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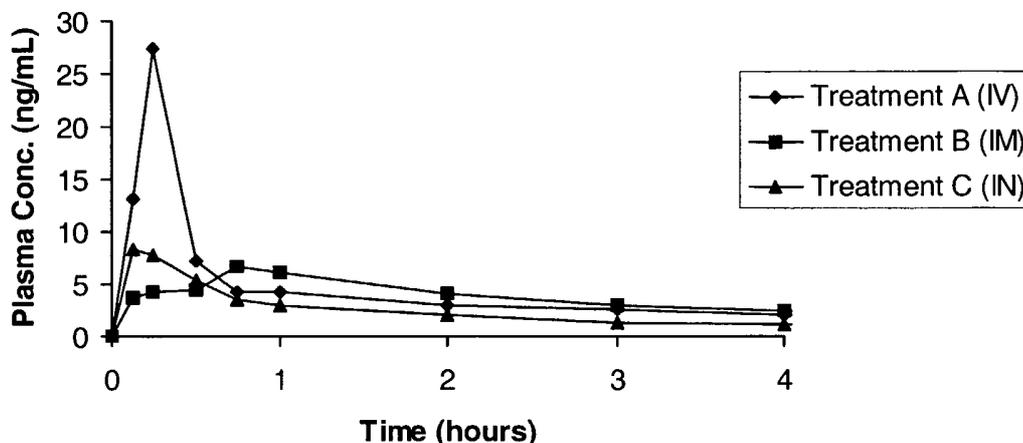
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(54) Title: INTRANASAL DELIVERY OF ANTIPSYCHOTIC DRUGS



(57) Abstract: An intranasal pharmaceutical composition is provided that comprises an antipsychotic drug, such as haloperidol, and a liquid vehicle. Methods of manufacture and administration of the composition are provided as well as methods of treatment of various psychotic episodes, diseases and/or disorders.

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INTRANASAL DELIVERY OF ANTIPSYCHOTIC DRUGS

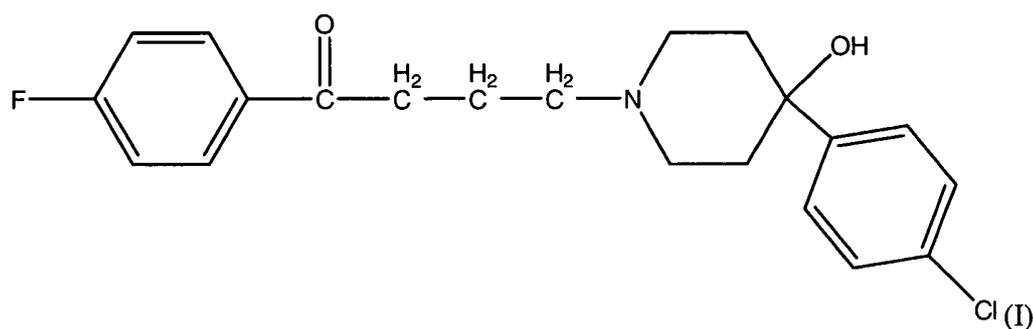
FIELD OF THE INVENTION

[0001] The present invention relates to methods and devices for intranasal delivery of antipsychotics, such as haloperidol.

BACKGROUND OF THE INVENTION

[0002] Haloperidol is a common antipsychotic drug for use in emergency situations due to its rapid onset of action, lack of cardiovascular adverse events, decreased respiratory depression, and a low to moderate sedation profile compared to other agents such as chlorpromazine and the benzodiazepines. Haloperidol is associated with a high incidence of extrapyramidal symptoms that can be treated effectively with anticholinergic agents. Newer antipsychotic agents have been developed to minimize the incidence of adverse events while improving treatment. Despite efforts to identify a superior antipsychotic, haloperidol remains the most widely used and cost-effective agent for rapid neuroleptization and is commonly used in studies as a standard measure of efficacy.

[0003] Haloperidol, a potent butyrophenone, has been used in clinical practice for more than three decades and is an effective antipsychotic used in a wide variety of psychiatric conditions. Haloperidol is a central dopaminergic receptor antagonist. The structure of haloperidol is given below by Formula I.



[0004] The chemical formulation of haloperidol is C₂₁H₂₃ClFNO₂ with a molecular weight of 375.87. It occurs as a white to faintly yellowish, amorphous or microcrystalline powder. The lactate salt is used to formulate the oral solution and immediate release injectable dosage forms. Lactic acid is used to adjust the injection to a pH of 3-3.8. Typical intramuscular doses range from 2-5 mg/dose in

clinical practice. The injection may be repeated as often as every hour although dosing intervals of 4 to 8 hours usually are sufficient. The peak plasma concentration following intramuscular administration occurs at approximately 20 minutes. Haloperidol is metabolized by the liver into inactive metabolites except for reduced haloperidol, which has very limited clinical activity. This metabolism is primarily mediated by the CYP3A4 isoenzyme. The half-life of the lactate formulation in man ranges from 10 to 38 hours.

[0005] The treatment of patients experiencing psychotic symptoms such as delirium, agitation, and violence is both challenging as well as dangerous for the patient and healthcare provider. This is especially relevant in the emergency room and intensive care settings. In many cases, psychological and behavioral methods for obtaining control are not adequate. It thus becomes necessary to treat patients using pharmacological avenues that are both safe and rapid. For treatment during acute psychotic episodes, desirable characteristics of an agent include rapid onset, moderate duration of therapeutic action, minimal side effects, predictable bioavailability, ease and safety of administration, and minimal patient discomfort on administration. To date, haloperidol has been the mainstay of treatment for this purpose. To achieve rapid tranquilization, the drug is usually given either intramuscularly or intravenously off-label.

[0006] The intravenous route is commonly used in intensive care settings. The primary route of administration for uncooperative patients is intramuscular injection. This route is the simplest in uncooperative, aggressive patients. However, significant drawbacks exist with this delivery method. For example, intramuscular administration can be painful and cause a patient already in a psychotic, fragile state of mind to feel even more insecure and increase their sense of being attacked. In addition, muscle enzyme levels may be affected. Both the intravenous and intramuscular routes require the use of needles which poses an infrequent but real risk of infection by blood-borne pathogens to both patients and staff.

[0007] U.S. Patent Publication No. 2003/0017118A1 discloses an inhaled dosage form for delivery of antipsychotic drugs. Although that publication describes an effective route of administration for antipsychotics for pulmonary

inhalation, the delivery of drugs to the lungs often causes coughing and gagging, which can serve to exacerbate the already difficult antipsychotic treatment process. Delivery of medications by oral inhalation is challenging. In standard oral inhalation with a metered dose inhaler, it is common that only 15% of the drug actually makes it to the lung for absorption. Most of the drug formulation impacts in the pharyngeal area and is swallowed. Oral inhalation requires a trained and cooperative patient. Particle size for oral inhalation needs to be less than 10 microns, with optimal particle sizes of less than 3 microns, to be respirable. Further, propellants are commonly required for pulmonary administration.

[0008] For at least the foregoing reasons, there is an unmet medical need for new formulations of antipsychotic drugs such as haloperidol that address one or more of the above disadvantages of current formulations.

SUMMARY OF THE INVENTION

[0009] Intranasal delivery of an antipsychotic, such as haloperidol, provides an alternative drug delivery route to parenteral, inhalation, oral and other routes of administration. Rapid systemic availability and the avoidance of hepatic first pass metabolism is possible with intranasal delivery of drugs.

[0010] In one embodiment, a device is provided for delivering an antipsychotic drug intranasally, comprising an intranasal unit or metered dose sprayer containing one or more doses of a sprayable, liquid solution including an amount of an antipsychotic drug effective to treat a psychotic episode. The antipsychotic drug can be haloperidol or a salt thereof, such as haloperidol lactate. Other suitable antipsychotic drugs include, without limitation, butyrophenones, phenothiazines, thiozanthenes, miscellaneous antipsychotics and "new generation" or "atypical" antipsychotics, including benperidol, droperidol, fluanisone, haloperidol decanoate, moperone chlorohydrate, pipamperone dichlorohydrate, trifluoperidol chlorohydrate, chlorpromazine, prochlorperazine, fluphenazine, trifluoperazine, perphenazine, acetophenazine, carphenazine, triflupromazine, mesoridazine, thioridazine, thiothixene, chlorprothixene, loxapine, molindone, pimozide, clozapine, risperidone, olanzapine, sertindole, supiride, amisulpride and remoxipride.

[0011] In another embodiment, a method of administering an antipsychotic drug to a patient also is provided. In one embodiment, the method includes the step of delivering intranasally, in a sprayable, aqueous solution, an amount of an antipsychotic drug such as haloperidol lactate effective to treat a psychotic episode.

[0012] In another embodiment, a method of treating a psychotic episode is provided. In one embodiment, the method includes the step of delivering intranasally an effective amount of an antipsychotic drug, such as haloperidol lactate, in a sprayable, aqueous solution. The related terms “therapeutically effective amount,” “prophylactically effective amount,” “effective amount” or “amount effective to treat” as used herein refer to an amount of antipsychotic drug or agent that is sufficient to elicit the required or desired therapeutic and/or prophylactic response, as the particular treatment context may require.

[0013] In still another embodiment, a sprayable solution (and methods for producing the sprayable solution) for use in an intranasal unit or metered dose sprayer is provided. In one embodiment, the solution comprises about 5 mg/ml to about 100 mg/ml of haloperidol or a dose equivalent thereof of another antipsychotic drug, water for injection, and one or more pharmaceutically acceptable excipients.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] Figure 1 is a graph showing plasma concentration levels of haloperidol after intranasal, intravenous and intramuscular drug delivery over 4 hours.

[0015] Figure 2 is a graph showing plasma concentration levels of haloperidol after intranasal, intravenous and intramuscular drug delivery over 48 hours.

DETAILED DESCRIPTION OF THE INVENTION

[0016] While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any way. Embodiments illustrated under

any heading may be combined with embodiments illustrated under any other heading.

[0017] The use of numerical values in the various ranges specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word “about.” In this manner, slight variations above and below the stated ranges can be used to achieve substantially the same results as values within the ranges. As used herein, the terms “about” and “approximately” when referring to a numerical value shall have their plain and ordinary meanings to one skilled in the art of pharmaceutical sciences or the art relevant to the range or element at issue. The amount of broadening from the strict numerical boundary depends upon many factors. For example, some of the factors to be considered may include the criticality of the element and/or the effect a given amount of variation will have on the performance of the claimed subject matter, as well as other considerations known to those of skill in the art. Thus, as a general matter, “about” or “approximately” broaden the numerical value, yet cannot be given a precise limit. For example, in some cases, “about” or “approximately” may mean $\pm 5\%$, or $\pm 10\%$, or $\pm 20\%$, or $\pm 30\%$ depending on the relevant technology. Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values.

Antipsychotic Drugs

[0018] The terms “antipsychotic,” “antipsychotic agent” and “antipsychotic drug,” and plurals thereof, are synonymous and denote a psychoactive drug that has the ability to calm psychotic states and/or make a psychotic patient more manageable. A psychotic state maybe characterized by psychosis—characterized, without limitation, by gross impairment in reality testing as evidenced by delusions, hallucinations, markedly incoherent speech or disorganized and agitated behavior without apparent awareness on the part of the patient of the incomprehensibility of his behavior. Antipsychotic drugs also are commonly referred to as neuroleptics or neuroleptic drugs.

[0019] Classes of antipsychotic drugs include butyrophenones, of which haloperidol is the most prominent member, but also include, without limitation, benperidol, droperidol, fluanisone, haloperidol decanoate, moperone chlorohydrate, pipamperone dichlorohydrate and trifluoperidol chlorohydrate; phenothiazines, such as chlorpromazine, prochlorperazine, fluphenazine, trifluoperazine, perphenazine, acetophenazine, carphenazine, triflupromazine, mesoridazine and thioridazine; thiozanthenes, such as thiothixene and chlorprothixene; miscellaneous antipsychotics, such as loxapine, molindone and pimozide; and “new generation” or “atypical” antipsychotics, such as clozapine, risperidone, olanzapine, sulpiride, amisulpride, remoxipride and setindole. Reference to any drug substance herein includes, unless specifically mentioned otherwise, pharmaceutically acceptable salts of that drug substance. For example, the term “haloperidol” refers both to haloperidol and to salts thereof, including, without limitation, haloperidol lactate. All described antipsychotic drugs can be formulated into a sprayable solution according to methods known in the pharmaceutical arts.

[0020] Haloperidol (and salt forms thereof, *e.g.*, lactate) has an accepted dosage range of about 0.1 mg to about 200 mg, or even higher in some cases. Dosing frequency typically ranges from 1 dose per hour to one single dose that is not repeated, as is necessary and effective to manage a patient’s symptoms. Tablet formulations available commercially include: 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg and 20 mg of haloperidol lactate. Liquid oral formulations include 1 mg/ml and 2 mg/ml solutions of haloperidol lactate. Parenteral formulations include 5 mg/ml (haloperidol lactate), 50 mg/ml (haloperidol decanoate) and 100 mg/ml (haloperidol decanoate) products.

[0021] Specific intranasal doses of haloperidol (or salt forms thereof) include any increment or range capable of being formed from about 0.1 mg to about 100 mg, including, without limitation: about 0.5 mg, about 1 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg,

about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg and about 100 mg.

[0022] In formulating a suitable dosage form for intranasal delivery, the concentration of the drug in the sprayable solution typically is at least about 5, at least about 10, at least about 11, at least about 12, at least about 13, at least about 14 or at least about 15 times that of an oral or injectable dose in order to achieve satisfactory doses in a typical 0.1 ml spray volume. In one embodiment, the concentration of psychotic drug (*e.g.* haloperidol) in a sprayable solution can range from about 0.25% to about 20%, about 0.5% to about 15%, or about 1.0% to about 10%, by weight. Illustrative intranasal psychotic drug solution concentrations for a sprayable solution are about 0.75%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19% and about 20%, by weight.

[0023] Haloperidol (and salt forms thereof) doses may be calculated based on the weight of the patient, for example about 0.005 mg/kg (weight of patient) to about 10 mg/kg, including, without limitation, about 0.01 mg/kg, about 0.05 mg/kg, about 0.1 mg/kg, about 0.5 mg/kg, about 1.0 mg/kg, about 2 mg/kg, about 5 mg/kg or about 10 mg/kg. Further, effective plasma levels of haloperidol lactate may include any increment in the range of from about 5 mg/l to about 25 mg/l, typically ranging from about 8 mg/l to about 17 mg/l, for example, and without limitation, about 8 mg/l, about 10 mg/l, about 12 mg/l, about 15 mg/l and about 18 mg/l.

[0024] As used herein, in the context of a dosage range, an "increment" can be any value within a range that can be physically delivered in the dosage form. Physical limitations of the intranasal metered dose spray device and in the ability to prepare precisely an intranasal solution with a given concentration of an antipsychotic active ingredient will limit the size of the increments, which include, without limitation, increments of 0.001, 0.01, 0.1 and 1.0 mg, mg/kg or mg/l, as is appropriate.

[0025] Dose equivalents for other antipsychotics are well established. In reference to a 2 mg dose of haloperidol lactate, Table A provides non-limiting examples of dose equivalents and suitable doses for certain other antipsychotics.

Table A*

Chemical classification	Drug Name Generic (Trade)	Dose equivalent** (mg)	Dose range (mg)** (frequency)
Phenothiazine	Chlorpromazine (Thorazine)	100	10-100 mg; q 4-8h
	Prochlorperazine (Compazine)	15	2.5-20 mg; q 4-6h
	Fluphenazine (Prolixin)	2	0.25-10 mg; q 6-8h
	Trifluoperazine (Stelazine)	5	1-2 mg; q 4-6h
	Perphenazine (Trilafon)	8	4-16 mg; q 6-12h
	Acetophenazine (Tindal)	20	20-60 mg; q 24h
	Carphenazine (Proketazine)	25	50-150 mg; q 8-24h
	Triflupromazine (Vesprin)	25	1-10 mg; q 6-24h
	Mesoridazine (Serentil)	50	25-50 mg; q 1-8h
	Thioridazine (Mellaril)	100	50-100 mg; q 6-12h
	Thioxanthine	Thiothixene (Navane)	4
Chlorprothixene (Taractan)		100	10-50 mg; q 6-8h
Butyrophenone	Haloperidol (Haldol)	2	0.5-20 mg; q 0.5-6h
Miscellaneous	Loxapine (Loxitane)	10	10-50 mg; q 4-6h
	Molindone (Moban)	10	1-75 mg; q 6-8h
	Pimozide (Orap)	2	1-16 mg; q 24h
New Generation	Clozapine (Clozapril)	50	25-300 mg; q 12-24h
	Risperidone (Risperdal)	1	1-6 mg; q 12-24h
	Olanzapine (Zyprexa)	1.5	5-20 mg; q 24h
	Sertindole (Serlect)	5	12-24 mg; q 24h

*See, for example, Table 9.3 of Julien, RM, A PRIMER OF DRUG ACTION, 8TH Ed., W. H., Freeman & Co. (1998), p. 259.

**Dose equivalents and dose ranges are approximate. Approximate clinical dose ranges and frequency of administration will differ, depending upon, without limitation, dosage form, patient status/characteristics and titration vs. maintenance.

[0026] U.S. Patent Publication No. 2003/0017118 is incorporated herein by reference in its entirety; this reference relates to use of various antipsychotic drugs for particulate delivery by the inhalation route and equivalent dosage ranges for those antipsychotics. Dose ranges, whether expressed in terms of mg per dose, mg

per kg of patient's weight, or mg/l, of patient's serum, plasma or blood, can readily be calculated based on the ratios presented in Table A, or based on any other equivalency data known in the pharmaceutical arts.

Unit Dose and Multi Dose Sprayers

[0027] An "intranasal" dosage form or "intranasally deliverable" dosage form is a dosage form suitable for delivering an active ingredient to mucosa of the nasal cavity and/or nasopharynx of a subject. Intranasal dosage forms typically introduce particles into the nasal cavity. Without being bound by theory, the particles are believed to be substantially retained in the nasal cavity and nasopharynx because: 1) the particles are introduced through the nose and 2) the particles are sufficiently large that they substantially do not travel past the nasopharynx and into the remainder of the respiratory system. This is in contrast to inhaled dosage forms that are administered orally, where particle size is gauged to reach the bronchii, the bronchiole and alveoli, as is shown, for illustrative purposes only, in U.S. Patent Publication No. 2003/0017118, in which an aerosolized antipsychotic drug is delivered by the inhalation route.

[0028] Described herein are devices and methods for delivering antipsychotic drugs intranasally, such as haloperidol. In one embodiment, the antipsychotic drugs are delivered in a liquid vehicle (*e.g.* solution or suspension) by a unit-dose delivery device or sprayer. In another embodiment, the drugs can be delivered by a multi-dose delivery device.

[0029] An "metered dose sprayer," "unit-dose sprayer," "metered dose delivery device" or an "unit-dose delivery device", in the context of intranasal delivery devices, are synonymous terms for a delivery device for repeated delivery of defined quantities of a drug product via the intranasal route. Such devices have the capability of consistently delivering a desired amount of a pharmaceutical composition and are easy to operate by patients and medical personnel. Further, they typically leave little or no remaining drug in the device and can thus be discarded without concern.

[0030] Intranasal unit dose sprayers are broadly available and modes of their use are well-known in the pharmaceutical field. Examples of an intranasal unit

dose sprayers are described in International Patent Publication No. WO 02/13886, designating the United States, and U.S. Patent Publication No. 2003/0163099, each of which are incorporated herein by reference in their entirety. The device of WO 02/13886 is programmable and provides individual vials for each dose. Another sprayer for intranasal use for delivery of multiple single doses of a powder from a single vial is described in United States Patent No. 6,055,979. Unit dose sprayers for intranasal use are broadly available commercially, for example, from Pfeiffer GmbH of Radolfzell, Germany. One illustrative intranasal unit dose sprayer is the "Unitdose Second Generation" sprayer from Pfeiffer.

[0031] In one embodiment, a composition of the invention is packaged in an intranasal unit dose sprayer comprising one to a plurality of dosage compartments, each compartment containing a single dose of the antipsychotic drug. The term "plurality" herein means more than one but less than about 100. For example, a plurality in the present context could illustratively represent about 5, about 10, about 20, about 30, about 40, about 50, about 60, about 70, about 80, or about 90 dosage compartments or any increment within the range of 2 to 100.

Liquid Vehicle

[0032] In one embodiment of a composition of the invention, the antipsychotic drug is dissolved and/or solubilized in a liquid vehicle. In one embodiment, the liquid vehicle comprises water and the formulation therefore is described as "aqueous" which includes suspensions, emulsions, liposomes, micellar systems and the like, in which the primary solvent is water. In other embodiments, the solvent system can be non-aqueous.

[0033] In another embodiment, where the antipsychotic drug is haloperidol, the haloperidol is solubilized in a solution of lactic acid. Without being bound by theory, it is believed that the lactic acid forms the lactate form of haloperidol and adjusts the pH to an acceptable level for intranasal administration. Other compounds can be used, as needed, to adjust, or to buffer the pH of the solution. In the case of haloperidol decanoate, which has low solubility in water, the drug product can include a suitable solubilizing compound or compounds, such as,

without limitation: an oil or an ester product thereof, a triglyceride, a cyclodextrin or a surfactant.

[0034] Many methods for solubilizing water-insoluble drug compounds, such those as certain of the antipsychotics useful in the drug products described herein, are known in the pharmaceutical arts and are appropriate so long as bioavailability of the antipsychotic drug is sufficient for treatment of a patient and adverse reactions, such as irritation to the nasal mucosa, are minimized. In other embodiments, the antipsychotic drug is solubilized in a glycol or in another organic solvents and/or solubilization systems as are known in the pharmaceutical arts.

[0035] Compositions of the invention can be prepared by any suitable process. In one embodiment, the process comprises steps of adding, in any order, the liquid vehicle, the antipsychotic drug and optionally one or more pharmaceutically acceptable excipients to a vessel to form a mixture and agitating the mixture to form the intranasally deliverable composition.

[0036] The intranasally deliverable composition can optionally be filtered, for example through a microporous filter. In one embodiment, the filter has an average pore size of about 10 μm to about 40 μm or about 15 μm to about 25 μm . In another embodiment, the filter has an average pore size of about 0.22 μm .

[0037] A composition of the invention can be placed in an intranasally deliverable composition (for example in one or more vials). The vials can be sealed and optionally sterilized, for example autoclaved. Either an aseptic process or terminal sterilization can be utilized to prepare compositions of the invention, for example where the composition and/or delivery device are to be sterilized.

Pharmaceutical Excipients

[0038] Compositions of the invention can, if desired, include one or more pharmaceutically acceptable excipients. The term "excipient" herein means any substance, not itself a therapeutic agent, used as a carrier or vehicle for delivery of a therapeutic agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a dose unit of the composition.

[0039] Excipients include, by way of illustration and not limitation, diluents; wetting agents; antioxidants, surfactants, preservatives, pH modifying agents; salts; natural and synthetic oils and esters thereof; surfactants; solubilizing compounds, such as cyclodextrins, triglycerides and phospholipids; surface modifying agents; substances added to mask or counteract a disagreeable taste or odor; flavors; sweeteners; chelating agents; preservatives; viscosity modifiers, such as thickening agents; dyes; coloring agents; fragrances; and substances added to improve appearance of the composition. Any such excipients can be used in any dosage forms of according to the present invention, including liquid, solid or semi-solid dosage forms. Each excipient, if desired, is typically present in an individual amount of about 0.0025% to about 10%, about 0.025% to about 5%, or about 0.25% to about 2.5%, by weight.

[0040] Acids, bases and buffers are collectively referred to herein as "pH modifying agents." Suitable candidates for any of these agents also are well-known in the pharmaceutical arts.

[0041] The foregoing excipients and classes of excipients can have multiple roles as is known in the art. Thus, the classification of excipients above is not to be construed as limiting in any manner.

Bioavailability

[0042] In various embodiments, upon intranasal administration of a haloperidol composition of the invention to a subject, the subject exhibits one or more of: (A) a T_{max} not greater than about 0.1, about 0.15, about 0.18, about 0.20, about 0.25, about 0.3 hours, about 0.5 hours, about 0.75 hours or about 1 hour; (B) a C_{max} of at least about 4, at least about 5, at least about 6, at least about 7, at least about 8, at least about 9, or at least about 10 ng/ml; and/or (C) an AUC of at least about 22, at least about 23, at least about 24, at least about 25, at least about 26, at least about 27, at least about 28, at least about 29, or at least about 30 ng*h/ml. In one such embodiment, the composition is administered to a subject in an amount corresponding to about 2.5 mg of haloperidol moiety.

[0043] In other embodiments, upon intranasal administration of a haloperidol composition of the invention to a subject, the subject exhibits one or more of: (A) a

T_{max} of about 0.1 to about 0.75 hours or about 0.125 to about 0.5 hours; (B) a C_{max} of about 4 to about 20 ng/ml or about 6 to about 17 ng/ml; and/or (C) an AUC of about 20 to about 50 ng*h/ml or about 25 to about 40 ng*h/ml. In one such embodiment, the composition is administered to a subject in an amount corresponding to about 2.5 mg of haloperidol moiety.

[0044] In other embodiments, upon intranasal administration of a haloperidol composition of the invention to a subject, the subject exhibits two or more of: (A) a T_{max} not greater than about 0.1, about 0.15, about 0.18, about 0.20, about 0.25, about 0.3 hours, about 0.5 hours, about 0.75 hours or about 1 hour; (B) a C_{max} of at least about 4, at least about 5, at least about 6, at least about 7, at least about 8, at least about 9, or at least about 10 ng/ml; and/or (C) an AUC of at least about 22, at least about 23, at least about 24, at least about 25, at least about 26, at least about 27, at least about 28, at least about 29, or at least about 30 ng*h/ml. In one such embodiment, the composition is administered to a subject in an amount corresponding to about 2.5 mg of haloperidol moiety.

[0045] In still other embodiments, upon intranasal administration of a haloperidol composition of the invention to a subject, the subject exhibits two or more of: (A) a T_{max} of about 0.1 to about 0.75 hours or about 0.125 to about 0.5 hours; (B) a C_{max} of about 4 to about 20 ng/ml or about 6 to about 17 ng/ml; and/or (C) an AUC of about 20 to about 50 ng*h/ml or about 25 to about 40 ng*h/ml. In one such embodiment, the composition is administered to a subject in an amount corresponding to about 2.5 mg of haloperidol moiety.

[0046] In other embodiments, upon intranasal administration of a haloperidol composition of the invention to a subject, the subject exhibits: (A) a T_{max} of about 0.1 to about 0.75 hours or about 0.125 to about 0.5 hours; (B) a C_{max} of about 4 to about 20 ng/ml or about 6 to about 17 ng/ml; and (C) an AUC of about 20 to about 50 ng*h/ml or about 25 to about 40 ng*h/ml. In one such embodiment, the composition is administered to a subject in an amount corresponding to about 2.5 mg of haloperidol moiety.

[0047] In yet other embodiments, upon intranasal administration of a haloperidol composition of the invention to a subject, the subject exhibits a plasma

concentration of haloperidol of one or more of the following: at least about 10 ng/ml 7.5 minutes after administration, at least about 5 ng/ml 15 minutes after administration, and at least about 0.5 ng/ml 1 hour after administration. In one such embodiment, the composition is administered to a subject in an amount corresponding to about 2.5 mg of haloperidol moiety.

[0048] In other embodiments, upon intranasal administration of a haloperidol composition of the invention to a subject, the subject exhibits a plasma concentration of haloperidol of one or more of the following: at least about 15 ng/ml 7.5 minutes after administration, at least about 10 ng/ml 15 minutes after administration, and at least about 1 ng/ml 1 hour after administration. In one such embodiment, the composition is administered to a subject in an amount corresponding to about 2.5 mg of haloperidol moiety.

Combination Therapy

[0049] In various embodiments, compositions of the invention can include a mixture of two or more antipsychotics. Such compositions also can include other active ingredients. For instance, the intranasal dosage form might include an anticholinergic agent, such as, without limitation: ipratropium bromide, atropine, scopolamine HBr (Hyoscine HBr), L-hyoscyamine (Anaspaz), L-alkaloids of belladonna (Belafoline), tincture of belladonna alkaloids, homatropine, homatropine methylbromide, methscopolamine (Pamine), anisotropine (Valpin), anisotropine with phenobarbital, clindinium (Quarzan), glycopyrrolate (Robinul), hexocyclim (Tral), isopropamide (Darbid), mepenzolate (Cantil), methantheline (Banthine), oxyphencyclimine (Daricon), propantheline (Pro-Banthine), tridihexethyl (Pathilon), dicyclomine (Bentyl), cyclopentolate (Cyclogyl), tropicamide (Mydriacyl), trihexyphenidyl (Artane), benztropine (Cogentin), orphenadrine HCl (Disipal), ethopropazine (Parsidol), diphenhydramine (Benadryl), cycrimine (Pagitane), biperiden (Akineton) benztropine, benzhexol, procyclidine and orphenadrine to reduce extrapyramidal symptoms.

[0050] Those skilled in the art will readily appreciate that numerous other embodiments, modifications and equivalents are contemplated and encompassed by the disclosure of the present invention.

[0051] All U.S. Patents and published U.S. patent applications listed herein are hereby incorporated by reference in their entirety. All patents, patent applications and publications referenced herein are hereby incorporated by reference herein to the fullest extent allowed under the law.

EXAMPLES

[0052] The following examples are for illustrative purposes only and are not to be construed as limiting the present invention in any manner.

Example 1 - Haloperidol intranasal formulation - 25 mg/ml

[0053] An intranasal drug product containing haloperidol was manufactured according to the following protocol. 1.18 grams of 85% USP lactic acid was added to approximately 50 g water for injection, USP with mixing. 2.5 grams of haloperidol was slowly added to the lactic acid solution while mixing until the haloperidol was dissolved. The solution was then brought to a volume of 100 ml, and was then filtered through a 22 μ m Millipak-20 filter and autoclaved. The solution was then dispensed in appropriate amounts into an intranasal metered dose sprayer to deliver a desired dose of haloperidol, such as 100 μ L (2.5 mg). For any metered dose sprayer, such as that of International Patent Publication WO 02/13886, the amount dispensed is that dosage amount plus a residual volume of solution that cannot be dispensed by the delivery device.

Example 2 - Antipsychotic Formulations

[0054] Additional intranasal formulations may be prepared as follows. Table B provides suitable ranges for these additional products.

Table B – additional antipsychotic compounds and ranges.

Drug substance	Concentration Range for Drug Product (mg/ml)	Dosage range (perdose)	Excipient
Haloperidol	about 10 to 100	0.5 mg to 100 mg	Lactic acid
Risperidone*	about 1 to 200	0.1 to 20	
Olanzapine*	about 50 to 200	5 to 20	
* In a mildly acidic aqueous system or a non-aqueous system			

[0055] Additional ingredients may be added to the formulations described above, including, sweeteners, flavors, colorings, buffers, salts, chelating agents, preservatives, and viscosity modifiers.

Example 3 - Bioavailability study comparing intranasal, intramuscular and intravenous administration of haloperidol lactate

[0056] A study was performed to compare the bioavailability of 2.5 mg haloperidol delivered intravenously (Treatment A), intramuscularly (Treatment B) and intravenously (Treatment C). The intranasal dosage form is described in Example 1, above. One spray containing 2.5 mg haloperidol in 100 μ L was administered to one nostril for each patient using a unit-dose spray pump (Pfeiffer of America, Princeton, NJ).

[0057] The intramuscular dose was given as a single injection of 0.5 ml of a 5.0 mg/ml solution of haloperidol lactate (Haloperidol Injection (5.0 mg/ml) by Ortho-McNeil). The intravenous dose was prepared by diluting 0.5 ml of a 5.0 mg/ml solution of haloperidol lactate in D₅W (5% dextrose in water) and was infused over 15 minutes.

[0058] Prior to dosing and at present time points, the motor portion (section III) of the Unified Parkinson's Disease Rating Scale, the Simpson Angus scale, and the Barnes Akathisia Scale were performed to monitor for the occurrence of extrapyramidal symptoms, tardive dyskinesia, tardive dystonia, and akathisia. Vital signs, including temperature, were also monitored.

[0059] Blood samples were collected in 10 ml tubes containing the anticoagulant sodium heparin. Serial blood samples were obtained by venipuncture according to the following schedule: 0 (pre-dose), 7.5, 15, 30, and 45 minutes, and 1, 2, 3, 4, 8, 16, 26, and 48 hours following administration. Actual sampling times were used in the pharmacokinetic analysis. After collection, the blood was centrifuged in a refrigerated centrifuge at 4 °C to separate the plasma and the cells, and the plasma was transferred to polypropylene tubes. The plasma was stored at or below -20 °C at the study site until it was shipped to the analytical laboratory.

[0060] Plasma concentrations of Haloperidol were determined using negative ion chemical ionization, selective ion monitoring GC/MS with a linear range of 0.100-50.00 ng/ml. Concentrations less than 0.100 ng/ml were reported as below quantitation limit (BQL).

[0061] Pharmacokinetic results of the study shown in Table C, below. The mean (n=4; 2 male, 2 female) plasma concentration versus time curve profiles over the first 4 hours are shown in Figure 1. As is shown, absorption of haloperidol following intranasal administration was rapid. Haloperidol concentrations reached a peak in one subject at 7.5 minutes, in two other subjects at 15 minutes, and at 30 minutes for the last subject.

[0062] Median T_{max} values were 15 and 37.5 minutes for the intranasal and intramuscular doses, respectively. One subject had an unexpected T_{max} of 16 hours following a gradual increase in plasma concentration over time after intramuscular administration. C_{max} values after the intranasal dose were slightly higher than values obtained after the intramuscular dose and occurred consistently earlier. One subject had a C_{max} of 16.2 ng/ml following intranasal administration. The other subjects had C_{max} values between 7.5-7.9 ng/ml after intranasal delivery.

[0063] Relative bioavailability (Relative F) of the intramuscular dose to intranasal dose was on average 48.6%. The absolute bioavailability (F) of haloperidol by intranasal and intramuscular routes were 63.8% and 134.5%, respectively. Clearance times were comparable between the administration routes, and intravenous and intranasal had similar half-lives.

Table C. Mean (CV as a %) single dose haloperidol lactate pharmacokinetic parameters following IV, IM and IN administration

PK Parameter	IV (2.5 mg)	IM (2.5 mg)	IN (2.5 mg)
T_{max} (h)*	0.25 (0.25-0.25)	0.625 (0.25-16)	0.25 (0.125-0.5)
C_{max} (ng/ml)	23.3 (65.37)	8.42 (91.41)	9.8 (43.57)
$T_{1/2}$ (h)	17.1 (45.5)	28.8 (19.1)	16.9 (45.0)
AUC_{0-t} (ng•h/ml)	50.77 (16.78)	59.69 (29.65)	31.67 (14.84)
$AUC_{0-\infty}$ (ng•h/ml)	60.4 (15.6)	81.8 (26.7)	37.9 (21.5)
MRT (h)	12.7 (29.6)	16.1 (35.3)	12.9 (22.7)
CL/F or CL_{ss}/F (L/h)	42.1 (15.5)	32.8 (33.9)	68.3 (20.3)
V_{ss} (L)	934.0 (44.9)	-	-
V_z/F (L)	1069 (51.5)	1356 (38.7)	1575 (39.4)
F (%)	assume 100%	134.5 (20.8)	63.8 (24.4)
Relative F (IM/IN) (%)	-	-	48.6 (29.4)
*median and range given for T_{max}			

[0064] These data demonstrate that haloperidol lactate is effectively delivered through the intranasal route, providing a safe and nonthreatening alternative to injection or inhalation of haloperidol.

[0065] Whereas particular embodiments of the invention have been described herein for the purpose of illustrating the invention and not for the purpose of limiting the same, it will be appreciated by those of ordinary skill in the art that numerous variations of the details, materials and arrangement of parts may be made within the principle and scope of the invention without departing from the invention as described in the appended claims.

WHAT IS CLAIMED IS:

1. A sprayable solution for use in an intranasal metered dose sprayer, comprising
 - a) about 0.25% to about 10%, by weight, haloperidol or a dose equivalent thereof of an antipsychotic drug other than haloperidol; and
 - b) a pharmaceutically acceptable excipient.
2. The sprayable solution of claim 1, further comprising a pH modifying agent.
3. The sprayable solution of claim 2 wherein the pH modifying agent is lactic acid.
4. The sprayable solution of claim 3, comprising about 0.25% to about 10% haloperidol lactate, by weight.
5. The sprayable solution of claim 1, comprising about 2.5% haloperidol lactate, by weight.
6. An intranasally deliverable pharmaceutical composition comprising haloperidol or a pharmaceutically acceptable salt thereof and an aqueous vehicle, wherein upon intranasal administration of the composition to a subject in an amount sufficient to provide about 2.5 mg of haloperidol, the subject exhibits a T_{max} not more than about 1 hour after administration.
7. The composition of claim 6 wherein the upon intranasal administration of the composition to a subject in an amount sufficient to provide about 2.5 mg of haloperidol, the subject exhibits a C_{max} of at least about 4 ng/ml.
8. The composition of claim 6 wherein upon intranasal administration of the composition to a subject in an amount sufficient to provide about 2.5 mg of haloperidol, the subject exhibits an $AUC_{(0-t)}$ of at least about 22 ng*h/ml.
9. The composition of any of claims 6, 7 or 8 wherein the composition further comprises lactic acid.
10. The composition of claim 9 wherein the composition comprises about 10 to about 50 mg of haloperidol, about 5 to about 20 mg of lactic acid 85%, USP, q.s. to 1.0 ml with water for injection.

11. An intranasally deliverable composition comprising haloperidol, lactic acid and water, wherein the composition is prepared by a process comprising steps of adding, in any order, the water, lactic acid and haloperidol to a vessel to form a mixture and agitating the mixture to form the intranasally deliverable composition.

12. The intranasally deliverable composition of claim 11, wherein the process further comprises steps of adding additional water to the mixture to form a volume-adjusted composition and filtering the volume-adjusted composition through a microporous filter to form the intranasally deliverable composition.

13. The intranasally deliverable composition of claim 12, wherein the filter has an average pore size of about 10 μm to about 40 μm .

14. The intranasally deliverable composition of claim 12, wherein the filter has an average pore size of about 0.22 μm .

15. The intranasally deliverable composition of claim 12, wherein the process further comprises steps of placing the intranasally deliverable composition in a vial, sealing the vial, and sterilizing the sealed vial.

16. The intranasally deliverable composition of claim 12, wherein sterilizing step comprises autoclaving.

17. A device for delivering an antipsychotic drug intranasally, comprising an intranasal metered dose sprayer containing one or more doses of a sprayable solution comprising an amount of an antipsychotic drug effective to treat a psychotic episode.

18. The device of claim 17, wherein the antipsychotic drug is haloperidol.

19. The device of claim 18, wherein the sprayable solution comprises an amount of haloperidol ranging from between about 5 mg/ml and about 100 mg/ml.

20. The device of claim 18, wherein the sprayable solution contains about 25 mg/ml haloperidol.

21. The device of claim 18, wherein the sprayable solution further comprises a pH modifying agent.

22. The device of claim 21, wherein the pH modifying agent is lactic acid.

23. The device of claim 18, wherein the sprayable solution comprises a lactate salt of haloperidol.
24. The device of claim 17, wherein the dose of haloperidol is present in an amount of about 1.0 mg and 10 mg.
25. The device of claim 17, wherein the antipsychotic drug is selected from the group consisting of haloperidol, benperidol, droperidol, fluanisone, haloperidol decanoate, moperone chlorohydrate, pipamperone dichlorohydrate, trifluoperidol chlorohydrate chlorpromazine, prochlorperazine, fluphenazine, trifluoperazine, perphenazine, acetophenazine, carphenazine, triflupromazine, mesoridazine, thioridazine, thiothixene, chlorprothixene, loxapine, molindone, pimozide, clozapine, risperidone, olanzapine, sertindole, supiride, amisulpride and remoxipride.
26. A method of treating a psychotic episode in a subject in need thereof, comprising the step of intranasally delivering a sprayable solution containing an amount of the antipsychotic drug sufficient to treat the psychotic episode.
27. The method of claim 26, wherein the antipsychotic drug is haloperidol.
28. The method of claim 26, wherein the sprayable solution comprises haloperidol in a concentration of about 10 mg/ml and about 100 mg/ml.
29. The method of claim 27, wherein the sprayable solution comprises about 25 mg/ml haloperidol.
30. The method of claim 26, wherein the sprayable solution further comprises a pH modifying agent.
31. The method of claim 30, wherein the pH modifying agent is lactic acid.
32. The method of claim 27, wherein the sprayable solution comprises a lactate salt of haloperidol.
33. The method of claim 26, wherein the haloperidol is present in a total amount of about 1.0 mg to about 10 mg.
34. The method of claim 33, wherein the haloperidol is present in a total amount of about 2.5 mg.

35. The method of claim 26 wherein the antipsychotic drug is delivered by a unit dose sprayer comprising a plurality of doses.
36. The method of claim 35, wherein the intranasal unit dose sprayer comprises a plurality of dosage compartments, each compartment containing a single dose of the antipsychotic drug.
37. The method of claim 26, wherein the antipsychotic drug is selected from the group consisting of haloperidol, benperidol, droperidol, fluanisone, haloperidol decanoate, moperone chlorohydrate, pipamperone dichlorohydrate, trifluoperidol chlorohydrate chlorpromazine, prochlorperazine, fluphenazine, trifluoperazine, perphenazine, acetophenazine, carphenazine, triflupromazine, mesoridazine, thioridazine, thiothixene, chlorprothixene, loxapine, molindone, pimozide, clozapine, risperidone, olanzapine, sertindole, supiride, amisulpride and remoxipride.
38. A method of administering an antipsychotic drug to a subject, comprising the step of intranasally delivering a sprayable solution to the subject containing an amount of an antipsychotic drug effective to treat a psychotic episode.
39. The method of claim 38, wherein the antipsychotic drug is haloperidol.
40. The method of claim 38, wherein the sprayable solution comprises an amount of haloperidol ranging from between about 10 mg/ml and about 100 mg/ml.
41. The method of claim 38, wherein the sprayable solution contains about 25 mg/ml haloperidol.
42. The method of claim 38, wherein the sprayable solution further comprises a pH modifying agent.
43. The method of claim 42, wherein the pH modifying agent is lactic acid.
44. The method of claim 38, wherein the sprayable solution comprises a lactate salt of haloperidol.
45. The method of claim 38, wherein the dose of haloperidol ranges from between 0.5 mg and 10 mg.
46. The method of claim 45, wherein the dose is about 2.5 mg haloperidol.

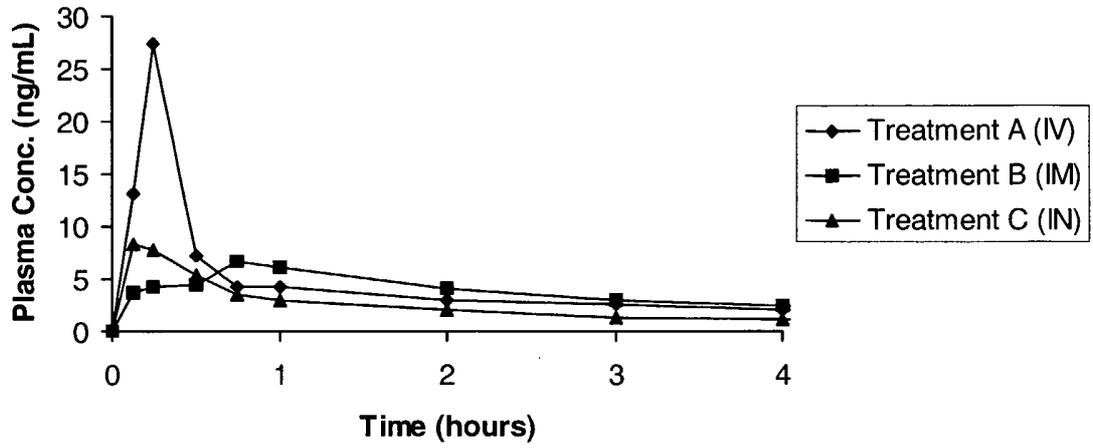


Fig. 1

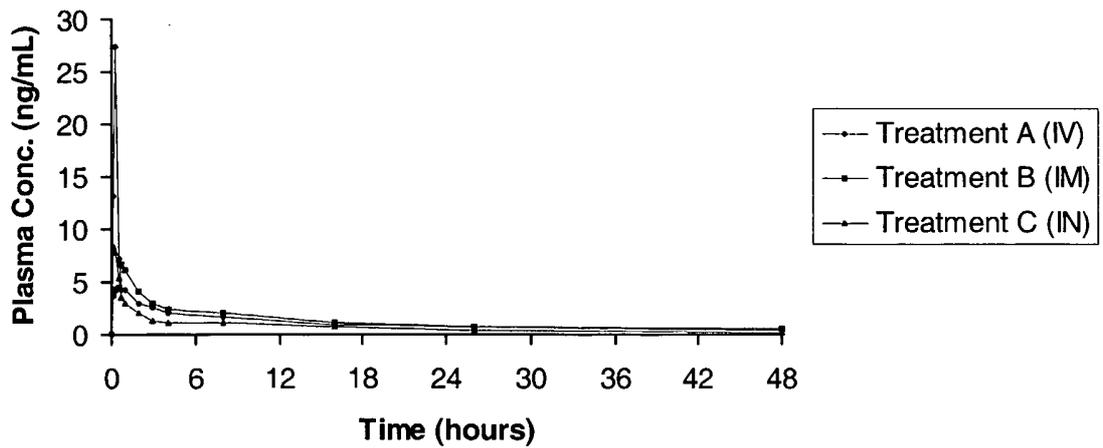


Fig. 2