazole, aripiprazole, brexpiprazole or cariprazine; tricyclics such as asenapine, clozapine, olanzapine, quetiapine or zotepine; blonanserin, pimavanserin, sertindole.

Second-generation antipsychotics that may be employed in compositions of the invention include serotonin-dopamine antagonists; substances that block or partially block serotonin 5-$HT_{2A}$ and/or 5-$HT_{1A}$ receptors and $D_2$ receptors simultaneously; substances showing an affinity for 5-$HT_{2A}$, $D_2$ and receptors of other systems such as cholinergic, histaminergic, 5-$HT_{1A}$, 5-$HT_{2c}$ receptors and the like; substances that block $D_2$ and $D_3$ subtypes of the $D_2$-like receptors.

By "$D_2$-like receptors" we mean the subfamily of dopamine receptors that bind the endogenous neurotransmitter dopamine comprising three G-protein coupled receptors that are coupled to $G_i/G_o$ and mediate inhibitory neurotransmission, of which include $D_2$, $D_3$, and $D_4$.

Optionally, antipsychotics that may be employed in compositions of the invention include partial dopamine receptor agonists comprising partial agonist at dopamine $D_2$ receptors acting as a functional antagonist in the mesolimbic dopamine pathway, but showing functional agonist activity in the mesocortical pathway.

Naturally-occurring antipsychotics such as l-stepholidine may also be employed in compositions of the invention.

Preferably, antipsychotics that act on the dopaminergic system only block the mesocortical pathway.

Substances that are $D_2$ antagonists may be employed in compositions of the invention. Preferably, these substances reduce dopaminergic neurotransmission in at least one of the four dopamine pathways. Dopamine pathways include the mesocortical pathway, the mesolimibic pathways, the nigrostriatal pathway and the tuberoinfundibular pathway. A preferred pathway is the mesolimbic pathway.

Preferred $D_2$ antagonists that may be employed in compositions of the invention include 3-PPP, aceprometazine, amisulpride, aripiprazole, BL-1020, blonanserin, buspirone, buspirone/testosterone, chlorprothixene, desmethoxyfallypride, doxepin, eticlopride, fallypride, flunarizine, hydroxyzine, imipramine, itopride, ketanserin, L-741,626, lumateperone, metoclopramide, ocaperidone, olanzapine, opipramol, panamesine, pimozide, pipamperone, pridopidine, raclopride, spiperone, stepholidine, tiotixene or trimethobenzamide

Preferred second-generation antipsychotics that may be employed in compositions of the invention include aripiprazole, asenapine, clozapine, aloperidon, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, cariprazine or ziprasidone.

More preferably, the composition of the invention comprises lurasidone or a pharmaceutically-acceptable salt, ester, solvate, polymorph, stereoisomer or mixture thereof.

In addition, second-generation antipsychotics employed in composition of the invention may be employed as a combination therapy such as olanzapine plus fluotexine.

Pharmaceutically-acceptable salts of antipsychotics may also be employed in compositions of the invention. By "pharmaceutically-acceptable salt" of an antipsychotic, we mean acid addition, or base addition, salts that may be used as pharmaceuticals. Such salts may be formed by conventional means, for example by reaction of a free acid or a free base form of an active ingredient with one or more equivalents of an appropriate acid or base, optionally in a solvent, or in a medium in which the salt is insoluble, followed by removal of said solvent, or said medium, using

standard techniques (e.g. in vacuo, by freeze-drying or by filtration). Salts may also be prepared by exchanging a counter-ion of a delivery agent in the form of a salt with another counter-ion, for example using a suitable ion exchange resin.

References made hereinafter to "active ingredients", "antipsychotic" and/or "antipsychotic drug" (whether used in a general sense, or with reference to a specific antipsychotic, such as lurasidone) are to be taken to include such active ingredients in the form of either the free acid or free base (as appropriate), and/or in the form of a pharmaceutically-acceptable salt, unless otherwise specified, and/or if the context dictates otherwise.

It has further been unexpectedly found that the additional presence of a sugar ester in solid compositions of the invention means those compositions are readily capable of self-emulsification when placed in contact with an aqueous environment.

Sugar esters that may be used in the compositions of the invention include monosaccharide and/or disaccharide esters, preferably disaccharide ester, and most preferably sucrose esters.

Sucrose esters that may be employed in compositions of the invention have a hydrophilic-lipophilic balance value of between 6 and 20. The term "hydrophilic-lipophilic balance" (HLB) is a term of art that will be well understood by those skilled in the art (see, for example, "The HLB System: A Time-Saving Guide to Emulsifier Selection", published by ICI Americas Inc, 1976 (revised 1980), in which document, Chapter 7 (pages 20-21) provides a method of how to determine HLB values). The longer the fatty acid chains in the sucrose esters and the higher the degree of esterification, the lower the HLB value. Preferred HLB values are between 10 and 20, more preferably between 12 and 20.

Sucrose esters thus include $C_{8-22}$ saturated or unsaturated fatty acid esters, preferably saturated fatty acid esters and preferably a $C_{10-18}$ fatty acid ester and most preferably a $C_{12}$ fatty acid ester. Particularly suitable fatty acids from which such sucrose esters may be formed include erucic acid, behenic acid, oleic acid, stearic acid, palmitic acid, myristic acid and lauric acid. A particularly preferred such fatty acid is lauric acid. Commercially-available sucrose esters include those sold under the trademark Surfhope® and Ryoto® (Mitsubishi-Kagaku Foods Corporation, Japan).

Sucrose esters may be diesters or monoesters of fatty acids, preferably monoesters, such as sucrose monolaurate. The skilled person will appreciate that the term "monolaurate" refers to a mono-ester of lauric acid, and that the terms "lauric acid ester" and "laurate" have the same meaning and can therefore be used interchangeably. Commercially available sucrose monolaurate products are also sometimes referred to as "sucrose laurate". Commercially-available sucrose monolaurate (or sucrose laurate) products such as Surfhope ® D-1216 (Mitsubishi-Kagaku Foods Corporation, Japan), which may contain small amounts of diesters and/or higher sucrose esters, and minor amounts of other sucrose esters and free sucrose, are suitable for use in the invention. The skilled person will understand that any reference to a specific sucrose ester herein includes commercially available products comprising that sucrose ester as a principle component.

Preferred sucrose esters contain only one sucrose ester, which means that a single sucrose ester (e.g. a commercially-available sucrose ester product) contains a single sucrose ester as the/a principle component (commercially available products may contain impurities, for example a monoester product may contain small amounts of diesters and/or higher esters, such products may be considered to "contain only one sucrose ester" in the context of the present invention). As used herein, the term "principle component" will be understood to refer to the major component (e.g. greater than about 50%, such as about 70% weight/weight or volume/volume) in a mixture of sucrose esters, such as commonly commercially available surfactant products, which are typically sold with a certain range of ester compositions.

A particularly preferred sucrose ester is sucrose monolaurate.

Solid compositions of the invention may exhibit surprisingly good bioavailability compared to corresponding compositions that do not include sucrose esters, and/or include different surfactants.

The active ingredient is thus dissolved and/or dispersed in a solvent system comprising at least one or more fatty acid as hereinbefore described, which means that solvent system may comprise other components.

Other components of the fatty acid-containing solvent system in which active ingredient is included include triglycerides and/or, preferably, monoacyl glycerols.

Triglycerides that may be mentioned include any ester that is derived from glycerol and three fatty acids, for example $C_{8-22}$ saturated or unsaturated fatty acids, at least two of which may be the same or different. Triglycerides may be derived from animal or vegetable fats. Preferred triglycerides include vegetable oils and fractions thereof, such as castor oil, peanut oil, corn oil, safflower oil, sesame oil, soybean oil, coconut oil, palm oils, medium chain triglyceride oils and, especially, olive oil.

Monoacyl glycerols (also known as "monoglycerides") that may be employed in compositions of the invention are composed of glycerol linked to a fatty acid, for example a $C_{8-22}$ saturated or unsaturated fatty acid, through an ester bond, and includes 1-monoacyl- and 2-monoacylglycerols. Monoacyl glycerols may be produced by a variety of techniques including enzymatic hydrolysis of triglycerides or diglycerides, by alkanoylation of glycerol, or glycerolysis reaction between triglycerides and glycerol, and/or are commercially-available. Suitable monoacyl glycerols include 2-oleoylglycerol, 2-arachidonoylglycerol, monolaurin, glycerol monomyristate, glycerol monopalmitate, glyceryl hydroxystearate and, preferably, glycerol monostearate, glycerol monooleate (e.g. Cithrol®) and glycerol monocaprylate (e.g. Capmul®).

It is preferred that compositions of the invention comprise one or more non-volatile monoacyl glycerol.

In this respect, we have found that the solubility of the aforementioned sucrose esters in the aforementioned fatty acids can be improved by the further inclusion of one or more such monoacyl glycerols, such as glycerol monostearate, glycerol monooleate (e.g. Cithrol™) and glycerol monocaprylate (e.g. Capmul®). Such monoacyl glycerols are good co-solvents for sucrose esters and are, at the same time, soluble and/or miscible with fatty acids, and are not detrimental to capsule shells.

The preferred compositions of the invention comprise an antipsychotic dissolved and/or dispersed in a $C_{8-22}$ fatty acid; a sucrose ester; and a monoacyl glycerol.

It is also preferred that compositions of the invention are in the main part presented in the form of liquid or solid solutions (as appropriate). It is thus preferred that at least about 50% (such as at least about 70%) of the molecules of the antipsychotic that are within a composition of the invention is present in dissolved form, a molecularly dispersed form, and/or are arranged in an amorphous form, such as in the form of small particles in such compositions. The term 'dissolved, or molecularly dispersed' may include a solid solution or a colloidal suspension, but does not include

that molecules of the antipsychotic are aggregated as solid particles, whether in crystalline or non-crystalline form. The term "dissolved" and/or "molecularly dispersed" form(s) may include that the molecules of the antipsychotic are dissolved in a colloidal structure (e.g. micellar, hexagonal and bilayer phases, which can be normal or reverse).

Preferred optional additional excipients in compositions of the invention include one or more surfactants. Surfactants that may be mentioned include polyoxyethylene esters (e.g. Myrj™), including polyoxyl 8 stearate (Myrj™ S8), polyoxyl 32 stearate (Gelucire® 48/16), polyoxyl 40 stearate (Myrj™ S40), polyoxyl 100 stearate (Myrj™ S100), and polyoxyl 15 hydroxystearate (Kolliphor® HS 15), polyoxyethylene alkyl ethers (e.g. Brij™), including polyoxyl cetostearyl ether (e.g. Brij™ CS12, CS20 and CS25), polyoxyl lauryl ether (e.g. Brij™ L9 and L23), and polyoxyl stearyl ether (e.g. Brij™ S10 and S20), and polyoxylglycerides (e.g. Gelucire®), including lauroyl polyoxylglycerides (Gelucire® 44/14) and stearoyl polyoxylglycerides (Gelucire® 50/13), sorbitan esters (e.g. Span™), including sorbitan monopalmitate (Span™ 40) and sorbitan monostearate (Span™ 60), and sodium lauryl sulfate.

Particular surfactants that may be used in liquid compositions of the invention include polysorbates (Tweens™), including polysorbate 40 (polyoxyethylene (20) sorbitan monopalmitate), polysorbate 60 (polyoxyethylene (20) sorbitan monostearate) and, preferably, polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate) and/or polysorbate 80 (polyoxyethylene (20) sorbitan monooleate).

Not including sucrose ester(s) that may be present in compositions of the invention, surfactants may be present in a total amount of up to about 30%, such as up to about 15%, by weight, based on the total weight of the composition.

Additional ingredients (excipients) may include solvents or co-solvents, such as water; alcohols, including lower alkyl (e.g. $C_{1-6}$ alkyl) alcohols, such as isopropyl alcohol and, particularly, ethanol (e.g. 70% ethanol, 90% ethanol, 95% ethanol, 99.5% ethanol or absolute ethanol); benzyl benzoate, ethyl lactate, ethyl oleate, glycerol, propylene glycol, polyethylene glycols, dimethylacetamide, N-methyl-2-pyrrolidone, and dimethyl sulfoxide; oils, such as vegetable oils (e.g. castor, peanut, corn, safflower, sesame, soybean, coconut, palm oils and, especially, olive oil); di- and triglycerides of fatty acids (e.g. medium chain monoglycerides); fatty alcohols (or long chain alcohols) (e.g. cetyl alcohol, cetostearyl alcohol and stearyl alcohol (e.g. Crodacol™ C70, C90, C95, CS50, CS90 and S95); sterols (or steroid alcohols) such as cholesterol and

phytosterols (e.g. campesterol, sitosterol, and stigmasterol); antioxidants (e.g. α-tocopherol, ascorbic acid, potassium ascorbate, sodium ascorbate, ascorbyl palmitate, butylated hydroxytoluene, butylated hydroxyanisole, dodecyl gallate, octyl gallate, propyl gallate, ethyl oleate, monothioglycerol, vitamin E polyethylene glycol succinate, or thymol); chelating (complexing) agents (e.g. edetic acid (EDTA), citric acid, tartaric acid, malic acid, cyclodextrins, maltol and galactose); preservatives (e.g. benzyl alcohol, boric acid, parabens, propionic acid, phenol, cresol, or xylitol); viscosity modifying agents or gelling agents (such as cellulose derivatives, including hydroxypropylcellulose, methylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose, etc., starches and modified starches, colloidal silicon dioxide, aluminium metasilicate, polycarbophils (e.g. Noveon®), carbomers (e.g. Carbopol®)); pH buffering agents (e.g. citric acid, maleic acid, malic acid, or glycine); colouring agents; penetration enhancers (e.g. isopropyl myristate, isopropyl palmitate, pyrrolidone, or tricaprylin); and other lipids (neutral and polar).

The compositions of the invention may include an aromatic carboxyl acid as an additional component. Suitable aromatic acids include benzoic acid optionally substituted with one or more groups selected from methyl, hydroxyl, amino, and/or nitro, for instance, benzoic acid, toluic acid or salicylic acid. Benzoic acid is particularly preferred.

Aromatic acids such as benzoic acid have been found to increase the solubility of the antipsychotic in the fatty acid, particularly in solid formulations. Suitably, the aromatic acid (e.g. benzoic acid) is present in an amount of up to 35 weight percent, preferably from 1 to 20 wt%.

Total amounts of such "additional" excipients are no more than about 40%, such as about 35% (e.g. about 25%), for example no more than about 30% (e.g. about 20%), such as about 25% (e.g. about 15%) by weight, based on the total weight of a composition of the invention.

It is preferred that compositions of the invention that are in the form of a solid in the main part comprise components that are solid at about 37°C below. That is, by weight, at least about 50% (such as at least about 70%) of the components in such a solid composition are solid at about 37°C or below.

In solid compositions of the invention, when other excipients, such as those mentioned above, are employed which happen to be substances that are liquid at about 37°C, it

is preferred that no more than about 10%, such as about 5% by weight, based on the total weight of a composition of the invention comprises such excipients.

It is further preferred that the compositions of the invention are not presented in the form of a water-in-oil, or an oil-in-water, emulsion prior to administration.

Compositions of the invention may be/are capable of self-emulsification when placed in contact with an aqueous environment.

Self-emulsification means that the solid compositions of the invention are capable of dispersing into various lipid structures and/or phases (e.g. emulsion droplets, liposomes, vesicles, bilayer sheets, micelles etc.) when placed in contact with an aqueous environment, with simple agitation and/or stirring, and without the need of high energy input (such as sonication, high shear mixing, homogenization, extrusion etc.). During self-emulsification, essentially no precipitation of active ingredient, will take place in the aqueous environment (whether this aqueous environment is inside or outside of the body), despite the amount of active ingredient in the formulation being significantly above the maximum solubility in that specific aqueous phase environment.

As used herein, the term "aqueous environment" may be understood to mean water or any medium that comprises water. Amounts of water that may be employed in aqueous environments include those necessary to induce the formation of a dispersion and/or an emulsion comprising active ingredient.

Hence, administration of compositions of the invention may lead to self-emulsification, wherein active ingredient is at least in part incorporated in lipid structures/phases (e.g. emulsion droplets, vesicles, micelles or the like). This feature has the potential to improve the bioavailability of the active ingredient as the latter will essentially be presented there in a solubilized state.

Compositions of the invention may be prepared by standard techniques, and using standard equipment, known to the skilled person, for example as described hereinafter. In this respect, the compositions of the invention may be combined with conventional pharmaceutical additives and/or excipients used in the art for relevant preparations, and incorporated into various kinds of pharmaceutical preparations using standard techniques (see, for example, Lachman et al, "The Theory and Practice of Industrial Pharmacy", Lea & Febiger, 3rd edition (1986); "Remington: The Science and Practice of Pharmacy", Troy (ed.), University of the Sciences in Philadelphia, 21st edition

(2006); and/or "Aulton's Pharmaceutics: The Design and Manufacture of Medicines", Aulton and Taylor (eds.), Elsevier, 4th edition, 2013).

Accordingly, compositions of the invention that are in the form of a liquid may be prepared by stirring together active ingredient along with the solvent system comprising a $C_{8-20}$ fatty acid as hereinbefore defined, and any other ingredients as mentioned hereinbefore at or above ambient (e.g. room) temperature until a solution is formed.

Conversely, compositions of the invention in the form of a solid may be prepared by stirring together active ingredient along with the $C_{12-22}$ fatty acid as hereinbefore defined, along with any other ingredients as mentioned hereinbefore at elevated temperature (e.g. about 60°C) until a solution is formed and thereafter cooling that solution to a lower temperature (e.g. about 20°C) whereupon the composition solidifies.

Alternative and/or additional process steps may also be employed to make compositions of the invention in the form of a solid, such as spray cooling, spray congealing, extrusion cooling and/or freeze casting, to promote solidification. Also, process media such as cooled air and other gases, dry ice and liquid nitrogen may be employed to the cooling step.

According to one aspect of the invention, the compositions of the invention may be solidified to uniform and spherical particles appropriate for a finished dosage form using spray congealing or prilling. The solidified particles are formed in a manner in which, preferably, a water-soluble excipient, more preferably a saccharide ester or a sucrose ester, is suspended in a mixture of low melting point ingredients and is congealed. After spray congealing, the resulting composition is allowed to cool and solidify.

In a preferred embodiment, the compositions of the invention may be made by feeding the precursor through a nozzle, producing a stable beam of solution which is broken up into sub-millimetre-sized, round droplets. The droplets may then be solidified by cooling as they fall through the rising cold nitrogen flow forming uniform and spherical particles.

Such processes may also comprise other process steps, such as high shear mixing and/or sonication (in the case of a solid composition of the invention) at an elevated

temperature to promote solubilisation and/or a uniform distribution of ingredients within the composition.

Compositions of the invention in the form of a solid may be solidified in any size and shape appropriate for a finished dosage form, and/or may be further processed after solidification by means of e.g. milling, screening, sieving, blending, coating, compression, and filling.

According to a further aspect of the invention, there is provided a process for the manufacture of a solid composition of the invention, wherein said process comprises the steps of:

i) stirring together an antipsychotic (or a salt thereof), along with the other ingredients including the $C_{12-22}$ fatty acid (and, if present, the sucrose ester and monoacyl glycerol) as hereinbefore defined, along with any other ingredients as mentioned hereinbefore at elevated temperature (e.g. about 60°C) until a solution is formed.

ii) cooling the solution of step i) to a lower temperature (e.g. about 20°C) allowing the composition to solidify, optionally in the form of multiparticulates; and

iii) optionally, further processing of the invention after step ii) by means of e.g. milling, screening, sieving, blending, coating, compression, and filling.

Step i) may also comprise other process steps, such as high shear mixing and/or sonication to promote solubilisation and/or uniform distribution of ingredients within the formulation.

Process media such as cooled air and other gases, dry ice and liquid nitrogen may be employed to the cooling step ii).

According to a further aspect of the invention, there is provided a process for the manufacture of a liquid pharmaceutical composition of the invention, wherein said process comprises the steps of:

i) stirring together an antipsychotic (or a salt thereof), along with the solvent system comprising a $C_{8-20}$ fatty acid (and, if present, monoacyl glycerol) as hereinbefore defined, along with any other ingredients as mentioned hereinbefore (e.g. sucrose ester) at ambient (e.g. room) temperature until a solution is formed;

ii) optionally, further processing of the invention after step i) by means of e.g. sieving, blending, coating, compression, and filling.

Step i) may also comprise other process steps, such as heating, high shear mixing and/or sonication to promote solubilisation and/or uniform distribution of ingredients within the formulation.

The processes according to the present invention can as such, once the specific components are identified and included, be practised by using conventional equipment for the manufacturing of pharmaceutical formulations.

Ambient temperature indicates a temperature between of about 20°C to about 25°C.

Preferred particle sizes include a weight- or volume-based average particle size of less than about 2 mm, such as less than about 1 mm. including less that about 0.75 mm in (e.g. the particles' largest) diameter.

Preferred particle shapes include spherical or substantially spherical, by which we mean that the particles possess an aspect ratio smaller than about 20, more preferably less than about 10, such as less than about 4, and especially less than about 2, and/or may possess a variation in radii (measured from the centre of gravity to the particle surface) in at least about 90% of the particles that is no more than about 50% of the average value, such as no more than about 30% of that value, for example no more than about 20% of that value.

Nevertheless, particles may be any shape, including irregular shaped (e.g. "raisin"-shaped), needle-shaped, disc-shaped, or cuboid-shaped particles. For a non-spherical particle, the size may be indicated as the size of a corresponding spherical particle of e.g. the same weight, volume or surface area.

According to a further aspect of the invention, there is provided the compositions of the invention for use in medicine (human and veterinary).

The compositions of the invention may be designed for immediate release (e.g. release in the stomach after swallowing), and/or may be targeted for delivery at the small intestine and/or the colon. Accordingly, compositions of the invention may be administered perorally to the gastrointestinal tract and protected by an appropriate extended/sustained release, controlled or delayed release (e.g. enteric) coating.

Compositions of the invention may be provided with such a protective coating as a single-unit dosage form (e.g. a composition of the invention may be filled into a dosage form, such as a capsule, which may be coated with a controlled and/or delayed release coating), and/or multiple-units comprising compositions of the invention (e.g. multiple pellets) may first be individually coated for controlled and/or delayed release and thereafter filled into a capsule that may be an immediate release capsule.

Targeted delivery that may be mentioned includes targeting release of the active ingredient to the distal parts of the small intestine (e.g. the ileum, including the terminal ileum) and/or the colon. Various methods may be employed to do this, including:

- derivatising active ingredient into a prodrug that is less degraded and/or absorbed in other parts of the gastrointestinal tract (compared to the active ingredient itself), for example by choosing a conjugate that may be removed by enzymes/microbiota in the colon;
- coating drug substances, units of compositions of the invention or entire dosage forms comprising compositions of the invention with a material (e.g. a polymer) that is degraded by the enzymes/microbiota in the colon;
- coating drug substances, units of compositions of the invention or entire dosage forms comprising compositions of the invention with a material (e.g. a polymer) that is insoluble in low pH (e.g. pH 1 to 6) but dissolves at higher pH (e.g. pH > 6), in a manner that targets the distal small intestine and/or the colon;
- coating drug substances, compositions of the invention or entire dosage forms comprising compositions of the invention with a material (e.g. a polymer) that is only sufficiently dissolved after a certain time whilst present in gastrointestinal fluids (e.g. a delayed release of several hours); and
- designing units of compositions of the invention or entire dosage forms comprising compositions of the invention to deliver the active ingredient based on luminal pressure.

(See, for example, the review article by Amidon et al, AAPS PharmSciTech, **16**, 731 (2015).) Two or more of the above (or other known) techniques may be combined to achieve a more reliable targeting to the distal small intestine and/or colon (e.g. combinations of pH-release systems and colon-specific biodegradable systems, or pH-release systems and time release systems).

In any event, when compositions of the invention (e.g. in appropriate dosage forms) reach the intended site of delivery they contact the aqueous environment there and

may release their contents such that the active ingredient is presented in a form in which it may be absorbed through the gastrointestinal mucosa (e.g. the mucosa of the small and/or large intestine).

In this respect, when compositions of the invention are administered to a patient and reach the relevant site, they may provide a higher intestinal absorption of active ingredient than is presently possible with existing pharmaceutical compositions, such as those described hereinbefore.

In addition, the compositions of the invention may increase the bioavailability of active ingredient, by decreasing its pre-systemic metabolism and/or or first-pass metabolism.

The compositions of the invention may have the potential to keep more active ingredient solubilized in gastrointestinal fluids, and thereby expose the intestinal enterocytes to high concentrations of active ingredient, so that the intestinal metabolic system is saturated and a relatively smaller portion of active ingredient is metabolized. In this way, it is expected that more non-metabolized active ingredient will traverse the intestinal cells and enter circulation.

The compositions of the invention may enhance intestinal lymphatic delivery, and thereby avoid to a great extent pre-systemic (first-pass) metabolism.

Compositions of the invention thus provide for improved peroral bioavailability as determined by an improved plasma concentration versus time profile (which can in turn be represented by a greater AUC and/or a more extended plasma concentration-time profile).

The compositions of the invention are particularly useful in the treatment of, or may be useful in the treatment of, a range of clinical psychotic conditions, including schizophrenia; schizoaffective disorder; bipolar disorder, severe depression/anxiety; obsessive-compulsive disorder (OCD) and/or ADHD; physical problems such as hiccups, problems with balance and nausea; or agitation and psychotic experiences in dementia.

The compositions of the invention are particularly useful in the treatment of schizophrenia or schizoaffective disorder.

Compositions of the invention may also be particularly useful in the treatment of bipolar disorder.

Compositions of the invention may also be used in the treatment of OCD/ADHD.

According to further aspects of the invention there are provided:

(i) a method of treatment of schizophrenia or schizoaffective disorder;

(ii) a method of treatment of easing the symptoms of schizophrenia or schizoaffective disorder such as delusions and hallucinations;

(iii) a method of treatment of bipolar disorder; and

(iv) a method of treatment of ADHD;

which methods comprise administration of a composition of the invention to patient suffering from, or susceptible to, the relevant conditions.

Schizoaffective disorder is a mental disorder in which a person experiences a combination of schizophrenia symptoms, such as hallucinations or delusions, and mood disorder symptoms, such as depression or mania.

Preferred substances that may be employed in compositions of the invention for use in the treatment of schizophrenia are first-generation antipsychotics such as chlorpromazine, fluphenazine, haloperidol, perphenazine, thioridazine, thiothixene or trifluoperazine.

More preferred substances that may be employed in compositions of the invention for use in the treatment of schizophrenia are second-generation antipsychotics such as aripiprazole, asenapine, cariprazine, clozapine, olanzapine, paliperidone, paliperidone palmitate, quetiapine, risperidone, ziprasidone and, particularly, lurasidone.

Preferred substances that may be employed in compositions of the invention for use in the treatment of bipolar disorder are aripiprazole, asenapine, cariprazine, clozapine, olanzapine, quetiapine, risperidone, ziprasidone and, particularly, lurasidone.

Preferred substances that may be employed in compositions of the invention for use in the treatment of ADHD are olanzapine, quetiapine or risperidone.

As used herein, "patients" includes animals, including mammalian (particularly human) patients.

As used herein, the term "therapeutically effective amount" refers to an amount of active ingredient that is capable of conferring a desired therapeutic effect on a treated patient, whether administered alone or in combination with another active ingredient. Such an effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of, or feels, an effect).

Thus, appropriate pharmacologically effective amounts of active ingredient include those that are capable of producing, and/or contributing to the production of, the desired therapeutic effect, such as treating schizophrenia or schizoaffective disorder; bipolar disorder and/or ADHD, as appropriate, irrespective of the mode of administration that is employed.

The amount of active ingredient that may be employed in a composition of the invention may thus be determined by the skilled person, in relation to the condition, and what will be most suitable for an individual patient. This is also likely to vary with the nature of the formulation, or the aspect of the invention, as well as the route of administration, the type and severity of the condition that is to be treated, as well as the age, weight, sex, renal function, hepatic function and response of the particular patient to be treated.

The total amount of antipsychotic that may be employed in a composition of the invention may be in the range of about 0.0005%, such as about 0.1% (e.g. about 1%, such as about 2%) to about 40%, such as about 30%, for example about 25%, by weight based upon the total weight of the composition.

The amount of the active ingredient may also be expressed as the amount in a unit dosage form comprising a composition of the invention. In such a case, the amount of active ingredient that may be present may be sufficient to provide a dose of active ingredient (calculated as the free acid/base) per unit dosage form that is in the range of between about 1 µg (e.g. about 5 µg) and about 200 mg, for example up to about 100 mg, including about 600 mg, such as about 40 mg (e.g. about 30 mg, such as about 20 mg).

Preferred ranges of active ingredient per unit dosage form for the treatment of schizophrenia, bipolar disorder and/or ADHD are between about 1 mg to about 200 mg, preferably about 20 mg or about 40 mg or about 80 mg, depending on the active ingredient that is employed, as well as the specific dosage form and the dosage regime that is employed. Thus, preferred ranges for e.g. a capsule to be taken once daily for

the treatment of schizophrenia, bipolar disorder and/or ADHD are between about 1 mg to about 400 mg, preferably 10 mg to about 200 mg, more preferably about 20 to 80 mg depending on the active ingredient that is employed.

Preferred ranges for e.g. a capsule (or other peroral dosage form, such as a tablet) comprising a composition comprising e.g. lurasidone to be taken once daily for the treatment of schizophrenia, bipolar/disorder and/or ADHD are between about 1 mg to about 200 mg, more preferably about 10 mg to about 150 mg, even more preferably about 20 mg to about 120 mg, calculated as the free base.

In any event, relevant indications, as well as pharmaceutically-acceptable salts, and doses, of active ingredients useful in the relevant indications include those that are known in the art and are described for the drugs in question to in the medical literature, such as Martindale – The Complete Drug Reference (39th Edition) and the documents referred to therein, the relevant disclosures in all of which documents are hereby incorporated by reference.

The compositions of the invention are mainly used as monotherapy, but may also be used as an auxiliary lithium or valproate therapy, preferably for adult patients suffering from bipolar I disorders.

All of the factors discussed above also render the compositions of the invention less susceptible to diversion and/or abuse than other, currently available antipsychotics containing pharmaceutical compositions. Upon dispersion or dissolution of a composition of the invention (or a dosage form containing one), either during, or for the purposes of, parenteral abuse, antipsychotics may be incorporated, integrated and/or entrapped in lipid structures which may be formed upon dispersion or dissolution of that composition (or are already present in that composition) in any aqueous environment.

In addition, the lipid structures incorporating antipsychotic may be cleared from the circulation (i.e. the blood stream) by cells of the mononuclear phagocyte system (MPS), which also would lower the plasma concentration of such molecularly dissolved, "free", antipsychotic (e.g. lurasidone) available for receptor binding. This effect may act to further discourage the abuse of compositions of the invention (and dosage forms containing them) by intravenous injection.

In order to abuse antipsychotic-containing compositions, the abuser typically dissolves/disperses the commercial (e.g. sublingual, transdermal or oral) formulation in water, then filters the solution/dispersion to remove excipients such as cellulose and silica particles before injecting the filtrate.

It is envisaged that, upon dispersion or dissolution of a composition of the invention for the purpose of parenteral abuse, antipsychotic (e.g. lurasidone) will be incorporated, or entrapped, in the aforementioned lipid structures, the size of which will likely not pass through many readily-available filters (such as disposable syringe filters and cigarette filters). This will reduce the concentration of antipsychotic in the filtrate. Even if the structures pass through the filter, or the solution/dispersion of the formulation in water is not filtered, the ability of the lipid structures to entrap antipsychotic (e.g. lurasidone) should still reduce the amount of free antipsychotic available for receptor binding.

Also, the filtrate is likely to be cloudy (and therefore not something an abuser would want to inject), and, if injected, physiological aversions to excipients, such as surfactants, that are present can be expected.

Furthermore, the separation of antipsychotic from the other components of the compositions of the invention, and subsequent ex vivo extraction and purification of antipsychotic (e.g. lurasidone), is likely to be extremely challenging to the abuser using standard techniques such as solvent extraction.

All of these factors render compositions of the invention less susceptible to diversion and/or abuse than other, currently available pharmaceutical compositions containing antipsychotic, such as lurasidone.

Compositions of the invention may be formulated with additional active ingredients, including (as appropriate) other psychoactive substance and/or lithium.

Compositions of the invention may also be formulated together with components which are known to enhance the uptake of lipid structures incorporating antipsychotics, e.g. lurasidone, by cells of the mononuclear phagocyte system (MPS), for example cetylmannoside (or any other fatty acid mannoside). Such a component may bind to the mannose receptors of the macrophage cells of the MPS and so enhance the ingestion of lipid structures incorporating antipsychotics, such as lurasidone, by the

macrophage and thereby the clearance of the lipid structures, and ultimately lurasidone, from circulation.

Wherever the word "about" is employed herein in the context of amounts, for example absolute amounts, such as doses, weights, volumes, etc., or relative amounts of individual constituents in a composition or a component of a composition (including concentrations and ratios), timeframes, etc., it will be appreciated that such variables are approximate and as such may vary by ± 10%, for example ± 5% and preferably ± 2% (e.g. ± 1%) from the actual numbers specified herein.

The invention is illustrated but in no way limited by way of the following examples:

Example 1

Solid Lurasidone Formulation

Lurasidone base (0.254 g; Tiefenbacher Nordics ApS, Denmark), myristic acid (1.000 g; Sigma-Aldrich Sweden AB), sucrose laurate (0.501 g; IMCD Nordic AB, Sweden), glycerol monostearate (0.675 g; IOI Oleo GmbH, Germany), cholesterol (0.050 g; Merck Chemical & Lifescience AB, Sweden) and propyl gallate (0.025 g; Sigma-Aldrich Sweden AB) were weighed into a 4 mL glass vial with a screw-cap. The sample was stirred by magnet at 65°C, and then sonicated in a sonication bath having a water temperature of 55°C until a visually isotropic clear lipid solution resulted at 60°C.

A minor part of the lipid solution at 60°C was withdrawn into a heated Pasteur pipette and immediately emptied dropwise on a flat stainless-steel lid cooled on ice, resulting in the formation of drop sized solid lipid pellets.

Example 2

Solid Lurasidone Formulation with Benzoic Acid

Lurasidone base (0.501 g), myristic acid (0.626 g), benzoic acid (0.350 g; Merck Chemical & Lifescience AB, Sweden), sucrose laurate (0.450 g), glycerol monostearate (0.550 g) and propyl gallate (0.025 g) were weighed into a 20 mL glass vial with a screw-cap. The sample was stirred by magnet at 65-70°C, and then sonicated in a sonication bath having a water temperature of 60°C until a visually isotropic clear lipid solution resulted at 60°C.

A minor part of the lipid solution at 60°C was withdrawn into a heated Pasteur pipette and immediately emptied dropwise on a flat stainless-steel lid cooled on ice, resulting in the formation of drop sized solid lipid pellets.

Example 3

Liquid Lurasidone Formulation

Lurasidone base (0.80 g), Oleic acid (3.50 g; Croda Nordica AB, Sweden), polysorbate 20 (1.50 g; Croda Nordica AB), polysorbate 80 (0.50 g; Croda Nordica AB), glycerol monocaprylate (1.50 g; Barentz ApS, Denmark) and glycerol monooleate (0.50 g; Croda Nordica AB) are weighed into a 20 mL glass vial with a screw-cap. The sample is stirred by magnet at room temperature, and for a short time at 35°C to facilitate dissolution of the monoglycerides, until a visually isotropic clear lipid solution results.

Example 4

Lurasidone Formulation Made by Prilling

Lurasidone base (5.000 g), myristic acid (6.250 g), benzoic acid (3.500 g), sucrose laurate (4.500 g), glycerol monostearate (10.500 g) and propyl gallate (0.250 g) are weighed into a 100 mL glass flask with a screw-cap. The sample is stirred with a magnet at 65-70°C, and then sonicated in a sonication bath having a water temperature of 60°C until a visually isotropic, clear lipid solution results at 60°C.

The lipid solution, kept at 70°C, is fed into the nozzle of prilling equipment. The nozzle has an orifice of 345 µm and vibrates at an amplitude of 3.70 kHz, producing a stable beam of lipid solution which is broken up into sub-millimetre sized round droplets. The droplets are then solidified by cooling as they fall through the rising cold nitrogen flow. The inlet temperature at the bottom of the column is below -20°C, and the outlet temperature at the top of the column is below -10°C. The solidified particles are uniform and spherical.

## Claims

1. A pharmaceutically-acceptable composition suitable for peroral administration to the gastrointestinal tract, in which an antipsychotic drug, or a pharmaceutically-acceptable salt thereof is dissolved and/or dispersed in at least one $C_{8-22}$ fatty acid.

2. The composition as claimed in Claim 1, wherein the composition is in the form of a liquid and the fatty acid is a $C_{8-20}$ fatty acid that is a liquid at about 40°C.

3. The composition as claimed in Claim 2, wherein the fatty acid is selected from the group consisting of caprylic acid, capric acid, oleic acid, linoleic acid, and combinations thereof.

4. The composition as claimed in Claim 3, wherein the $C_{8-20}$ fatty acid is oleic acid.

5. The composition as claimed in any one of Claims 2 to 4, wherein the composition comprises a polysorbate.

6. The composition as claimed in Claim 5, wherein the polysorbate comprises polyoxyethylene (20) sorbitan monolaurate and/or polyoxyethylene (20) sorbitan monooleate.

7. The composition as claimed in Claim 1, wherein the composition is in the form of a solid and the fatty acid is a $C_{12-22}$ fatty acid that is a solid at about 37°C.

8. The composition as claimed in Claim 7, wherein the fatty acid is selected from the group consisting of lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, behenic acid, and combinations thereof.

9. The composition as claimed in Claim 8, wherein the fatty acid is myristic acid.

10. The composition as claimed in any one of Claims 7 to 9, wherein the composition comprises a sucrose ester with a hydrophilic-lipophilic balance value of between 6 and 20.

11. The composition as claimed in Claim 10, wherein the sucrose ester is sucrose monolaurate or sucrose laurate.

12. The composition as claimed in any one of the preceding claims, wherein the composition further comprises one or more monoacyl glycerol.

13. The composition as claimed in Claim 12 wherein the monoacyl glycerol is selected from the group consisting of 2-oleoylglycerol, 2-arachidonoylglycerol, monolaurin, glycerol monomyristate, glycerol monopalmitate, glyceryl hydroxystearate and mixtures thereof, preferably, from the group consisting of glycerol monostearate, glycerol monooleate and glycerol monocaprylate.

14. The composition as claimed in Claim 12 or Claim 13 wherein the monoacyl glycerol is selected from the group glycerol monostearate, glycerol monooleate and glycerol monocaprylate.

15. The composition as claimed in Claim 14 wherein the monoacyl glycerol is glycerol monostearate.

16. The composition as claimed in any one of the preceding claims wherein the composition includes one or more additional ingredients.

17. The composition as claimed in Claim 16, wherein the total amount of the one or more additional ingredients is no more than about 40% by weight, based on the total weight of a composition of the invention.

18. The composition as claimed in Claim 16 or Claim 17, wherein an additional ingredient is an aromatic carboxylic acid.

19. The composition as claimed in Claim 18, wherein the aromatic carboxylic acid is benzoic acid.

20. The composition as claimed in any one of the preceding claims, wherein the antipsychotic drug is lurasidone.

21. The composition as claimed in any one of the preceding claims, wherein at least about 50% of the molecules of the antipsychotic drug are present in dissolved, and/or in molecularly dispersed, form.

22. The composition as claimed in any one of the preceding claims, which is suitable for consumption and/or ingestion within the gastrointestinal tract.

23. A dosage form comprising a composition as defined in any one of the preceding claims and a pharmaceutically-acceptable carrier that is capable of releasing the composition within the gastrointestinal tract.

24. The dosage form as claimed in Claim 23, wherein the carrier is capable of releasing the composition within the small intestine.

25. The dosage form as claimed in Claim 23 or Claim 24, wherein the carrier is capable of releasing the composition within the terminal ileum and/or colon.

26. The dosage form as claimed in any one of Claims 23 to 25, wherein the carrier is an optionally-coated capsule.

27. A composition as defined in any one of Claims 1 to 22, or a dosage form as defined in any one of Claims 23 to 26, for use in human and/or veterinary medicine.

28. A composition as defined in any one of Claims 1 to 22, or a dosage form as defined in any one of Claims 23 to 26, for use in a method of treatment of one or more of schizophrenia, a schizoaffective disorder, including easing the symptoms thereof, bipolar disorder, attention deficit hyperactivity disorder or obsessive-compulsive disorder.

29. The use of a composition as defined in any one of Claims 1 to 22, or a dosage form as defined in any one of Claims 23 to 26, for the manufacture of a medicament for a method of treatment of one or more of schizophrenia, a schizoaffective disorder, including easing the symptoms thereof, bipolar disorder, attention deficit hyperactivity disorder or obsessive-compulsive disorder.

30. A method of treatment of one or more of schizophrenia, a schizoaffective disorder, including easing the symptoms thereof, bipolar disorder, attention deficit hyperactivity disorder or obsessive-compulsive disorder, which method comprises administering a composition as defined in any one of Claims 1 to 22, or a dosage form as defined in any one of Claims 23 to 26, to a person suffering from, or susceptible to, the relevant condition.

31. A process for the preparation of a composition as defined in any one of Claims 1 to 22, which comprises the step of dissolving and/or dispersing the antipsychotic drug or salt thereof in the one or more fatty acids.

32. A process for the preparation of a dosage form as defined in any one of Claims 23 to 26, which comprises the step of loading a composition as defined in any one of Claims 1 to 21 into a carrier as defined in any one of Claims 23 to 26.

33. A process as claimed in Claim 32, which further comprises a process step as claimed in Claim 31.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2020/050892

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/107 A61K9/14 A61K9/16 A61K9/20 A61P25/18
ADD. A61K9/48

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 A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 14 July 2020 | 23/07/2020 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | van de Wetering, P |

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# INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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