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(54) Title: PHARMACEUTICAL FORMULATIONS CONTAINING QUETIAPINE

(57) Abstract: The invention provides novel dosage forms of quetiapine and its salts, particularly quetiapine hemifumarate including wax dosage forms, press-coat dosage forms, and sprinkle dosage forms, and other novel dosage forms. The invention also provides sustained release and pulsed release dosage forms of quetiapine and its salts. Methods of making novel quetiapine dosage forms are given. Use of said compositions for the manufacture of medicaments for treating shizophenia and other neuropsychiatric disorders by administering an effective amount of the dosage forms disclosed herein, either alone or in combination with one or more other medicaments, are also provided by the invention.

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PHARMACEUTICAL FORMULATIONS CONTAINING QUETIAPINE

BACKGROUND

[0001] Quetiapine and its salts, particularly quetiapine hemifumarate, have been employed as pharmaceutically active agents in the treatment of schizophreniza and bipolar mania.

[0002] Quetiapine is an antipsychotic drug of the dibenzothiazepine class; chemical name 2-[2-(4-dibenzo[*b,f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate. Quetiapine acts as an antagonist at several neurotransmitter receptors including the dopamine D_1 and D_2 receptors, the serotonin $5HT_{A1}$ and $5HT_2$ receptors, the histamine H_1 receptor, and adreneric α_1 and α_2 receptors. Quetiapine is thought to exert its antipsychotic effects primarily via antagonism of the dopamine D2 receptor the serotonin 5HT2 receptor.

[0003] Quetiapine is currently formulated as 25 mg, 100 mg, 200 mg, and 300 mg tablets for twice a day or three times per day administration. Previously described formulations of quetiapine have certain properties that are not ideal in all situations. For example previously disclosed formulations do not provide a constant or substantially constant level of quetiapine for 24 hours at steady-state. These previous formulations provide quetiapine blood or plasma concentrations that vary with time, i.e., at certain time points between administrations there are higher concentrations of quetiapine than at other times. This means that at certain time points a 24-hour period, a patient may receive therapeutically effective amounts of quetiapine, while at other time points the concentration of quetiapine in the blood may fall below therapeutic levels (i.e., symptomatic relief may not be maintained).

[0004] While some sustained release formulations of quetiapine have been disclosed (See US Patent No. 5,948,437), these formulations require a gelling agent for sustained release. Improved control of pharmacokinetic properties may be achieved with alternative formulations.

[0005] Control of quetiapine plasma levels may be useful during treatment. For example, when a patient presents with acute psychosis, it may be desirable to introduce an immediate large dosage of quetiapine, followed by the maintenance of a sustained plasma

level of quetiapine. Currently, these plasma levels can be effected only by administering multiple dosages. Single dosage forms that provide particular plasma profiles of quetiapine are thus desirable.

[0006] Additionally for some patients, the quetiapine dosage required for therapeutic effect is quite high, especially if a sustained release dosage form is administered. For example, the largest current dosage form is a 300 mg tablet, administered two or three times daily. Thus an equivalent once a day dosage form would contain up to 900 mg of quetiapine. When a high dosage of quetiapine is combined with excipients, the resulting dosage form (e.g., tablets, capsules, etc.) may be considerably larger than is desirable. Also, the dosage form can be undesirably large when quetiapine is combined with other active agents, especially other high dose active agents. The large size of these dosage forms can be difficult for patients, especially elderly patients, to swallow. Further, large dosage form size may increase the risk of choking upon oral administration and may reduce patient compliance. There thus exists a need for a dosage form comprising a high dose amount of quetiapine that has a smaller size than conventional dosage forms containing substantially the same dose amount of quetiapine.

[0007] The present invention addresses these and other needs for improved quetiapine dosage forms, particularly controlled release and sustained release dosage forms.

SUMMARY OF THE INVENTION

[0008] In a first aspect, a quetiapine solid dosage formulation comprises a matrix, wherein the matrix comprises a pharmaceutically effective amount of quetiapine and a wax material.

[0009] A method of making the wax formulation comprising hot melting a waxy material to form a melt, granulating quetiapine with the melt to form a granulate; milling the granulate; and compressing granulate to form a matrix is also provided.

[0010] A press-coat dosage form comprising a core composition comprising quetiapine, and a waxy material; and a coating composition comprising hydrophilic polymer, wherein the coating composition is press-coated onto the core composition is provided.

[0011] In another aspect, the invention provides a press-coat dosage form comprising a core composition comprising quetiapine and carnauba wax; and a coating composition

comprising quetiapine and a polymeric material, such as hydroxypropylmethyl cellulose (HPMC), wherein the coating composition is press-coated onto the core. Alternatively the press-coat dosage form comprises a core composition comprising quetiapine or a pharmaceutically acceptable salt thereof and a polymeric material, for example hydroxypropylmethyl cellulose (HPMC).

[0012] A method for preparing a press-coat dosage form comprising providing a core composition comprising quetiapine and a waxy material, providing a coating composition comprising the quetiapine and a hydrophilic polymer, and press-coating the coating composition onto the core composition to provide the press-coat dosage form is also provided.

[0013] Controlled release dosage forms can be characterized by certain dissolution profiles. A controlled release dosage form comprises a pharmaceutically effective amount of quetiapine and at least one excipient, exhibiting a dissolution profile such that at 4 hours after combining the dosage form with a dissolution media about 50 to about 95% of the quetiapine or its salt is released.

[0014] In another aspect the invention provides a controlled release dosage form comprising a pharmaceutically effective amount of quetiapine and at least one excipient, exhibiting a dissolution profile such that at 4 hours after combining the dosage form with a dissolution media less than about 50 to 95 % of the quetiapine is released.

[0015] The invention also provides a controlled release dosage form comprising a pharmaceutically effective amount of quetiapine and at least one excipient, exhibiting a dissolution profile such that at 16 hours after combining the dosage form with a dissolution media less that 90 % of the quetiapine is released.

[0016] In a further aspect the invention provides a controlled release dosage form comprising a pharmaceutically effective amount of quetiapine and at least one excipient, exhibiting a dissolution profile such that at 1 hour after combining the dosage form with a dissolution media about 5 to about 15% of the quetiapine is released, at 2 hours after combining the dosage form with a dissolution media about 10 to about 25% of the quetiapine is released, at 4 hours after combining the dosage form with a dissolution media about 15 to about 35% of the quetiapine is released, at 8 hours after combining the dosage form with a dissolution media about 25 to about 50% of the quetiapine is released.

[0017] Controlled release dosage forms of quetiapine may be characterized by certain plasma level profiles of quetiapine. For example, an oral dosage form comprises quetiapine in controlled release form which provides a maximum concentration of quetiapine (Cmax) and a concentration of quetiapine at about 24 hours after administration (C24), wherein the ratio of Cmax to C24 is less than about 4:1.

[0018] In another aspect, an oral dosage form comprises quetiapine in controlled release form, which, at steady-state, provides a maximum quetiapine concentration (C_{max}), a quetiapine plasma concentration at about 12 hours after administration (C_{12}), and an quetiapine plasma concentration at about 24 hours after administration (C_{24}). The average quetiapine plasma concentration produced by this dosage form between C_{max} and C_{12} is substantially equal to the average quetiapine plasma concentration between C_{12} and C_{24}.

[0019] Pulsed release formulations are also provided. An oral dosage form comprises quetiapine in controlled release form, which, at steady-state, provides a first maximum plasma concentration of quetiapine (C_{max1}) between 0 hours and about 12 hours after administration, and a second maximum plasma concentration of quetiapine (Cmax2) between about 12 hours and about 24 hours after administration.

[0020] The invention provides sustained release oral dosage forms. The invention provides a sustained release oral dosage form of quetiapine comprising a first subunit and a second subunit, wherein the first subunit comprises quetiapine and a first release-retarding material and the second subunit comprises quetiapine and a second release-retarding material. The first and second release-retarding material can be the same or different. The dosage form, at steady-state, provides a maximum plasma concentration of the quetiapine (C_{max}) and an plasma concentration of quetiapine at about 24 hours after administration (C_{24}), wherein the ratio of C_{max} to C_{24} is less than about 4:1.

[0021] The invention provides controlled release dosage forms that may be characterized by values for the Area Under the Curve (AUC) of the plasma level of quetiapine versus time after administration. A controlled release dosage form of quetiapine provides an AUC between 0 and 24 hours after administration that is more than 80 percent and less than 120 percent of the AUC provided by an equivalent weight of SEROQUEL between 0 and 24 hours after administration.

[0022] The invention provides a methods of treating psychosis, comprising orally

administering to a human on a once-daily basis an oral sustained release dosage form comprising quetiapine which, at steady-state, provides a maximum quetiapine plasma concentration (Cmax) and an quetiapine plasma concentration at about 24 hours after administration (C24), wherein the ratio of Cmax to C24 is less than about 4:1.

[0023] The invention provides controlled release wax dosage forms, press-coat dosage forms, sprinkle dosage forms, and taste masked dosage forms of quetiapine and at least one excipient having the dissolution profiles described above. The inventions also provides wax dosage forms, press-coat dosage forms, sprinkle dosage forms, and taste masked dosage forms that produce certain plasma levels of quetiapine upon administration. For example the invention provides such dosage forms characterized by the plasma concentration of quetiapine described above.

[0024] The invention also provides wax dosage forms, press-coat dosage forms, sprinkle dosage forms, and taste masked dosage forms as sustained release oral dosage forms comprising a first subunit and a second subunit. The first subunit comprises quetiapine and a first release-retarding material and the second subunit comprises quetiapine and a second release-retarding material, wherein the first and second release-retarding material can be the same or different, and wherein the dosage form, at steady-state, provides a maximum quetiapine plasma concentration (Cmax) and an quetiapine plasma concentration at about 24 hours after administration (C24), wherein the ratio of Cmax to C24 is less than about 4:1.

[0025] The invention further provides wax dosage forms, press-coat dosage forms, sprinkle dosage forms, and taste masked dosage forms as controlled release oral dosage forms which provides the AUC values described above.

[0026] These and other embodiments of the invention, as well as additional inventive features, will be apparent from the description of the invention provided herein.

DETAILED DESCRIPTION OF THE INVENTION

[0027] The invention relates to improved formulations comprising quetiapine such as, for example, controlled release formulations, including, but not limited to wax formulations, press-coated formulations, easily administrable formulations, enteric-coated formulations, osmotic pump technology formulations, tamper-resistant formulations, and combination formulations. Solid dosage forms of quetiapine include wax formulations, and may have a

size that is substantially smaller than the size of a same strength dosage form of SEROQUEL, the marketed form of quetiapine hemifumarate.

[0028] One type of formulation provided by the invention is a controlled release formulation. Controlled release formulations, such as longer acting formulations that can be administered once daily or even less frequently, are particularly desirable for quetiapine. Controlled release formulations may provide many inherent therapeutic benefits that are not achieved with corresponding short acting, immediate release preparations. This is especially true in the treatment of schizophrenia and bipolar mania, for the alleviation of psychosis, where blood levels of a medicament must be maintained at a therapeutically effective level to provide symptomatic relief. Unless conventional rapid acting drug therapy is carefully administered at frequent intervals to maintain effective steady-state blood levels of quetiapine, peaks and valleys in the blood level of quetiapine occur because of the rapid absorption, systemic excretion of the compound, and metabolic inactivation, thereby producing special problems in maintaining efficacy. Additionally patient compliance, which can be problematic among psychiatric patients, may be improved with dosage formulations that can be administered less frequently. It is also preferred that controlled release dosage forms do not contain a gelling agent or contain a gelling agent only in the coat.

[0029] Controlled release formulations of quetiapine may be formulated using osmotic pump technology. This technology uses osmotic pressure to deliver quetiapine at a controlled rate. Osmotic pump, dosage formulations include a semi-permeable membrane surrounding a core that contains at least two components, one component comprising quetiapine, the other comprising an osmotic push layer, such as an osmotically active polymer. Some time after the dosage form is swallowed water enters the membrane causing the push layer to swell, releasing quetiapine at a controlled rate through a laser-drilled hole in the membrane. Osmotic pump technology thus may be useful in certain quetiapine formulations.

[0030] Sustained release formulations of quetiapine can be administered once daily or even less frequently. Sustained release formulations can be based on matrix technology. In this technology quetiapine is embedded in an excipient that makes a non-disintegrating core called a matrix. Diffusion of quetiapine occurs through the core.

[0031] While sustained release formulations of quetiapine have been disclosed, these

formulations comprise a gelling agent. A preferred sustained release formulation is one that does not comprise a gelling agent. Formulations with gelling agents do not extend release of the drug beyond about five hours due to attrition of the gel when fully hydrated in the gastrointestinal tract. In addition, these formulations exhibit different release characteristics when administered with food.

[0032] In certain circumstances, delayed release formulations of quetiapine are desirable. Quetiapine is known to cause somnolence and orthostatic hypotension in some patients. Other active agents, with which quetiapine may be combined in a combination dosage, cause gastric irritation. Thus controlled release formulations, such as delayed release formulations, with a time-delay before significant plasma levels of quetiapine are achieved, which avoid an initial burst of quetiapine, or which are formulated so that release of quetiapine in the stomach is avoided, may be useful for minimizing these side effects. A delayed release coated tablet can comprise a core comprising quetiapine and at least one excipient, free of stabilizer; and a first coating of a water-insoluble, water-permeable film-forming polymer, a plasticizer and a water-soluble polymer, and a second coating of a methacrylic polymer and a plasticizer for the methacrylic polymer. Delayed release dosage forms, including delayed release tablets can exhibit specific dissolution profiles.

[0033] Semi-delayed release dosage forms, which are a type of pulsed- release dosage form, of quetiapine are provided. Such dosage forms provide a moderate dosage immediately after administration and a larger dosage some hours after administration. Such semi-delayed release dosage forms are particularly useful for providing a moderate dosage of quetiapine upon AM administration and a larger dosage at night.

[0034] In other circumstances it may be desirable to precisely control the plasma levels of quetiapine for a number of hours after administration. Pulsed release formulations, containing some combination of immediate release, sustained release, and delayed release formulations in the same dosage form can be used in place of multiple immediate and sustained release dosages in such situations. Other types of pulse release formulations,

provided herein, which are tailored to provide a particular plasma level profile are useful in other types of clinical situations.

[0035] Enteric coated formulations, which protect the stomach against the irritant effects of quetiapine, are also desirable. Such formulations can be coated with a composition that is non-toxic and includes a pharmaceutically acceptable enteric polymer, which is predominantly soluble in the intestinal fluid, but substantially insoluble in the gastric juices.

[0036] Another issue is that the current tablet formulations may be inadequate for juvenile and elderly patients who require dosage forms that are easy to swallow. Easily administered formulations, such as chewable tablets, sprinkle forms, liquid formulations, taste-masked formulations, and fast dissolve tablets are thus desirable.

[0037] Patients suffering from schizophrenia or bipolar mania often take multiple medications to effectively control their symptoms or to alleviate side effects caused by antipsychotic medications. Combinations, which contain quetiapine and also contain one or more other active agents typically prescribed for patients suffering from schizophrenia or bipolar mania, are convenient for administration and also to improve patient compliance. For example, schizophrenia patients frequently receive other neuroleptic (antipsychotic) agents, antiparkinsonian agents to treat the tardive dyskinesia associated with neuroleptic use, sedatives, anxiolytics, antidepressants, and/ or antacids. Thus formulations which incorporate both quetiapine and one or more of these other active agents in a single dosage forms are desirable.

CHEMICAL DESCRIPTION AND TERMINOLOGY

[0038] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising", "having", "including", and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods

described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[0039] The term "active agent" is meant to include solvates (including hydrates) of the free compound or salt, crystalline and non-crystalline forms, as well as various polymorphs. Unless otherwise specified, the term "active agent" is used herein to indicate quetiapine. For example, an active agent can include all optical isomers of the compound and all pharmaceutically acceptable salts thereof either alone or in combination.

[0040] Unless otherwise specified, or clearly indicated by the text, "quetiapine" includes both the free base of quetiapine, 2-[2-(4-dibenzo[*b,f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol, and all pharmaceutically acceptable salts of this compound. The preferred quetiapine salt is quetiapine hemifumarate. The term "quetiapine or its salts" indicates quetiapine free base or any pharmaceutically acceptable salts of quetiapine.

[0041] Certain formulations described herein may be "coated". The coating can be a suitable coating, such as, a functional or a non-functional coating, or multiple functional and/or non-functional coatings. By "functional coating" is meant to include a coating that modifies the release properties of the total formulation, for example, a sustained release coating. By "non-functional coating" is meant to include a coating that is not a functional coating, for example, a cosmetic coating. A non-functional coating can have some impact on quetiapine release due to the initial dissolution, hydration, perforation of the coating, etc., but would not be considered to be a substantial deviation from the non-coated composition.

[0042] "Pharmaceutically acceptable salts" includes derivatives of the disclosed compounds, wherein the parent compound is modified by making non-toxic acid or base salts thereof, and further refers to pharmaceutically acceptable solvates, including hydrates, of such compounds and such salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like, and combinations comprising one or more of the foregoing salts. The pharmaceutically acceptable salts include

non-toxic salts and the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, non-toxic acid salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; other acceptable inorganic salts include metal salts such as sodium salt, potassium salt, cesium salt, and the like; and alkaline earth metal salts, such as calcium salt, magnesium salt, and the like, and combinations comprising one or more of the foregoing salts. Pharmaceutically acceptable organic salts includes salts prepared from organic acids such as acetic, trifluoroacetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, mesylic, esylic, besylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like; organic amine salts such as triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, and the like; and amino acid salts such as arginate, asparginate, glutamate, and the like, and combinations comprising one or more of the foregoing salts.

[0043] The term "oral dosage form" is meant to include a unit dosage form prescribed or intended for oral administration. An oral dosage form may or may not comprise a plurality of subunits such as, for example, microcapsules or microtablets, packaged for administration in a single dose.

[0044] The term "releasable form" is meant to include immediate release, controlled release, and sustained release forms. Certain release forms can be characterized by their dissolution profile. "Dissolution profile" as used herein, means a plot of amount of active ingredient released as a function of time. The dissolution profile can be measured utilizing the Drug Release Test <724>, which incorporates standard test USP 26 (Test <711>). A profile is characterized by the test conditions selected. Thus the dissolution profile can be generated at a preselected apparatus, shaft speed, temperature, volume, and pH of the dissolution media.

[0045] A first dissolution profile can be measured at a pH level approximating that of the stomach. A second dissolution profile can be measured at a pH level approximating that

of one point in the intestine or several pH levels approximating multiple points in the intestine.

[0046] A highly acidic pH may simulate the stomach and a less acidic to basic pH can simulate the intestine. By the term "highly acidic pH" it is meant a pH of about 1 to about 4. By the term "less acidic to basic pH" is meant a pH of greater than about 4 to about 7.5, preferably about 6 to about 7.5. A pH of about 1.2 can be used to simulate the pH of the stomach. A pH of about 6.0 to about 7.5, preferably about 7.5 can be used to simulate the pH of the intestine.

[0047] Release forms may also be characterized by their pharmacokinetic parameters. "Pharmacokinetic parameters" are parameters, which describe the *in vivo* and *in vitro* characteristics of quetiapine over time, including for example the dissolution characteristics and plasma concentration of quetiapine. By "C_{max}" is meant the measured concentration of quetiapine in the plasma at the point of maximum concentration. By "C_{24}" is meant the concentration of quetiapine in the plasma at about 24 hours. The term "T_{max}" refers to the time at which the concentration of quetiapine in the plasma is the highest. "AUC" is the area under the curve of a graph of the concentration of quetiapine (typically plasma concentration) vs. time, measured from one time to another.

[0048] By "sequestered form" is meant an ingredient that is not released or substantially not released at one hour after the intact dosage form comprising quetiapine is orally administered. The term "substantially not released" is meant to include the ingredient that might be released in a small amount, as long as the amount released does not affect or does not significantly affect efficacy when the dosage form is orally administered to mammals, for example, humans, as intended.

[0049] By "immediate release" is meant a conventional or non-modified release form in which greater then or equal to about 50% or more preferably about 75% of quetiapine is released within two hours of administration, preferably within one hour of administration.

[0050] By "controlled release" is meant a dosage form in which the quetiapine release is controlled or modified over a period of time. Controlled can mean, for example, sustained, delayed or pulsed release at a particular time. Alternatively, controlled can mean that the quetiapine release is extended for longer than it would be in an immediate release dosage for, i.e., at least over several hours.

[0051] By "delayed release" is meant that there is a time-delay before significant plasma levels of quetiapine are achieved. A delayed release quetiapine avoids an initial burst of quetiapine, or can be formulated so that quetiapine release in the stomach is avoided.

[0052] A "pulsed release" formulation can contain a combination of immediate release, sustained release, and/or delayed release formulations in the same dosage form. A "semi-delayed release" formulation is a "pulsed released formulation in which a moderate dosage is provided immediately after administration and a larger dosage some hours after administration.

[0053] By the term "same strength dosage form" is a dosage form that contains the same amount of quetiapine by weight as the dosage form to which it is compared. The correct weight for comparison is the weight of quetiapine free base or the weight of quetiapine free base present in whatever quetiapine salt the dosage form contains. For example a dosage form containing 115.13 mg quetiapine hemifumarate is a 100 mg dosage of quetiapine.

[0054] The terms "sustained release" or "extended release" are meant to include the release of quetiapine at such a rate that blood (e.g., plasma) levels are maintained within a therapeutic range but below toxic levels for at least about 8 hours, preferably at least about 12 hours after administration at steady-state. The term "steady-state" means that a plasma level for a given active agent, such as quetiapine, has been achieved and which is maintained with subsequent doses of the drug at a level which is at or above the minimum effective therapeutic level and is below the minimum toxic plasma level for a given active agent.

[0055] The term "subunit" is meant to include a composition, mixture, particle, etc., that can provide an oral dosage form alone or when combined with other subunits. By "part of the same subunit" is meant to refer to a subunit comprising certain ingredients. For example, a subunit comprising quetiapine and an additional active ingredient may be placed together with additional subunits in a capsule to provide an oral dosage form.

[0056] The term "thermo-responsive" as used herein includes thermoplastic compositions capable of softening, or becoming dispensable in response to heat and hardening again when cooled. The term also includes thermotropic compositions capable of undergoing change in response to the application of energy in a gradient manner. These compositions are temperature sensitive in their response to the application or withdrawal of

energy. In certain embodiments thermo-responsive compositions possess the physical property of exhibiting solid, or solid-like properties at temperatures up to about 32 °C, and become fluid, semisolid, or viscous when at temperatures above about 32 °C, usually in the range of about 32 °C to about 40 °C. Thermo-responsive compositions, including thermo-responsive carriers, have the property of melting, dissolving, undergoing dissolution, softening, or liquefying and thereby forming a dispensable composition at the elevated temperatures. The thermo-responsive carrier can be lipophilic, hydrophilic, or hydrophobic. Another property of a thermo-responsive carrier is its ability to maintain the stability of the agent contained therein during storage and during delivery of the agent. A thermo-responsive composition can be easily excreted, metabolized, or assimilated, upon being dispensed into a biological environment.

[0057] By "water-soluble" active agent is meant an active agent, including quetiapine hemifumarate, or any other active agent that may be used in combination with quetiapine that is at least slightly water-soluble (for example, about 1 to about 10 mg/ml at 25°C). Preferably, all active agents are moderately water-soluble (for example, less than about 100 mg/ml at 25°C), or highly water-soluble (for example, greater than about 100 mg/ml at 25°C).

[0058] By "water-insoluble" or "poorly soluble"active agent, it is meant an agent having a water solubility of less than 1 mg/ml, and in some cases even less than 0.1 mg/ml.

[0059] By "SEROQUEL" is meant the trademarked form of quetiapine hemifumarate marketed by AstraZeneca, Wilmington DE described in the FDA Product Insert for this compound as revised January 2001. This dosage form may contain povidone in a weight: weight ratio of about 0.072: 1 to quetiapine hemifumarate, dibasic dicalcium phosphate dihydrate in a weight: weight ratio of about 0.087: 1 to quetiapine hemifumarate, microcrystalline cellulose in a weight: weight ratio of about 0.286: 1 to quetiapine hemifumarate, sodium starch glycolate in a weight: weight ratio of about 0.072: 1 to quetiapine hemifumarate, lactose monohydrate in a weight: weight ratio of about 0.194: 1 to quetiapine hemifumarate, magnesium stearate in a weight: weight ratio of about 0.026: 1 to quetiapine hemifumarate, hydroxypropyl methyl cellulose in a weight: weight ratio of about 0.043: 1 to quetiapine hemifumarate, polyethyleneglycol in a weight: weight ratio of about 0.009: 1 to quetiapine hemifumarate, and titanium dioxide in a weight: weight ratio of about

0.016: 1 to quetiapine hemifumarate. SEROQUEL is provided as a tableted dosage form. The following dosage sizes are currently available: 25 mg, 100 mg, 200 mg, and 300 mg, where the weights are reported as weight of quetiapine free base in the tableted dosage form.

DOSAGE FORMS: RELEASE PROPERTIES

[0060] The dosage forms comprising quetiapine can be characterized by the release properties of the formulation. Certain dosage form can be targeted release formulations wherein release occurs in a particular segment of the gastrointestinal tract, for example in the small intestine. Alternatively, the dosage forms can be immediate or modified release dosage forms in which the rate of quetiapine release in the blood stream is regulated.

IMMEDIATE RELEASE DOSAGE FORMS

[0061] An immediate release dosage form is one in which the release properties of the dosage form are essentially the unmodified inherent release rate. Immediate release dosage forms generally also have dissolution profiles in any given media that are unmodified from those of quetiapine alone in the same media. An immediate release dosage form preferably results in delivery of greater than or equal to about 50% of the quetiapine in the dosage form within about 2 hours of administration, or in certain embodiments greater than or equal to about 75% of the quetiapine within about 2 hours of administration, and in certain other embodiments results in delivery of greater than or equal to about 75% of the quetiapine within 1 hour of administration. An immediate release dosage form may contain optional excipients so long as the excipients do not significantly extend the release time of the drug.

SUSTAINED RELEASE DOSAGE FORMS

[0062] A sustained release form is a form suitable for providing controlled release of quetiapine over a period of time (e.g., 8 hours, 12 hours, 24 hours). Sustained release dosage forms of quetiapine may release quetiapine at a rate independent of pH, for example, about pH 1.6 to about 7.2. Preferably, the sustained release form avoids "dose dumping," the production of a rapid rise in the blood or plasma concentration of quetiapine, upon oral administration. The sustained release oral dosage form can be formulated to provide for an increased duration of anti-psychotic action permitting effective once-daily dosing. Generally

in a sustained release dosage form the quetiapine release extends longer e.g, by several hours, than quetiapine release from the immediate release dosage form.

[0063] A sustained release dosage form generally comprises a release-retarding material. The release-retarding material can be, for example, in the form of a matrix or a coating. Quetiapine in sustained release form may be, for example, a particle of quetiapine that is combined with a release-retarding material. The release-retarding material is a material that permits release of quetiapine at a sustained rate in an aqueous medium. The release-retarding material can be selectively chosen so as to achieve, in combination with the other stated properties, a desired *in vitro* release rate.

[0064] Release-retarding materials can be hydrophilic and/ or hydrophobic polymers. Release-retarding materials include, for example acrylic polymers, alkylcelluloses, shellac, zein, hydrogenated vegetable oil, hydrogenated castor oil, and combinations comprising one or more of the foregoing materials. The oral dosage form can contain between about 1% and about 80% (by weight) of the release-retarding material. Suitable acrylic polymers include, for example, acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), poly(methacrylic acid anhydride), methyl methacrylate, polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, glycidyl methacrylate copolymers, and combinations comprising one or more of the foregoing polymers. The acrylic polymer may comprise a methacrylate copolymers described in NF XVII as fully polymerized copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

[0065] Suitable alkylcelluloses include, for example, ethylcellulose. Those skilled in the art will appreciate that other cellulosic polymers, including other alkyl cellulosic polymers, can be substituted for part or all of the ethylcellulose.

[0066] Other suitable hydrophobic materials are water-insoluble with more or less pronounced hydrophilic trends. The hydrophobic material may have a melting point of about 30 °C to about 200 °C, more preferably about 45 °C to about 90 °C. The hydrophobic material can include neutral or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including fatty acid esters, fatty

acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic acid, stearyl alcohol, hydrophobic and hydrophilic materials having hydrocarbon backbones, and combinations comprising one or more of the foregoing materials. Suitable waxes include beeswax, glycowax, castor wax, carnauba wax and wax-like substances, e.g., material normally solid at room temperature and has a melting point of from about 30 °C to about 100 °C, and combinations comprising one or more of the foregoing waxes.

[0067] In other embodiments, the release-retarding material may comprise digestible, long chain (e.g., C_8 - C_{50}, preferably C_{12} -C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils, waxes, and combinations comprising one or more of the foregoing materials. Hydrocarbons having a melting point of between about 25 °C and about 90 °C may be used. Of these long chain hydrocarbon materials fatty (aliphatic) alcohols are preferred. The oral dosage form can contain up to about 60% by weight of at least one digestible, long chain hydrocarbon.

[0068] Further, the sustained-release matrix can contain up to 60% by weight of at least one polyalkylene glycol.

[0069] Alternatively, the release-retarding material may comprise polylactic acid, polyglycolic acid, or a co-polymer of polylactic and polyglycolic acid.

[0070] Release-modifying agents, which affect the release properties of the release-retarding material, may optionally be used. The release-modifying agent may, for example, function as a pore-former. The pore former can be organic or inorganic, and may include materials that can be dissolved, extracted or leached from the coating in the environment of use. The pore-former can comprise one or more hydrophilic polymers, such as hydroxypropylmethylcellulose, lactose, metal stearates, polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain, and combinations comprising one or more of the foregoing release-modifying agents.

[0071] The release-retarding material can also optionally include other additives such as an erosion-promoting agent (e.g., starch and gums); and/or a semi-permeable polymer. In addition to the above ingredients, a sustained release dosage form may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art. The release-retarding

material can also include an exit means comprising at least one passageway, orifice, or the like. The passageway can have any shape, such as round, triangular, square, elliptical, irregular, etc.

[0072] The sustained release dosage form comprising quetiapine and a release-retarding material may be prepared by a suitable technique for preparing quetiapine dosage forms as described in detail below. The quetiapine and release-retarding material may, for example, be prepared by wet granulation techniques, melt extrusion techniques, etc. To obtain a sustained release dosage form, it may be advantageous to incorporate an additional hydrophobic material.

[0073] Quetiapine in sustained release form can include a plurality of substrates comprising the active ingredient, which substrates are coated with a sustained release coating comprising a release-retarding material. The sustained release preparations may thus be made in conjunction with a multiparticulate system, such as beads, ion-exchange resin beads, spheroids, microspheres, seeds, pellets, granules, and other multiparticulate systems in order to obtain a desired sustained release of quetiapine. The multiparticulate system can be presented in a capsule or other suitable unit dosage form.

[0074] In certain cases, more than one multiparticulate system can be used, each exhibiting different characteristics, such as pH dependence of release, time for release in various media (e.g., acid, base, simulated intestinal fluid), release in vivo, size, and composition.

[0075] In some cases, a spheronizing agent, together with the active ingredient can be spheronized to form spheroids. Microcrystalline cellulose and hydrous lactose impalpable are examples of such agents. Additionally (or alternatively), the spheroids can contain a water insoluble polymer, preferably an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In this formulation, the sustained release coating will generally include a water insoluble material such as a wax, either alone or in admixture with a fatty alcohol, or shellac or zein.

[0076] Spheroids or beads, coated with an active ingredient can be prepared, for example, by dissolving the active ingredient in water and then spraying the solution onto a substrate, for example, sugar spheres NF21, 18/20 mesh, using a Wurster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the active

ingredient binding to the substrates, and/or to color the solution, etc. The resulting substrate-active material may optionally be overcoated with a barrier material, to separate the quetiapine from the next coat of material, e.g., release-retarding material. Preferably, the barrier material is a material comprising hydroxypropyl methylcellulose. However, any film-former known in the art may be used. Preferably, the barrier material does not affect the dissolution rate of the final product.

[0077] To obtain a sustained release of quetiapine in a manner sufficient to provide an anti-psychotic effect for sustained durations, the substrate comprising quetiapine can be coated with an amount of release-retarding material sufficient to obtain a weight gain level from about 2 to about 30%, although the coating can comprise a be greater or lesser weight percent depending upon the physical properties of quetiapine or its particular salt and the desired release rate, among other things. Moreover, there can be more than one release-retarding material used in the coating, as well as various other pharmaceutical excipients.

[0078] The release-retarding material may thus be in the form of a film coating comprising a dispersion of a hydrophobic polymer. Solvents typically used for application of the release-retarding coating include pharmaceutically acceptable solvents, such as water, methanol, ethanol, methylene chloride, and combinations comprising one or more of the foregoing solvents.

[0079] In addition, the sustained release profile of quetiapine release in the formulations (either *in vivo* or *in vitro*) can be altered, for example, by using more than one release-retarding material, varying the thickness of the release-retarding material, changing the particular release-retarding material used, altering the relative amounts of release-retarding material, altering the manner in which the plasticizer is added (e.g., when the sustained release coating is derived from an aqueous dispersion of hydrophobic polymer), by varying the amount of plasticizer relative to retardant material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

[0080] In addition to or instead of being present in a matrix, the release-retarding agent can be in the form of a coating. Optionally, the dosage forms can be coated, or a gelatin capsule can be further coated, with a sustained release coating such as the sustained release coatings described herein. Such coatings are particularly useful when the subunit comprises quetiapine in releasable form, but not in sustained release form. The coatings may

include a sufficient amount of a hydrophobic material to obtain increase the weight of the dosage form about 2 to about 30 percent, although the coating can increase the weight of the dosage form by a larger percent depending on the physical properties quetiapine or the particular quetiapine salt utilized and the desired release rate, among other things.

[0081] The sustained release formulations preferably release quetiapine slowly, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the formulations can be altered, for example, by varying the amount of retardant, e.g., hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

DELAYED RELEASE DOSAGE FORMS

[0082] Delayed release dosage forms provide a time-delay before significant plasma levels of quetiapine are achieved. A delayed release formulation of quetiapine can avoid an initial burst of quetiapine (i.e. "dose dumping"), or can be formulated so that release of quetiapine in the stomach is avoided and absorption is effected in the small intestine.

[0083] Delayed release tablets may comprise a core, a first coating and optionally a second coating. The core may include quetiapine, and excipients, notably a lubricant, and a binder and/or a filler, and optionally a glidant as well as other excipients.

[0084] Examples of suitable lubricants include stearic acid, magnesium stearate, glyceryl behenate, talc, mineral oil (in PEG), etc. Examples of suitable binders include water-soluble polymers, such as modified starch, gelatin, polyvinylpyrrolidone, polyvinyl alcohol, etc. Examples of suitable fillers include lactose, microcrystalline cellulose, etc. An example of a glidant is silicon dioxide (AEROSIL, Degussa).

[0085] The core may contain, by dry weight from about 10 to about 98% quetiapine or a salt thereof, from about 0.5 to about 10% lubricant, and from about 90 % to about 1.5% binder or filler.

[0086] In certain embodiments the core may contain, by dry weight, about 70 to about 98% quetiapine or a salt thereof, about 0.5 to about 10% lubricant, and about 2 to about 20% binder or filler.

[0087] The first coating may be, for example, a semi-permeable coating to achieve delayed release of quetiapine. The first coating may comprise a water-insoluble film-forming polymer, together with a plasticizer and a water-soluble polymer. The water-insoluble film-forming polymer can be a cellulose ether, such as ethylcellulose, a cellulose ester, such as cellulose acetate, polyvinylalcohol, etc. A suitable film-forming polymer is ethylcellulose (available from Dow Chemical under the trade name ETHOCEL). Other excipients can optionally also be present in the first coating, as for example acrylic acid derivatives (such and EUDRAGIT, Roehm Pharma), pigments, etc.

[0088] The first coating may contain from about 20 to about 85% water-insoluble film-forming polymer (e.g. ethylcellulose), about 10 to about 75% water-soluble polymer (e.g. polyvinylpyrrolidone), and about 5 to about 30% plasticizer. The relative proportions of ingredients, notably the ratio of water-insoluble film-forming polymer to water-soluble polymer, can be varied depending on the release profile to be obtained (where a more delayed release is generally obtained with a higher amount of water-insoluble film-forming polymer).

[0089] The weight ratio of first coating to tablet core can be about 1:30 to about 3:10, preferably about 1:10.

[0090] The optional second coating may be designed to protect the coated tablet core from coming into contact with gastric juice, thereby preventing a food effect. The second coating may comprise an enteric polymer of the methacrylic type and optionally a plasticizer. The second coating can contain, by weight, about 40 to about 90% enteric polymer (e.g. EUDRAGIT L30D-55, Degussa, Piscataway, NJ) and about 10 to about 60% plasticizer (e.g. triethyl citrate, polyethylene glycol). The relative proportions of ingredients, notably the ratio of methacrylic polymer to plasticizer can be varied according to methods known to those of skill in the art of pharmaceutical formulation.

[0091] A process for preparing a delayed release dosage form of quetiapine comprises manufacturing a core by, for example, wet or dry granulation techniques. Alternatively, quetiapine and lubricant may be mixed in a granulator and heated to the melting point of the lubricant to form granules. This mixture can then be mixed with a suitable filler and compressed into tablets. Alternatively, quetiapine and a lubricant (e.g. mineral oil in PEG) may be mixed in a granulator, e.g. a fluidized bed granulator and then into tablets. Tablets

may be formed by standard techniques, e.g. on a (rotary) press (for example KILIAN) fitted with suitable punches. The resulting tablets are hereinafter referred as tablet cores.

[0092] The coating process can be as follows. Ethylcellulose and polyethylene glycol (e.g. PEG 1450) are dissolved in a solvent such as ethanol; polyvinylpyrrolidone is then added. The resulting solution is sprayed onto the tablet cores, using a coating pan or a fluidized bed apparatus.

[0093] The process for applying the second coating can be as follows. Triethyl citrate and polyethylene glycol (e.g. PEG 1450) are dissolved in a solvent such as water; methacrylic polymer dispersion is then added. If present, silicon dioxide can be added as a suspension. The resulting solution is sprayed onto the coated tablet cores, using a coating pan or a fluidized bed apparatus.

[0094] The weight ratio of the second coating to coated tablet core is about 1:30 to about 3:10, preferably about 1:10.

[0095] An exemplary delayed release dosage form comprises a core containing quetiapine, polyvinylalcohol, and glyceryl behenate; a first coating of ethylcellulose, polyvinylpyrrolidone, and polyethylene glycol, and a second coating of methacrylic acid co-polymer type C, triethyl citrate, polyethylene glycol, and optionally containing silicon dioxide.

PULSED RELEASE DOSAGE FORMS

[0096] A pulsed released formulation can contain a combination of immediate release, sustained release, and/or delayed release formulations in the same dosage form. For example, a pulsed released dosage form of quetiapine may provide an increase in plasma concentration shortly after AM administration following by a second maxima in plasma concentration several hours later, preferably in the late afternoon.

[0097] An exemplary pulsed release dosage form may provide at least a part of the dose with a pulsed delayed release of the drug and another part of the formulation with rapid or immediate release. The immediate and pulsed delayed release of the drug can be achieved according to different principles, such as by single dose layered pellets or tablets, by multiple dose layered pellets or tablets, or by two or more different fractions of single or multiple dose layered pellets or tablets, optionally in combination with pellets or tablets having instant

release. Multiple dose layered pellets may be filled into a capsule or together with tablet excipients compressed into a multiple unit tablet. Alternatively, a multiple dose layered tablet may be prepared.

[0098] Single dose layered pellets or tablets giving one single delayed release pulse of the drug may be prepared. The single dose layered pellets or tablets may comprise a core material, optionally layered on a seed/sphere, the core material comprising quetiapine together with a water swellable substance; a surrounding lag time controlling layer, and an outer coating layer positioned to cover the lag time controlling layer. Alternatively, the layered pellets or tablets may comprise a core material comprising quetiapine; a surrounding layer comprising a water swellable substance; a surrounding lag time controlling layer; and an outer coating layer positioned to cover the lag time controlling layer.

[0099] Multiple dose layered pellets or tablets giving two or more delayed release pulses of the drug may be prepared comprising a core material, optionally layered on a seed/sphere comprising quetiapine and a water swellable substance, a surrounding lag time controlling layer, a layer comprising quetiapine optionally together with a water swellable substance; optionally a separating layer which is water-soluble or rapidly disintegrating in water; and an outer coating layer. Alternatively, a multiple dose layered pellet or tablet may comprise a core material, optionally layered on a seed/sphere, comprising quetiapine; a surrounding layer comprising a water swellable substance; a surrounding lag time controlling layer; a layer comprising quetiapine; optionally a separating layer; and an outer coating layer.

[0100] The core material comprising quetiapine can be prepared either by layering the drug onto a seed, such as for instance a sugar sphere seed, or by extrusion/ spheronization of a mixture comprising the drug and pharmaceutically acceptable excipients. It is also possible to prepare the core material by using tablet technology, i.e. compression of drug granules and optionally pharmaceutically acceptable excipients into a tablet core. For pellets of the two types, i.e. single or multiple dose pellets, which have the drug deposited onto a seed/sphere by layering, it is also possible to have an optional layer comprising a water swellable substance beneath the drug-containing layer in the core material. The seeds/spheres can be water insoluble and comprise different oxides, celluloses, organic polymers, and other materials, alone or in mixtures, or can be water soluble and comprise different inorganic salts, sugars and other materials, alone or in mixtures. Further, the seeds/spheres may comprise

quetiapine in the form of crystals, agglomerates, compacts etc. The size of the seeds may be about 0.1 to about 2 mm. Before the seeds are layered, the active substance may be mixed with further components to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture.

[0101] Optionally an osmotic agent is placed in the core material. Such an osmotic agent is water soluble and will provide an osmotic pressure in the tablet. Examples of osmotic agents are magnesium sulfate, sodium chloride, lithium chloride, potassium chloride, potassium sulfate, sodium carbonate, lithium sulfate, calcium bicarbonate, sodium sulfate, calcium lactate, urea, magnesium succinate, sucrose or mixtures thereof.

[0102] Water swellable substances suitable for the dosage forms are compounds, which are able to expand when they are exposed to an aqueous solution, such as intestinal fluid. One or more water swellable substances may be present in the core material together with quetiapine and optionally pharmaceutically acceptable excipient(s). Alternatively, one or more water swellable substances are included in a swelling layer applied onto the core material. As a further alternative, swellable substances(s) they may also be present in an optional swelling layer situated beneath the drug containing layer, if a layered seed or sphere is used as the core material.

[0103] The amount of water swellable substance(s) in the swelling layer or in the core material is chosen in such a way that the core material or the swelling layer in contact with an aqueous solution, such as intestinal fluid, will expand to such a degree that the surrounding lag-time controlling membrane ruptures. A water swellable substance may also be included in the drug comprising layer of the multiple layered pellets or tablets to increase dissolution rate of the drug fraction.

[0104] Suitable substances which can be used as water swellable substances include, for example, low-substituted hydroxypropyl cellulose, e.g. L-HPC; cross-linked polyvinyl pyrrolidone (PVP-XL), e.g. KOLLIDON CL and POLYPLASDONE XL; cross-linked sodium carboxymethylcellulose, e.g. AC-DI- SOL, PRIMELLOSE; sodium starch glycolate, e.g. PRIMOJEL; sodium carboxymethylcellulose, e.g. NYMCEL ZSB10; sodium carboxymethyl starch, e.g. EXPLOTAB; ion-exchange resins, e.g. DOWEX or AMBERLITE; microcrystalline cellulose, e.g. AVICEL; starches and pregelatinized starch,

e.g. STARCH 1500, SEPSITAB ST200; formalin-casein, e.g. PLAS-VITA, and combinations comprising one or more of the foregoing water swellable substances.

[0105] The lag time controlling layer may be a semipermeable membrane comprising a water resistant polymer that is semipermeable for an aqueous solution, such as intestinal fluid. Suitable polymers are cellulose acetate, ethylcellulose, polyvinyl acetate, cellulose acetate butyrate, cellulose acetate propionate, acrylic acid copolymers, such as EUDRAGIT RS or RL, and combinations comprising one or more of the foregoing polymers. The polymer may optionally comprise pore-forming agents, such as a water soluble substance, e.g. sucrose, salt; or a water soluble polymer e.g., polyethylene glycol. Also pharmaceutically acceptable excipients such as fillers and membrane strength influencing agents such as talc, aerosil, or sodium aluminium silicate may be included.

[0106] There is at least one lag time controlling layer present in the pulsed release dosage form. The lag time controlling layer positioned nearest the inner core material is constructed in the form of a semipermeable membrane that will disrupt after a desired time after ingestion. A desired lag time may be adjusted by the composition and thickness of the layer. The amount of substances forming such a disrupting semipermeable membrane, i.e. a lag time controlling layer, may be about 0.5 to about 25 % of the weight of the core material including swelling substances or a swelling layer, preferably about 2 to about 20% by weight.

[0107] The lag time controlling layer may comprise a mixture of ethylcellulose and talc. In some embodiments the mixture contains about 10% to about 80% w/w of talc.

[0108] Before applying the outer coating layer onto the layered pellets or tablets, they may optionally be covered with one or more separating layers comprising excipients. This separating layer separates the composition of the layered pellets or tablets from the outer enteric coating layer. Suitable materials for the optional separating layer are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, and combinations comprising one or more of the foregoing materials, substances, and other additives may also be included into the separating layer.

[0109] When the optional separating layer is applied to the layered pellets or tablets it may constitute a variable thickness. The maximum thickness of the optional separating layer

is normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and may act as a pH-buffering zone. The optional separating layer may improve the chemical stability of the active substance and/or the physical properties of the dosage form.

[0110] Finally, the layered pellets or tablets are covered by one or more outer coating layers using a suitable coating technique. The outer coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. Suitable methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethylcellulose, shellac or other suitable coating layer polymer(s).

[0111] The applied polymer containing layers, and specially the outer coating layers, may also contain pharmaceutically acceptable plasticizers to obtain desired mechanical properties.

EXEMPLARY FORMULATIONS

[0112] The various release properties described above may be achieved in a variety of different ways. Suitable formulations include, for example, wax formulations, press coat formulations, easily administered formulations, osmotic pump dosage forms, etc.

WAX FORMULATIONS

[0113] A wax formulation is a solid dosage form comprising the quetiapine, most preferably quetiapine hemifumarate, in a waxy matrix. The waxy matrix may be prepared by hot melting a suitable wax material and using the melt to granulate quetiapine. The matrix material comprises the waxy material and quetiapine.

[0114] The wax material can be, for example, an amorphous wax, an anionic wax, an anionic emulsifying wax, a bleached wax, a carnauba wax, a cetyl esters wax, a beeswax, a castor wax, a cationic emulsifying wax, a cetrimide emulsifying wax, an emulsifying wax, a glyceryl behenate, a microcrystalline wax, a nonionic wax, a nonionic emulsifying wax, a paraffin, a petroleum wax, a spermaceti wax, a white wax, a yellow wax, and combinations comprising one or more of the foregoing waxes. These and other suitable waxes are known

to those of skill in the art. A cetyl ester wax, for example, may have a molecular weight of about 470 to about 490, and is a mixture containing primarily esters of saturated fatty alcohols and saturated fatty acids. When the waxy material contains only carnauba wax and no other waxy material is used, the matrix may be coated with a functional coating. When the waxy material includes glyceryl behenates and carnauba wax, the matrix can be used without a coating, but may have either a cosmetic coating or a functional coating depending on the precise release profile and appearance desired.

[0115] The wax material can be used at about 16% to about 35%, preferably about 20% to about 32%, more preferably about 24% to about 31%, and most preferably about 28% to about 29% of the total weight of the matrix material. When a combination of wax is used, e.g., carnauba wax and glyceryl behenate, the component waxes can be used in a suitable ratio. Certain formulations include the wax material component from 100 to about 85 parts carnauba wax and from 0 to about 15 parts glyceryl behenate. In formulations that have a combination of carnauba wax and castor wax, for example, the wax component may have about 100 to about 85 parts carnauba wax and 0 to about 15 parts castor wax. When carnauba wax, glyceryl behenate, and castor wax are present, the carnauba wax can comprise at least about 85% of the waxy material and the balance of the waxy material may be made up of a combination of glyceryl behenate and castor wax, in a suitable relative proportion.

[0116] Optionally, fatty acids and fatty acid soaps can be present in the waxy dosage form. In some cases, the fatty acids and/or fatty acid soaps can replace a portion of the wax or waxes. These optional fatty acids and fatty acid soaps can be those that are generally used in the pharmaceutical industry as tableting lubricants, such as, for example, solid fatty acids (for example fatty acids having from about 16 to about 22 carbon atoms), and the alkaline earth metal salts thereof, particularly the magnesium and calcium salts, and combinations comprising one or more of the foregoing fatty acids. The fatty acid can be, for example, stearic acid. The optional fatty acids and fatty acid soaps, when present, can be used in amounts of up to about 10% of the total weight of the matrix material, or about 2.5% to about 9%, or about 2.7% to about 8.6%, or from about 3% to about 6% of the total weight of the matrix material. An amount of up to about 2% of the total core formulation of the optional fatty acid materials may be used as a blend with the melt granulate. Amounts of at least

about 1% may be used in this fashion with the remainder being added to the waxes for melting and granulating quetiapine.

[0117] To prepare the dosage form, the waxes may be melted and used to granulate quetiapine. The granulate may be allowed to cool and then be milled to a proper size. Advantageously, the granulate is milled to an average particle size of about 75 microns to about 850 microns, preferably about 150 microns to about 425 microns. The milled granulate may be mixed with optional processing aids. The processing aids include, for example, hydrophobic colloidal silicon dioxide (such as CAB-O-SIL M5). Hydrophobic silicon dioxide may be used in amounts of less than or equal to about 0.5%, but individual formulations can be varied as required. The blend of the waxy granulate and the processing aids, if any, may be compressed and then optionally coated.

[0118] The wax dosage form can include, for example, compressed coated or uncoated tablets, compressed pellets contained in capsules, or loose powder or powder filled capsules.

[0119] Thus in a first embodiment the invention pertains to a solid dosage formulation comprising a matrix, wherein the matrix comprises a pharmaceutically effective amount of quetiapine or a pharmaceutically acceptable salt thereof; and a wax material. It is preferred that the matrix comprises a pharmaceutically effective amount of quetiapine hemifumarate.

[0120] In certain embodiments the wax material includes carnauba wax, glyceryl behenate, castor wax, or any combination thereof.

[0121] In some embodiments the matrix in the wax formulation is coated with a coating composition. The coating composition may be either a functional coating composition or a non-function coating composition.

[0122] When the coating composition is a functional coating composition the wax formulation may comprise a water in-soluble component; and a water-soluble component.

[0123] When the coating composition is a non-functional coating composition, the coating composition may comprise a water-soluble component in the substantial absence of a non-water-permeable component. The non-functional coating composition may comprise pharmaceutically acceptable dyes, pigments, or mixtures thereof.

[0124] The wax formulation, comprising a matrix of quetiapine and a wax material, may further comprise a processing aid. Examples of processing aids are given above.

[0125] The wax formulation may also include an additional active agent in the matrix, e.g. the formulation may be a combination of quetiapine and another anti-psychotic active agent.

[0126] In certain embodiments the wax formulation comprising a matrix comprising quetiapine, and a wax material, is formulated as a sustained release dosage formulation.

[0127] An embodiment of the invention is directed to a quetiapine wax having a size that is substantially smaller than the size of a same strength dosage form of SEROQUEL.

[0128] The invention also includes a method of making a wax formulation comprising matrix, the method comprising: hot melting a waxy material to form a melt, granulating quetiapine with the melt to form a granulate; milling the granulate; and compressing the granulate to form a matrix. This method may further comprise: blending the granulate with a processing aid; prior to compressing the granulate to form a matrix. The method may further comprise coating the matrix with a functional and/ or a non-functional coating.

[0129] The invention also pertains to the wax formulation made by the method of the invention.

PRESS COAT FORMULATIONS

[0130] A press coat oral dosage form of quetiapine or a salt thereof comprises a core composition and a coating composition press-coated on the core. The core composition comprises a waxy material and quetiapine or its salt and the coating composition comprises a hydrophilic polymer and optionally quetiapine or its salt. Preferably the quetiapine is in the form of quetiapine hemifumarate.

[0131] The core composition of the press coat dosage from comprises a waxy material. The waxy material can be a hydrophobic waxy material to provide controlled release of quetiapine. In pharmaceutical and/or veterinary products, for example, such waxy materials may be, for example, carnauba wax, tribehenin, fatty alcohols (particularly those having 12-24 carbon atoms, such as lauryl alcohol, myristyl alcohol, stearyl alcohol, palmityl

alcohol, etc.), fatty acids (particularly those having 12-24 carbon atoms, such as lauric acid, myristic acid, stearic acid, palmitic acid, etc), polyethylenes, castor wax, C_{16-30} fatty acid triglycerides, beeswax, and combinations comprising one or more of the foregoing waxes.

[0132] The coating composition comprises a hydrophilic polymer. The hydrophilic polymer can provide for controlled release of quetiapine. The hydrophilic polymer providing controlled release may be a film-forming polymer, such as a hydrophilic cellulose polymer. Such a hydrophilic cellulose polymer may be hydroxyalkyl cellulose polymer, for example hydroxyethylcellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropylmethylcellulose (HPMC), hydroxypropylethylcellulose (HPEC), hydroxypropylpropylcellulose (HPPC), hydroxypropylbutylcellulose (HPBC), and combinations comprising one or more of the foregoing polymers.

[0133] Both the core composition and the coating composition may further include a filler, such as a water insoluble filler, water soluble filler, and mixtures thereof. A water insoluble filler can be talc or a calcium salt such as a calcium phosphate, e.g., a dicalcium phosphate. The filler in the coating composition can be the same or different as the filler in the core composition, if any. For example, the core composition can include a water-soluble filler while the coating composition can include a water-insoluble filler.

[0134] Optional excipients can also be present in the core composition and the coating composition, including lubricants (such as talc and magnesium stearate), glidants (such as fumed or colloidal silica), pH modifiers (such as acids, bases and buffer systems), pharmaceutically useful processing aids, and combinations comprising one or more of the foregoing excipients. Excipients in the coating composition can be the same or different as those in the core composition.

[0135] In formation of the dosage form, the core composition can be press-coated with the press-coat composition coating formulation to form a tablet. The tablet can be further coated with optional additional coatings. The additional coatings can be pH-dependent or pH-independent, aesthetic or functional, and can include quetiapine in immediate or controlled release. The optional additional coating can include quetiapine or salt thereof or a different active agent than is contained in the core composition and the coating composition. The additional coating may, for example, include an immediate release dosage form of quetiapine hemifumarate.

[0136] In forming the dosage form, the core composition components (quetiapine, wax, and optional excipients) are blended together and compressed into suitable cores. The blending can take place in a suitable order of addition. The cores may be blended by starting with the smallest volume component and then successively adding the larger volume components. Another process is to melt the wax and to blend quetiapine and optional excipients into the melted wax. Alternatively, quetiapine, wax and optional excipients can be blended together and then subjected to a temperature at which the wax will melt. Once cooled, the solidified mass can be milled into granules for compaction into cores.

[0137] The press coat formulations may have substantially zero order, first order, or second order release rate profiles by adjusting the amount of quetiapine in the core composition and the coating composition. The ratio of quetiapine in the core composition ($Core_{AA}$) to quetiapine in the coating composition ($Coat_{AA}$) may be about 1:99 to about 99:1, about 95:5 to about 5:99, or about 9:1 to about 1:9. For the highly soluble active agents, including quetiapine hemifumarate and other highly soluble active agents that may be used in combination with quetiapine hemifumarate, a $Core_{AA}$:$Coat_{AA}$ ratio of about 3:4 to about 5:3 can provide a substantially zero order release rate, a $Core_{AA}$:$Coat_{AA}$ of less than about 3:4 can provide a substantially first order release rate, and a $Core_{AA}$:CoatAA of greater than about 5:3 can provide a substantially second order release rate.

[0138] The press coat formulations can be 25 mg, 100 mg, 200 mg, or 300 mg press coated tablets. One exemplary press coat quetiapine formulation comprises 10 mg quetiapine in an immediate release coating composition and 100 mg quetiapine between the core composition and the coating composition. In this example, the 0-4 hour cumulative release of quetiapine in 0.1 N hydrochloric acid may be at least about 25% to about 50%, or is some embodiments about 35% to about 40%, of the loaded dose, and the 0-12 hour cumulative release of quetiapine in 0.1 N hydrochloric acid may be at least about 75%, more preferably at least about 85%, of the dosage form dose. In another example, a 300 mg quetiapine hemifumarate formulation comprises a 3:2:1 (core:press coat:immediate release coat) ratio, e.g., a core composition comprising 150 mg of quetiapine hemifumarate, a coating composition comprising 100 mg of quetiapine hemifumarate, and an immediate release loading dose comprising 50 mg of quetiapine hemifumarate.

[0139] Thus an embodiment of the invention pertains to a press-coat dosage form comprising a core composition comprising an active agent, which active agent is quetiapine or a pharmaceutically acceptable salt thereof, a waxy material; and a coating composition comprising a hydrophilic polymer, wherein the coating composition is press-coated onto the core composition. Preferably the active agent is quetiapine hemifumarate.

[0140] The invention also pertains to a press-coat dosage form comprising a core composition comprising an active agent, which is quetiapine or a pharmaceutically acceptable salt thereof, a waxy material; and a coating composition comprising a hydrophilic polymer, wherein the coating composition which also contains quetiapine or a pharmaceutically acceptable salt thereof, is press-coated onto the core. Preferably the quetiapine in the coating composition is in the form of quetiapine hemifumarate.

[0141] In some embodiments the ratio of quetiapine in the core composition of the press-coat dosage form to quetiapine in the coating composition is about 1:99 to about 99:1. Other embodiments pertain to a quetiapine press-coat formulation in which the ratio of quetiapine in the core composition to quetiapine in the coating composition is greater than about 5:3.

[0142] In certain embodiments the waxy material of the press-coat dosage form core is carnauba wax, tribehenin, fatty alcohols, lauryl alcohol, myristyl alcohol, stearyl alcohol, palmityl alcohol, fatty acids, lauric acid, myristic acid, stearic acid, palmitic acid, polyethylenes, castor wax, C16-30 fatty acid triglycerides, beeswax, or any combination thereof. In some embodiments the hydrophilic polymer in the coating composition of the quetiapine press-coat dosage form comprises a hydrophilic cellulose polymer.

[0143] An embodiment of the invention pertains to a quetiapine press-coat dosage comprising a core composition comprising an active agent, which is quetiapine hemifumarate and wherein the hydrophilic cellulose polymer is hydroxypropylmethyl cellulose (HPMC).

[0144] Another embodiment of the invention pertains to a quetiapine press-coat dosage form comprising a core composition comprising an active agent which is quetiapine or quetiapine hemifumarate, carnauba wax; and a coating composition comprising quetiapine or quetiapine hemifumarate and hydroxypropylmethyl cellulose (HPMC),
wherein the coating composition is press-coated onto the core.

[0145] Yet another embodiment of the invention pertains to a quetiapine press-coat dosage form comprising a core composition comprising quetiapine hemifumarate and carnauba wax, a coating composition comprising quetiapine hemifumarate, and hydroxypropylmethyl cellulose (HPMC), wherein the coating composition is press-coated onto the core, and an additional coating composition comprising quetiapine hemifumarate. In some embodiments of the invention the additional coating composition is an immediate release coating composition.

[0146] In some embodiments of the invention the press-coat dosage form contains quetiapine in the core composition and quetiapine in the coating composition present in amounts effective to provide a substantially zero order release profile.

[0147] In other embodiments of the invention the quetiapine in the core composition and quetiapine in the coating composition are present in amounts effective to provide a substantially first order release profile.

[0148] In still other embodiments of the invention the quetiapine in the core composition and quetiapine in the coating composition are present in amounts effective to provide a substantially second order release profile.

[0149] The invention also provides a method for preparing a press-coat dosage form, the method comprising providing a core composition comprising quetiapine or a pharmaceutically acceptable salt thereof and a waxy material, providing a coating composition comprising quetiapine or a pharmaceutically acceptable salt thereof and a hydrophilic polymer, and press-coating the coating composition onto the core composition to provide the press-coat dosage form.

EASILY ADMINISTERED DOSAGE FORMS

[0150] The invention provides easily administerable dosage forms for administration to patients who have difficulty swallowing, to reduce the risk of choking upon administration, and to improve patient compliance. Such dosage forms are particularly useful for administration to elderly and juvenile patients. The invention provides, for example, sprinkle dosage forms, taste-masked liquid dosage forms and fast-dissolve dosage forms.

CHEWABLE TABLETS

[0151] Another solid dosage form is a chewable tablet containing quetiapine. A chewable tablet comprises a chewable base and optionally a sweetener. The chewable base comprises an excipient such as, for example, mannitol, sorbitol, lactose, or a combination comprising one or more of the foregoing excipients. The optional sweetener used in the chewable dosage form may be, for example, sucrose, liquid glucose, sorbitol, dextrose, isomalt, liquid maltitol, aspartame, lactose, and combinations comprising one ore more of the foregoing sweeteners. In certain cases, the chewable base and the sweetener may be the same component. The chewable base and optional sweetener may comprise about 50 % to about 90 % by weight of the total weight of the dosage form.

[0152] The chewable dosage form may additionally contain preservatives, agents that prevent adhesion to oral cavity and crystallization of sugars, flavoring agents, souring agents, coloring agents, and combinations comprising one or more of the foregoing agents. Glycerin, lecithin, hydrogenated palm oil or glyceryl monostearate may be used as a protecting agent of crystallization of the sugars in an amount of about 0.04 to about 2.0 weight % of the total weight of the ingredients, to prevent adhesion to oral cavity and improve the soft property of the products. Additionally, isomalt or liquid maltitol may be used to enhance the chewing properties of the chewable dosage form.

[0153] A method of making a chewable dosage form of quetiapine is similar to the method used to make soft confectionary. The method generally involves the formation of a boiled sugar-corn syrup blend to which is added a frappe mixture. The boiled sugar-corn syrup blend may be prepared from sugar and corn syrup blended in parts by weight ratio of 90: 10 to 10: 90. This blend may be heated to temperatures above 250 °F to remove water and to form a molten mass. The frappe mixture may be prepared from gelatin, egg albumen, milk proteins such as casein, and vegetable proteins such as soy protein, and the like which are added to a gelatin solution and rapidly mixed at ambient temperature to form an aerated sponge like mass. The frappe mixture is then added to the molten candy base and mixed until homogenous at temperatures between 150 °F to about 250 °F. A wax matrix containing quetiapine may then be added as the temperature of the mix is lowered to about 120 °F to about 194 °F, whereupon additional ingredients such as flavors, colorants, and preservatives may be added. The formulation is further cooled and formed to pieces of desired dimensions.

FAST DISSOLVING DOSAGE FORMS

[0154] Another oral dosage form is a non-chewable, fast dissolving dosage form of quetiapine. These dosage forms can be made by methods known to those of ordinary skill in the art of pharmaceutical formulations. For example, Cima Labs has produced oral dosage forms including microparticles and effervescents, which rapidly disintegrate in the mouth and provide adequate taste-masking. Cima Labs has also produced a rapidly dissolving dosage form containing an active agent and a matrix that includes a nondirect compression filler and a lubricant. Zydis (ZYPREXA) is produced by Eli Lilly as a rapidly dissolvable, freeze-dried, sugar matrix formulated as a rapidly dissolving tablet. U.S. Pat. No. 5,178,878 and U.S. Pat. No. 6,221,392 provide teachings regarding fast-dissolve dosage forms.

[0155] An exemplary fast dissolve dosage form includes a mixture incorporating a water and/or saliva activated effervescent, a disintegration agent, and microparticles. The microparticles incorporate quetiapine together with a protective material substantially encompassing quetiapine. The term "substantially encompassing" as used in this context means that the protective material substantially shields quetiapine from contact with the environment outside of the microparticle. Thus, each microparticle may incorporate a discrete mass of quetiapine covered by a coating of the protective material, in which case the microparticle can be referred to as a "microcapsule". Alternatively or additionally, each microparticle may have quetiapine dispersed or dissolved in a matrix of the protective material. The mixture including the microparticles and effervescent agent may be present as a tablet of a size and shape adapted for direct oral administration to a patient. The tablet is substantially completely disintegrable upon exposure to water and/or saliva. The effervescent disintegration agent is present in an amount effective to aid in disintegration of the tablet, and to provide a distinct sensation of effervescence when the tablet is placed in the mouth of a patient.

[0156] The effervescent sensation is not only pleasant to the patient but also tends to stimulate saliva production, thereby providing additional water to aid in further effervescent action. Thus, once the tablet is placed in the patient's mouth, it will disintegrate rapidly and substantially completely without any voluntary action by the patient. Even if the patient does not chew the tablet, disintegration will proceed rapidly. Upon disintegration of the tablet, the

microparticles are released and can be swallowed as a slurry or suspension of the microparticles. The microparticles are thus transferred to the patient's stomach for dissolution in the digestive tract and systemic distribution of the pharmaceutical ingredient.

[0157] The term effervescent disintegration agent(s) includes compounds that evolve gas. Effervescent agents may evolve gas by means of chemical reactions that take place upon exposure of the effervescent disintegration agent to water and/or to saliva in the mouth. The bubble or gas generating reaction is most often the result of the reaction of a soluble acid source and an alkali metal carbonate or carbonate source. The reaction of these two general classes of compounds produces carbon dioxide gas upon contact with water included in saliva.

[0158] Such water-activated materials should be kept in a generally anhydrous state with little or no absorbed moisture or in a stable hydrated form since exposure to water will prematurely disintegrate the tablet. The acid sources or acid may be any which are safe for human consumption and may generally include food acids, acid anhydrides and acid salts. Food acids include citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, and succinic acids, etc. Because these acids are directly ingested, their overall solubility in water is less important than it would be if the effervescent tablet formulations of the present invention were intended to be dissolved in a glass of water. Acid anhydrides and acid of the above-described acids may also be used. Acid salts may include sodium, dihydrogen phosphate, disodium dihydrogen pyrophosphate, acid citrate salts and sodium acid sulfite.

[0159] Carbonate sources include dry solid carbonate and bicarbonate salts such as sodium bicarbonate, sodium carbonate, potassium bicarbonate and potassium carbonate, magnesium carbonate and sodium sesquicarbonate, sodium glycine carbonate, L-lysine carbonate, arginine carbonate, amorphous calcium carbonate, and combinations comprising one or more of the foregoing carbonates.

[0160] The effervescent disintegration agent is not always based upon a reaction which forms carbon dioxide. Reactants which evolve oxygen or other gasses which are safe for human patients, including pediatric patients, are also within the scope of the invention. Where the effervescent agent includes two mutually reactive components, such as an acid source and a carbonate source, it is preferred that both components react substantially completely. Therefore, an equivalent ratio of components, which provides for equal

equivalents, is preferred. For example, if the acid used is diprotic, then either twice the amount of a mono-reactive carbonate base, or an equal amount of a di-reactive base should be used for complete neutralization to be realized. However, the amount of either acid or carbonate source may exceed the amount of the other component. This may be useful to enhance taste and/or performance of a tablet containing an overage of either component. In this case, it is acceptable that the additional amount of either component may remain unreacted.

[0161] In general, the amount of effervescent disintegration agent useful for the formation of tablets is about 5% to about 50% by weight of the final composition, preferably about 15% to about 30% by weight thereof, and most preferably about 20% to about 25% by weight of the total composition.

[0162] More specifically, tablets according to the present invention should contain an amount of effervescent disintegration agent effective to aid in the rapid and complete disintegration of the tablet when orally administered. By "rapid", it is understood that the tablets should disintegrate in the mouth of a patient in less than 10 minutes, and or in certain embodiments between about 30 seconds and about 7 minutes, preferably tablets should dissolve in the mouth in between about 30 seconds and about 5 minutes. Disintegration time in the mouth can be measured by observing the disintegration time of the tablet in water at about 37 °C. The tablet is immersed in the water without forcible agitation. The disintegration time is the time from immersion for substantially complete dispersion of the tablet as determined by visual observation. As used herein, the term "complete disintegration" of the tablet does not require dissolution or disintegration of the microcapsules or other discrete inclusions.

[0163] Quetiapine may be formulated in microparticles. Each microparticle incorporates quetiapine in conjunction with a protective material. The microparticle may be provided as a microcapsule or as a matrix-type microparticle. Microcapsules may incorporate a discrete mass of quetiapine surrounded by a discrete, separately observable coating of the protective material. Conversely, in a matrix-type particle, quetiapine is dissolved, suspended or otherwise dispersed throughout the protective material. Certain microparticles may include attributes of both microcapsules and matrix-type particle. For example, a microparticle may incorporate a core incorporating a dispersion of quetiapine in a

first protective material and a coating of a second protective material, which may be the same as or different from the first protective material surrounding the core. Alternatively, a microparticle may incorporate a core consisting essentially of quetiapine and a coating incorporating the protective material, the coating itself having some of the pharmaceutical ingredient dispersed within it.

[0164] The microparticles may be about 75 to about 600 microns mean outside diameter, and more preferably between about 150 and about 500 microns. Microparticles above about 200 microns may be used. Thus, the microparticles may be between about 200 mesh and about 30 mesh U.S. standard size, and more preferably between about 100 mesh and about 35 mesh.

[0165] Tablets can be manufactured by well-known tableting procedures. In common tableting processes, the material to be tableted is deposited into a cavity, and one or more punch members are then advanced into the cavity and brought into intimate contact with the material to be pressed, whereupon compressive force is applied. The material is thus forced into conformity with the shape of the punches and the cavity. Hundreds, and even thousands, of tablets per minute can be produced in this fashion.

[0166] Another exemplary fast-dissolve dosage form is a hard, compressed, rapidly dissolvable dosage form adapted for direct oral dosing. The dosage form includes quetiapine, often in the form of a protected particle, and a matrix. The matrix includes a nondirect compression filler and a lubricant, although, it may include other ingredients as well. The dosage form is adapted to rapidly dissolve in the mouth of a patient, yet it has a friability of about 2% or less when tested according to the U.S.P. Generally, the dosage form will also have a hardness of at least about 1.5- 2.0 kP. Not only does the dosage form dissolve quickly, it does so in a way that provides a positive organoleptic sensation to the patient. In particular, the dosage form dissolves with a minimum of unpleasant grit, which is tactilely very inconsistent with organoleptic sensation of the dosage form.

[0167] The protective materials may include a polymers conventionally utilized in the formation of microparticles, matrix-type microparticles and microcapsules. Among these are cellulosic materials such as naturally occurring cellulose and synthetic cellulose derivatives; acrylic polymers and vinyl polymers. Other simple polymers include proteinaceous materials such as gelatin, polypeptides and natural and synthetic shellacs and waxes. Protective

polymers may also include ethylcellulose, methylcellulose, carboxymethyl cellulose and acrylic resin material sold under the registered trademark EUDRAGIT by Rhone Pharma GmbH of Weiterstadt, Germany.

[0168] Generally, when a coating is used, the coating may be used at greater than or equal to about 5 percent based on the weight of the resulting particles. More preferable, the coating should constitute at least about 10 percent by weight of the particle. The upper limit of protective coating material used is generally less critical, except that where a rapid release of the active ingredient is desired, the amount of coating material should not be so great that the coating material impedes the release profile of quetiapine or pharmaceutical ingredient when ingested. In certain embodiments it is possible to use a coating that is greater than 100 percent of the weight of the core, thereby providing a relatively thick coating.

[0169] The filler comprises nondirect compression fillers. Exemplary fillers include, for example, nondirect compression sugars and sugar alcohols, which meet the specifications discussed above. Such sugars and sugar alcohols include, without limitation, dextrose, mannitol, sorbitol, lactose, and sucrose. Of course, dextrose, for example, can exist as either a direct compression sugar, i.e., a sugar that has been modified to increase its compressibility, or a nondirect compression sugar.

[0170] Generally, the balance of the formulation can be matrix. Thus the percentage of filler can approach 100% by weight. However, generally, the amount of nondirect compression filler is about 25 to about 95%, preferably about 50% to about 95% and more preferably about 60 % to about 95%.

[0171] In the fast-dissolve dosage form, a relatively high proportion of lubricant should be used. Lubricants, and in particular, hydrophobic lubricants such as magnesium stearate, are generally used in an amount of about 0.25% to about 5%, according to the Handbook of Pharmaceutical Excipients. It has been found that the amount of lubricant used can be double, triple or even quadruple that proposed previously. Specifically, the amount of lubricant used can be about 1% to about 2.5% by weight, and more preferably about 1.5% to about 2% by weight. Despite the use of this relatively high weight % of lubricant, the formulations exhibit a superior compressibility, hardness, and rapid dissolution within the mouth.

[0172] Hydrophobic lubricants include, for example, alkaline stearates, stearic acid,

mineral and vegetable oils, glyceryl behenate, sodium stearyl fumarate, and combinations comprising one or more of the foregoing lubricants. Hydrophilic lubricants can also be used.

[0173] The dosage forms may have a hardness of at least about 1.5 kP and are designed to dissolve spontaneously and rapidly in the mouth of a patient in less than about 90 seconds to thereby liberate the particles. Preferably the dosage form will dissolve in less than about 60 seconds and even more preferably about 45 seconds. This measure of hardness is based on the use of small tablets of less than about 0.25 inches in diameter. A hardness of at least about 2.0 kP is preferred for larger tablets. Direct compression techniques are preferred for the formation of the tablets.

SPRINKLE DOSAGE FORMS

[0174] Sprinkle dosage forms include particulate or pelletized forms of quetiapine, optionally having functional or non-functional coatings, with which a patient or a caregiver can sprinkle the particulate/pelletized dose into drink or onto soft food. A sprinkle dosage form may comprise particles of about 10 to about 100 micrometers in their major dimension. Sprinkle dosage forms may be in the form of optionally coated granules or as microcapsules. Sprinkle dosage forms may be immediate or controlled release formulations such as sustained release formulations. See U.S. Pat. No. 5,084,278, which is hereby incorporated by reference for its teachings regarding microcapsule formulations, which may be administered as sprinkle dosage forms.

[0175] Thus an embodiment of the invention provides a dosage form of quetiapine comprising an easily openable capsule enclosing a plurality of micropellets, where each of the micropellets comprises a seed coated with a first coating mixture of quetiapine and polyvinylpyrrolidone and coated thereon with a second coating mixture of about 90% to about 70% by weight of a non-hydrophilic polymer and about 10% to about 30% of a hydrophilic polymer.

[0176] In certain embodiments the non-hydrophilic polymer is ethyl cellulose. The hydrophilic polymer may be hydroxypropyl methyl cellulose.

[0177] The weight of the second coating mixture is about 5-10% of the weight of the micropellets before the second coating is applied. In certain embodiments of the invention

the second coating mixture comprises about 3 parts ethylcellulose to 1 about part hydroxypropylcellulose.

[0178] The invention includes a quetiapine sprinkle dosage form wherein the polyvinylpyrrolidone used in the first coating has a molecular weight of about 30,000 to about 50,000; preferably the polyvinylpyrrolidone has a molecular weight of about 40,000.

[0179] The seed of the sprinkle dosage form may be a sugar seed and have a mesh size of 60/80.

[0180] In certain embodiments the micropellets of the quetiapine sprinkle dosage form have a mean diameter of about 0.5 to about 0.7 mm.

[0181] The invention also pertains to a quetiapine sprinkle dosage form formulated as a sustained release dosage form.

TASTE MASKED SOLID DOSAGE FORMS

[0182] A solid oral dosage form may comprise a taste-masked dosage form. The taste-masked dosage forms may be liquid dosage forms such as those disclosed by F.H. Faulding, Inc. (U.S. Pat. No. 6,197,348).

[0183] A solid taste masked dosage form comprises a core element comprising quetiapine and a coating surrounding the core element. The core element comprising quetiapine may be in the form of a capsule or be encapsulated by micro-encapsulation techniques, where a polymeric coating is applied to the formulation. The core element includes quetiapine and may also include carriers or excipients, fillers, flavoring agents, stabilizing agents and/or colorants.

[0184] The taste masked dosage form may include about 77 weight% to about 100 weight%, preferably about 80 weight% to about 90 weight%, based on the total weight of the composition of the core element including quetiapine; and about 20 weight% to about 70 weight%, of a substantially continuous coating on the core element formed from a coating material including a polymer. The core element includes about 52% to about 85% by weight of quetiapine; and approximately 5% to about 25% by weight of a supplementary component selected from waxes, water insoluble polymers, enteric polymers, and partially water soluble polymers, other suitable pharmaceutical excipients, and combinations comprising one or more of the foregoing components.

[0185] The core element optionally include carriers or excipients, fillers, flavoring agents, stabilizing agents, colorants, and combinations comprising one or more of the foregoing additives. Suitable fillers include, for example, insoluble materials such as silicon dioxide, titanium dioxide, talc, alumina, starch, kaolin, polacrilin potassium, powdered cellulose, and microcrystalline cellulose, and combinations comprising one or more of the foregoing fillers. Soluble fillers include, for example, mannitol, sucrose, lactose, dextrose, sodium chloride, sorbitol, and combinations comprising one or more of the foregoing fillers. The filler may be present in amounts of up to about 75 weight% based on the total weight of the composition.

[0186] The core element may be in the form of a powder, for example, having a particle size range of about 35 μm to about 125 μm. The small particle size facilitates a substantially non-gritty feel in the mouth. Small particle size also minimizes break-up of the particles in the mouth, e.g. by the teeth. When in the form of a powder, the taste masked dosage form may be administered directly into the mouth or mixed with a carrier such as water, or semi-liquid compositions such as syrups, yogurt, and the like. However, the taste masked quetiapine may be provided in any suitable unit dosage form.

[0187] The coating material of the taste-masked formulation may take a form that provides a substantially continuous coating and still provides taste masking. In some cases, the coating also provides controlled release of quetiapine. The polymer used in taste masked dosage form coating may be a water insoluble polymer such as, for example, ethyl cellulose. The coating material of the taste masked dosage form may further include a plasticizer.

[0188] A method of preparing taste-masked pharmaceutical formulations such as powdered formulations includes mixing a core element and a coating material in a diluent and spray drying the mixture to form a taste-masked formulation. Spray drying of the pharmaceutically active ingredient and polymer in the solvent involves spraying a stream of air into an atomized suspension so that solvent is caused to evaporate leaving quetiapine coated with the polymer coating material.

[0189] For a solvent such as methylene chloride, the solvent concentration in the drying chamber may be maintained above about 40,000 parts, or about 40,000 to about 100,000 parts per million of organic solvent. The spray-drying process for such solvents may be conducted at a process temperature of about 5°C to about 35°C. Spray drying of the

dosage forms may be undertaken utilizing either rotary, pneumatic or pressure atomizers located in either a co-current, counter-current or mixed-flow spray dryer or variations thereof. The drying gas may be heated or cooled to control the rate of drying. A temperature below the boiling point of the solvent may be used. Inlet temperatures may be about 40 oC to about 120 oC and outlet temperatures about 5 oC to about 35 oC.

[0190] The coat formation may be optimized to meet the needs of the material or application. Controlling the process parameters including temperature, solvent concentration, spray dryer capacity, atomizing air pressure, droplet size, viscosity, total air pressure in the system and solvent system, allows the formation of a range of coats, ranging from dense, continuous, non-porous coats through to more porous microcapsule/polymer matrices.

[0191] A post-treatment step may be used to remove residual solvent. The post treatment may include a post drying step including drying the final product on a tray and drying the product at a bed temperature sufficient to remove excess solvent, but not degrade quetiapine. Preferably the drying temperature is in the range of about 35 °C to about 4 °C. Once completed, the product may be collected by a suitable method, such as collection by sock filters or cyclone collection.

[0192] Thus, in one embodiment the invention includes a chewable taste-masked dosage form, comprising: a microcapsule of about 10 microns to about 1.5 mm in diameter having a core comprising a pharmaceutically active agent, which is quetiapine or a pharmaceutically acceptable salt thereof, and a polymer mixture coating having sufficient elasticity to withstand chewing; the polymeric mixture coating comprising: about 50% by weight of a polymer that forms a polymeric film at temperatures of at least about 30 °C; and about 50% by weight of a low temperature film forming copolymer that forms a polymeric film at temperatures less than about 25 °C; and the polymeric mixture coating is adapted to release the pharmaceutically active agent in the stomach. Preferably the active agent is quetiapine hemifumarate.

[0193] The invention includes a taste-masked quetiapine dosage form in which the polymer that forms a polymeric film at temperatures of at least about 30 oC is an ethyl cellulose.

[0194] The invention also includes a taste-masked quetiapine dosage form in which the low temperature film forming copolymer is a methacrylic acid ester copolymer or a

styrene acrylate copolymer. In other embodiments of the taste-masked dosage the low temperature film forming polymer comprises a polymethacrylic acid ester copolymer having a weight average molecular weight of about 800,000.

[0195] In certain embodiments the core of the taste-masked quetiapine dosage form described above further comprises a diluent.

[0196] The polymer coating of the chewable taste-masked quetiapine dosage form may further comprise a plasticizer. Suitable plasticizers, include, but are not limited to polyethylene glycol, triacetin, vinylpyrrolidone, diethyl phthallate, dibutylsebacate, or a citric acid ester, and combinations thereof.

[0197] The invention also includes a taste-masked quetiapine solid, preferably chewable, dosage form, wherein the dosage form is a sustained release dosage form.

TASTE MASKED LIQUID DOSAGE FORMS

[0198] Liquid dosage forms of quetiapine that provide adequate taste masking may also be formulated. A taste masked liquid dosage form can comprise a suspension of microcapsules taste masked as a function of the pH of a suspending medium and a polymer coating. Many active agents are less soluble at higher or lower pH than at the pH value of the mouth, which is around 5.9. In these cases, quetiapine can be insufficiently solubilized to be tasted if the equilibrium concentration is below the taste threshold. However, problems can arise if all of the suspended particles are not swallowed because quetiapine, which remains in the mouth, is then able to dissolve at the pH of the mouth. The use of polymeric coatings on quetiapine particles, which inhibit or retard the rate of dissolution and solubilization of quetiapine is one means of overcoming the taste problems with delivery of quetiapine in suspension. The polymeric coating allows time for all of the particles to be swallowed before the taste threshold concentration is reached in the mouth.

[0199] Optimal taste masked liquid formulations may be obtained when consideration is given to: (i) the pH of maximum insolubility of quetiapine; (ii) the threshold concentration for taste of quetiapine; (iii) the minimum buffer strength required in the medium to avoid delayed or after taste; (iv) the pH limit beyond which further increase or decrease of pH leads to unacceptable instability of quetiapine; and (v) the compatibility and chemical, physical and microbial stability of the other ingredients to the pH values of the medium.

[0200] A taste masked liquid dosage form thus comprises quetiapine, a polymer with a quaternary ammonium functionality encapsulating quetiapine, and a suspending medium adjusted to a pH at which quetiapine remains substantially insoluble, for suspending the encapsulated quetiapine. Quetiapine is taste masked by the combination of the polymer and suspending medium.

[0201] Quetiapine may be in the form of its neutral or salt form and may be in the form of particles, crystals, microcapsules, granules, microgranules, powders, pellets, amorphous solids or precipitates. The particles may further include other functional components. Quetiapine may have a defined particle size distribution, preferably in the region of about 0.1 to about 500 μm, more preferably about 1 to about 250 μm, and most preferably about 10 to about 150 μm, where there is acceptable mouth feel and little chance of chewing on the residual particles and releasing quetiapine to taste.

[0202] The taste masked liquid dosage form may include, along with quetiapine, other functional components present for the purpose of modifying the physical, chemical, or taste properties of quetiapine. For example quetiapine may be in the form of ion-exchange or cyclodextrin complexes or quetiapine may be included as a mixture or dispersion with various additives such as waxes, lipids, dissolution inhibitors, taste-masking or -suppressing agents, carriers or excipients, fillers, and combinations comprising one or more of the foregoing components.

[0203] The polymer used to encapsulate the pharmaceutically active ingredient or the pharmaceutical unit is preferably a polymer having a quaternary ammonium functionality, i.e., a polymer having quaternary ammonium groups on the polymer backbone. These polymers are more effective in preventing the taste perception of quetiapine when the resulting microcapsules are formulated as suspensions that may be stored for long periods despite their widely recognized properties of being permeable to water and dissolved quetiapine. A suitable polymer is a copolymer of acrylic and methacrylic acid esters with quaternary ammonium groups. The polymer may be a copolymer of methyl methacrylate and triethylammonium methacrylate. Specific examples of suitable polymer include EUDRAGIT RS or EUDRAGIT RL, available from Röhm America, LLC, Piscataway, NJ used individually or in combination tochange the permeability of the coat. A polymer coat having a blend of the RS or RL polymer along with other pharmaceutically acceptable polymers may

also be used. These other polymers may be cellulose ethers such as ethyl cellulose, cellulose esters such as cellulose acetate and cellulose propionate, polymers that dissolve at acidic or alkaline pH, such as EUDRAGIT E, cellulose acetate phthalate, and hydroxypropylmethyl cellulose phthalate.

[0204] The quantity of polymer used in relation to quetiapine is about 0.01-10:1, preferably about 0.02-1:1, more preferably about 0.03-0.5:1 and most preferably about 0.05-0.3:1 by weight.

[0205] The quetiapine particle may be suspended, dispersed or emulsified in the suspending medium after encapsulation with the polymer. The suspending medium may be a water-based medium, but may be a non-aqueous carrier as well, constituted at an optimum pH for quetiapine or pharmaceutical unit, such that quetiapine remains substantially insoluble. The pH and ionic strength of the medium may be selected on the basis of stability, solubility and taste threshold to provide the optimum taste masking effect, and which is compatible with the stability of quetiapine the polymer coat and the coating excipients.

[0206] Buffering agents may be included in the suspending medium for maintaining the desired pH. The buffering agents may include dihydrogen phosphate, hydrogen phosphate, amino acids, citrate, acetate, phthalate, tartrate salts of the alkali or alkaline earth metal cations such as sodium, potassium, magnesium, calcium, and combinations comprising one or more of the foregoing buffering agents. The buffering agents may be used in a suitable combination for achieving the required pH and may be of a buffer strength of about 0.01 to about 1 moles/liter of the final formulation, preferably about 0.01 to about 0.1 moles/liter, and most preferably about 0.02 to about 0.05 moles/liter.

[0207] The taste masked liquid dosage form may further include other optional dissolved or suspended agents to provide stability to the suspension. These include suspending agents or stabilizers such as, for example, methyl cellulose, sodium alginate, xanthan gum, (poly)vinyl alcohol, microcrystalline cellulose, colloidal silicas, bentonite clay, and combinations comprising one or more of the foregoing agents. Other agents used include preservatives such as methyl, ethyl, propyl and butyl parabens, sweeteners such as sucrose, saccharin sodium, aspartame, mannitol, flavorings such as grape, cherry, peppermint, menthol and vanilla flavors, and antioxidants or other stabilizers, and combinations comprising one or more of the foregoing agents.

[0208] A method of preparing a taste masked dosage form for oral delivery, comprises encapsulating quetiapine with a polymer having a quaternary ammonium functionality; and adding a suspending medium adjusted to a pH at which quetiapine is substantially insoluble, for suspending the encapsulated quetiapine; wherein quetiapine is taste masked by the combination of the polymer and the medium. In the process, the polymer for encapsulation of quetiapine or the quetiapine-containing particle is dissolved in a solution or solvent chosen for its poor solubility for quetiapine and good solubility for the polymer. Examples of appropriate solvents include but are not limited to methanol, ethanol, isopropanol, chloroform, methylene chloride, cyclohexane, and toluene, either used in combination or used alone. Aqueous dispersions of polymers may also be used for forming quetiapine microparticles.

[0209] Encapsulation of quetiapine or pharmaceutical unit by the polymer may be performed by a method such as suspending, dissolving, or dispersing the pharmaceutically active ingredient in a solution or dispersion of polymer coating material and spray drying, fluid-bed coating, simple or complex coacervation, coevaporation, co-grinding, melt dispersion and emulsion-solvent evaporation techniques, and the like.

[0210] Polymer coated quetiapine powder can also as an alternative be applied for the preparation of reconstitutable powders, ie; dry powder quetiapine products that are reconstituted as suspensions in a liquid vehicle such as water before usage. The reconstitutable powders have a long shelf life and the suspensions, once reconstituted, have adequate taste masking.

[0211] One aspect of the invention pertains to a taste-masked liquid dosage form, comprising: particles of an active agent, wherein the active agent is quetiapine or a pharmaceutically acceptable salt thereof; and a polymer encapsulating the particles, wherein the polymer has quaternary ammonium groups on the polymer backbone; and a liquid suspending medium for suspending the encapsulated particles, wherein the liquid suspending medium comprises a water-based medium adjusted to a predetermined pH at which quetiapine remains substantially insoluble. Preferably the active agent is quetiapine hemifumarate.

[0212] The polymer encapsulating the particles may be a copolymer of acrylic and methacrylic acid esters with quaternary ammonium groups, or a copolymer of methyl methacrylate and triethylammonium methacrylate.

[0213] In certain embodiments of the invention the ratio of polymer to active agent in the taste masked quetiapine liquid dosage form is about 0.01:1 to about 10:1.

[0214] The invention also provides a taste-masked quetiapine liquid dosage form, in which quetiapine is in the form of ion-exchange complex, a cyclodextrin complex, or a mixture with a wax, a lipid, a dissolution inhibitor, a taste-masking agent, a taste-suppressing agent, a carrier, an excipient, a filler, or a combination comprising at least one of the foregoing forms.

[0215] The invention includes taste-masked quetiapine liquid dosage forms as described above further comprising an additional polymer, wherein the additional polymer is a cellulose ether, a cellulose ester, and polymers that dissolve at acidic or alkaline pH.

[0216] The invention includes taste-masked quetiapine liquid dosage forms as described above, wherein the suspending medium further comprises a buffering agent.

[0217] The invention also includes embodiments in which the buffering agent of the taste-masked quetiapine liquid dosage form has a buffer strength of 0.1 to 1 moles/liter.

[0218] The invention includes taste-masked liquid dosage forms as described above, which further comprise a stabilizer, wherein the stabilizer is methyl cellulose, sodium alginate, xanthan gum, (poly)vinyl alcohol, microcrystalline cellulose, colloidal silicas, bentonite clay, or a combination of any of the foregoing stabilizers.

[0219] In certain embodiments the invention includes taste-masked quetiapine liquid dosage forms as described above wherein the particle size is about 0.1 to about 500 micrometers.

[0220] In certain embodiments the taste-masked quetiapine liquid dosage form is a fast-dissolve form.

OSMOTIC PUMP DOSAGE FORMS

[0221] Another dosage form of quetiapine is one formulated with "osmotic pump" technology, such as OROS technology (Alza Corporation, Mountain View, CA). Such

dosage forms have a fluid-permeable (semipermeable) membrane wall, an osmotically active expandable driving member (the osmotic push layer), and a density element for delivering quetiapine. In an osmotic pump dosage form, the active material may be dispensed through an exit means comprising a passageway, orifice, or the like, by the action of the osmotically active driving member. Quetiapine of the osmotic pump dosage form may be formulated as a thermo-responsive formulation in which quetiapine is dispersed in a thermo-responsive composition. Alternatively, the osmotic pump dosage form may contain a thermo-responsive element comprising a thermo-responsive composition at the interface of the osmotic push layer and quetiapine composition.

[0222] The osmotic pump dosage form comprises a semipermeable membrane. The capsule or other dispenser of the osmotic pump dosage form can be provided with an outer wall comprising the selectively semipermeable material. A selectively permeable material is one that does not adversely affect a host or animal, is permeable to the passage of an external aqueous fluid, such as water or biological fluids, while remaining essentially impermeable to the passage of quetiapine, and maintains its integrity in the presence of a thermotropic thermo-responsive composition; that is it does not melt or erode in its presence. The selectively semipermeable material forming the outer wall is substantially insoluble in body fluids, nontoxic, and non-erodible.

[0223] Representative materials for forming the selectively semipermeable wall include semipermeable homopolymers, semipermeable copolymers, and the like. Suitable materials include, for example, cellulose esters, cellulose monoesters, cellulose diesters, cellulose triesters, cellulose ethers, cellulose ester-ethers, and combinations comprising one or more of the foregoing materials. These cellulosic polymers have a degree of substitution, D.S., on their anhydroglucose unit from greater than 0 up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups originally present on the anhydroglucose unit that are replaced by a substituting group, or converted into another group. The anhydroglucose unit can be partially or completely substituted with groups such as acyl, alkanoyl, aroyl, alkyl, alkenyl, alkoxy, halogen, carboalkyl, alkylcarbamate, alkylcarbonate, alkylsulfonate, alkylsulfamate, and like semipermeable polymer forming groups.

[0224] Other selectively semipermeable materials include, for example, cellulose

acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tri-cellulose alkanylates, mono-, di- and tri-alkenylates, mono-, di- and tri-aroylates, and the like, and combinations comprising one or more of the foregoing materials. Exemplary polymers including cellulose acetate having a D.S. of 1.8 to 2.3 and an acetyl content of about 32 to about 39.9%; cellulose diacetate having a D.S. of 1 to 2 and an acetyl content of about 21 to about 35%; cellulose triacetate having a D.S of 2 to 3 and an acetyl content of about 34 to about 44.8%, and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propionyl content of about 38.5%; cellulose acetate propionate having an acetyl content of about 1.5 to about 7% and an propionyl content of about 39% to about 42%; cellulose acetate propionate having an acetyl content of about 2.5% to about 3%, an average propionyl content of about 39.2% to about 45% and a hydroxyl content of about 2.8% to about 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of about 13% to about 15%, and a butyryl content of about 34% to about 39%; cellulose acetate butyrate having an acetyl content of about 2% to about 29.5%, a butyryl content of about 17% to about 53%, and a hydroxyl content of about 0.5% to about 4.7%; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trioctanoate, and cellulose tripropionate; cellulose diesters having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dicarpylate and the like; mixed cellulose esters such as cellulose acetate valerate, cellulose acetate succinate, cellulose propionate succinate, cellulose acetate octanoate, cellulose valerate palmitate, cellulose acetate heptonate, and the like, and combinations comprising one or more of the foregoing polymers.

[0225] Additional selectively semipermeable polymers include, for example, acetaldehyde dimethyl cellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose dimethylaminoacetate, semi-permeable polyamides, semipermeable polyurethanes, semi-permeable polysulfanes, semipermeable sulfonated polystyrenes, cross-linked, selectively semipermeable polymers formed by the coprecipitation of a polyanion and a polycation, selectively semipermeable silicon rubbers, semipermeable polystyrene derivates, semipermeable poly(sodium styrenesulfonate), semipermeable poly(vinylbenzyltrimethyl) ammonium chloride polymers, and combinations comprising one or more of the foregoing polymers.

[0226] The osmotically expandable driving member, or osmotic push layer, of the soft capsule osmotic pump dosage form is swellable and expandable inner layer. The materials used for forming the osmotic push layer, are neat polymeric materials, and/or polymeric materials blended with osmotic agents that interact with water or a biological fluid, absorb the fluid, and swell or expand to an equilibrium state. The polymer should exhibit the ability to retain a significant fraction of imbibed fluid in the polymer molecular structure. Such polymers may be, for example, gel polymers that can swell or expand to a very high degree, usually exhibiting about a 2 to 50-fold volume increase. Swellable, hydrophilic polymers, also known as osmopolymers, can be non-cross-linked or lightly cross-linked. The cross-links can be covalent or ionic bonds with the polymer possessing the ability to swell but not dissolve in the presence of fluid. The polymer can be of plant, animal or synthetic origin. Polymeric materials useful for the present purpose include poly(hydroxyalkyl methacrylate) having a molecular weight of about 5,000 to about 5,000,000, poly(vinylpyrrolidone) having a molecular weight of about 10,000 to about 360,000, anionic and cationic hydrogels, poly(electrolyte) complexes, poly(vinyl alcohol) having a low acetate residual, a swellable mixture of agar and carboxymethyl cellulose, a swellable composition comprising methyl cellulose mixed with a sparingly crosslinked agar, a water-swellable copolymer produced by a dispersion of finely divided copolymer of maleic anhydride with styrene, ethylene, propylene, or isobutylene, water swellable polymer of N-vinyl lactams, and the like, and combinations comprising one or more of the foregoing polymers. Other gelable, fluid imbibing and retaining polymers useful for forming the osmotic push layer include pectin having a molecular weight ranging from about 30,000 to about 300,000, polysaccharides such as agar, acacia, karaya, tragacanth, algins and guar, acidic carboxy polymer and its salt derivatives, polyacrylamides, water-swellable indene maleic anhydride polymers; polyacrylic acid having a molecular weight of about 80,000 to about 200,000, polyethylene oxide polymers having a molecular weight of about 100,000 to about 5,000,000, and greater, starch graft copolymers, polyanions and polycations exchange polymers, starch-polyacrylonitrile copolymers, acrylate polymers with water absorbability of about 400 times its original weight, diesters of polyglucan, a mixture of cross-linked polyvinyl alcohol and poly(N-vinyl-2-pyrrolidone), zein available as prolamine, poly(ethylene glycol) having a molecular weight

of about 4,000 to about 100,000, and the like, and combinations comprising one or more of the foregoing polymers.

[0227] The osmotically expandable driving layer of the osmotic pump dosage form may further contain an osmotically effective compound (osmagent) that can be used neat or blended homogeneously or heterogeneously with the swellable polymer, to form the osmotically expandable driving layer. Such osmagents include osmotically effective solutes that are soluble in fluid imbibed into the swellable polymer, and exhibit an osmotic pressure gradient across the semipermeable wall against an exterior fluid. Suitable osmagents include, for example, solid compounds such as magnesium sulfate, magnesium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium sulfate, mannitol, urea, sorbitol, inositol, sucrose, glucose, and the like, and combinations comprising one or more of the foregoing osmagents. The osmotic pressure in atmospheres, atm, of the osmagents may be greater than about zero atm, and generally about zero atm to about 500 atm, or higher.

[0228] The swellable, expandable polymer of the osmotically expandable driving layer, in addition to providing a driving source for delivering quetiapine from the dosage form, may also function as a supporting matrix for an osmotically effective compound. The osmotic compound can be homogeneously or heterogeneously blended with the polymer to yield the desired expandable wall or expandable pocket. The composition in a presently preferred embodiment comprises (a) at least one polymer and at least one osmotic compound, or (b) at least one solid osmotic compound. Generally, a composition will comprise about 20% to about 90% by weight of polymer and about 80% to about 10% by weight of osmotic compound, with a presently preferred composition comprising about 35% to about 75% by weight of polymer and about 65% to about 25% by weight of osmotic compound.

[0229] Quetiapine of the osmotic pump dosage form may be formulated as a thermo-responsive formulation in which quetiapine is dispersed in a thermo-responsive composition. Alternatively, the osmotic pump dosage form may contain a thermo-responsive element comprising a thermo-responsive composition at the interface of the osmotic push layer and quetiapine composition. Representative thermo-responsive compositions and their melting points are as follows: Cocoa butter (32 °C-34 °C), cocoa butter plus 2% beeswax (35 °C-37 °C), propylene glycol monostearate and distearate (32 °C-35 °C), hydrogenated oils such as hydrogenated vegetable oil (36 °C-37.5 °C), 80% hydrogenated vegetable oil and 20%

sorbitan monopalmitate (39°C-39.5 °C), 80% hydrogenated vegetable oil and 20% polysorbate 60, (36 °C-37 °C), 77.5% hydrogenated vegetable oil, 20% sorbitan trioleate, 2.5% beeswax and 5.0% distilled water, (37 °C-38 °C), mono-, di-, and triglycerides of acids having from 8-22 carbon atoms including saturated and unsaturated acids such as palmitic, stearic, oleic, lineolic, linolenic and archidonic; triglycerides of saturated fatty acids with mono- and diglycerides (34 °C-35.5 °C), propylene glycol mono- and distearates (33 °C-34 °C), partially hydrogenated cottonseed oil (35 °C-39 °C), a block polymer of polyoxy-alkylene and propylene glycol; block polymers comprising 1,2-butylene oxide to which is added ethylene oxide; block copolymers of propylene oxide and ethylene oxide, hardened fatty alcohols and fats (33 °C-36 °C), hexadienol and hydrous lanolin triethanolamine glyceryl monostearate (38 °C), eutectic mixtures of mono-, di-, and triglycerides (35 °C-39 °C), WITEPSOL#15, triglyceride of saturated vegetable fatty acid with monoglycerides (33.5 °C-35.5 °C), WITEPSOL H32 free of hydroxyl groups (31 °C-33 °C), WITEPSOL W25 having a saponification value of 225-240 and a melting point of (33.5 °C-35.5 °C), WITEPSOL E75 having a saponification value of 220-230 and a melting point of (37 °C-39 °C), a polyalkylene glycol such as polyethylene glycol 1000, a linear polymer of ethylene oxide (38 °C-41 °C), polyethylene glycol 1500 (38 °C-41 °C), polyethylene glycol monostearate (39 °C-42.5 °C), 33% polyethylene glycol 1500, 47% polyethylene glycol 6000 and 20% distilled water (39 °C-41 °C), 30% polyethylene glycol 1500, 40% polyethylene glycol 4000 and 30% polyethylene glycol 400, (33 °C-38 °C), mixture of mono-, di-, and triglycerides of saturated fatty acids having 11 to 17 carbon atoms, (33 °C-35 °C), and the like. The thermo-responsive compositions, including thermo-responsive carriers are useful for storing quetiapine in a solid composition at a temperature of about 20 °C to about 33 °C, maintaining an immiscible boundary at the swelling composition interface, and for dispensing the agent in a flowable composition at a temperature greater than about 33 °C and preferably between about 33 °C and about 40 °C.

[0230] The amount of quetiapine present in the osmotic pump dosage form is about 25 mg to about 2 g or more. The osmotic dosage form may be formulated for once daily or less frequent administration.

[0231] Quetiapine in the osmotic pump dosage form may be formulated by a number of techniques known in the art for formulating solid and liquid oral dosage forms. Quetiapine

formulations of the osmotic pump dosage form may be formulated by wet granulation. In an exemplary wet granulation method, quetiapine and the ingredients comprising the quetiapine layer are blended using an organic solvent, such as isopropyl alcohol-ethylene dichloride 80:20 v:v (volume:volume) as the granulation fluid. Other granulating fluid such as denatured alcohol 100% may be used for this purpose. The ingredients forming the quetiapine layer are individually passed through a screen such as a 40-mesh screen and then thoroughly blended in a mixer. Next, other ingredients comprising the quetiapine layer are dissolved in a portion of the granulation fluid, such as the cosolvent described above. Then the latter prepared wet blend is slowly added to the quetiapine blend with continual mixing in the blender. The granulating fluid is added until a wet blend is produced, which wet mass then is forced through a screen such as a 20-mesh screen onto oven trays. The blend is dried for about 18 to about 24 hours at about 30 °C to about 50 °C. The dry granules are sized then with a screen such as a 20-mesh screen. Next, a lubricant is passed through a screen such as an 80-mesh screen and added to the dry screen granule blend. The granulation is put into milling jars and mixed on a jar mill for about 1 to about 15 minutes. The push layer may also be made by the same wet granulation techniques. The compositions are pressed into their individual layers in a KILIAN press-layer press.

[0232] Another manufacturing process that can be used for providing the quetiapine layer and osmotically expandable driving layer comprises blending the powered ingredients for each layer independently in a fluid bed granulator. After the powered ingredients are dry blended in the granulator, a granulating fluid, for example, poly(vinyl-pyrrolidone) in water, or in denatured alcohol, or in 95:5 ethyl alcohol/water, or in blends of ethanol and water is sprayed onto the powders. Optionally, the ingredients can be dissolved or suspended in the granulating fluid. The coated powders are then dried in a granulator. This process granulates the ingredients present therein while adding the granulating fluid. After the granules are dried, a lubricant such as stearic acid or magnesium stearate is added to the granulator. The granules for each separate layer are pressed then in the manner described above.

[0233] The osmotic push quetiapine formulation and osmotic push layer of the osmotic push dosage form may also be manufactured by mixing quetiapine with composition forming ingredients and pressing the composition into a solid lamina possessing dimensions that correspond to the internal dimensions of the compartment. In another manufacture,

quetiapine, other quetiapine composition-forming ingredients, and a solvent are mixed into a solid, or a semisolid, by methods such as ballmilling, calendaring, stirring or rollmilling, and then pressed into a preselected layer forming shape. Next, a layer of a composition comprising an osmopolymer and an optional osmagent are placed in contact with the layer comprising quetiapine. The layering of the first layer comprising quetiapine and the second layer comprising the osmopolymer and optional osmagent composition can be accomplished by using a conventional layer press technique. The semipermeable wall can be applied by molding, spraying or dipping the pressed bilayer's shapes into wall forming materials. An air suspension coating procedure which includes suspending and tumbling the two layers in current of air until the wall forming composition surrounds the layers is also used to form the semi-permeable wall of the osmotic dosage forms.

[0234] The dispenser of the osmotic pump dosage form may be in the form of a capsule. The capsule may comprise an osmotic hard capsule and/or an osmotic soft capsule. The osmotic hard capsule may be composed of two parts, a cap and a body, which are fitted together after the larger body is filled with quetiapine. The osmotic hard capsule may be fitted together by slipping or telescoping the cap section over the body section, thus completely surrounding and encapsulating quetiapine. Hard capsules may be made by techniques known in the art.

[0235] The soft capsule of the osmotic pump dosage form may be a one-piece osmotic soft capsule. Generally, the osmotic soft capsule is of sealed construction encapsulating quetiapine. The soft capsule may be made by various processes, such as the plate process, the rotary die process, the reciprocating die process, and the continuous process.

[0236] Materials useful for forming the capsule of the osmotic pump dosage form are commercially available materials including gelatin, gelatin having a viscosity of about 5 to about 30 millipoises and a bloom strength up to about 150 grams; gelatin having a bloom value of about 160 to about 250; a composition comprising gelatin, glycerine, water and titanium dioxide; a composition comprising gelatin, erythrosin, iron oxide and titanium dioxide; a composition comprising gelatin, glycerine, sorbitol, potassium sorbate and titanium dioxide; a composition comprising gelatin, acacia, glycerin, and water; and the like, and combinations comprising one or more of the foregoing materials.

[0237] The semipermeable wall forming composition can be applied to the exterior surface of the capsule in laminar arrangement by molding, forming, air spraying, dipping or brushing with a semipermeable wall forming composition. Other techniques that can be used for applying the semipermeable wall are the air suspension procedure and the pan coating procedures. The air suspension procedure includes suspending and tumbling the capsule arrangement in a current of air and a semipermeable wall forming composition until the wall surrounds and coats the capsule. The procedure can be repeated with a different semipermeable wall forming composition to form a semipermeable laminated wall.

[0238] Exemplary solvents suitable for manufacturing the semipermeable wall include inert inorganic and organic solvents that do not adversely harm the materials, the capsule wall, quetiapine, the thermo-responsive composition, the expandable member, or the final dispenser. Solvents for manufacturing the semipermeable wall may be aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents, and combinations comprising one or more of the foregoing solvents. Particular solvents include acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cyclooctane, benzene, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, water, and mixtures thereof such as acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride, methanol, and combinations comprising one or more of the foregoing solvents. The semipermeable wall may be applied at a temperature a few degrees less than the melting point of the thermo-responsive composition. Alternatively, the thermo-responsive composition can be loaded into the dispenser after applying the semipermeable wall.

[0239] The exit means or hole in the osmotic pump dosage form, for releasing quetiapine, can be formed by mechanical or laser drilling, or by eroding an erodible element in the wall, such as a gelatin plug. The orifice can be a polymer inserted into the

semipermeable wall, which polymer is a porous polymer and has at least one pore, or which polymer is a microporous polymer and has at least one micro-pore.

CONTROLLED RELEASE FORMULATION FOR RELEASE INTO THE STOMACH AND UPPER GASTROINTESTINAL TRACT

[0240] An exemplary controlled release formulation for release of quetiapine in the stomach and gastrointestinal tract is one in which quetiapine is dispersed in a polymeric matrix that is water-swellable rather than merely hydrophilic, that has an erosion rate that is substantially slower than its swelling rate, and that releases quetiapine primarily by diffusion. The rate of diffusion of quetiapine out of the matrix can be slowed by increasing quetiapine particle size, by the choice of polymer used in the matrix, and/or by the choice of molecular weight of the polymer. The matrix is a relatively high molecular weight polymer that swells upon ingestion, preferably to a size that is at least about twice its unswelled volume, and that promotes gastric retention during the fed mode. Upon swelling, the matrix may also convert over a prolonged period of time from a glassy polymer to a polymer that is rubbery in consistency, or from a crystalline polymer to a rubbery one. The penetrating fluid then causes release of quetiapine in a gradual and prolonged manner by the process of solution diffusion, i.e., dissolution of quetiapine in the penetrating fluid and diffusion of the dissolved drug back out of the matrix. The matrix itself is solid prior to administration, and once administered, remains undissolved in (i.e., is not eroded by) the gastric fluid for a period of time sufficient to permit the majority of quetiapine to be released by the solution diffusion process during the fed mode. The rate-limiting factor in the release of quetiapine may be therefore controlled diffusion of quetiapine from the matrix rather than erosion, dissolving or chemical decomposition of the matrix.

[0241] For soluble active agents such as quetiapine, the swelling of the polymeric matrix thus achieves two objectives: (i) causing the tablet to swell to a size large enough to cause it to be retained in the stomach during the fed mode, and (ii) retarding the rate of diffusion of the soluble active agent long enough to provide multi-hour, controlled delivery of the active agent into the stomach. For active agents that are either sparingly soluble, of limited solubility, or of high solubility, and that experience any of the specific problems enumerated above upon reaching the lower GI tract prior to absorption into the bloodstream,

the swelling of the polymeric matrix (i) renders the matrix sufficiently large to cause retention in the stomach during the fed mode, and (ii) localizes the release of quetiapine to the stomach and small intestine so that the agent may have its full effect without substantial colonic degradation, inactivation, or loss of bioavailability.

[0242] The water-swellable polymer forming the matrix is a polymer that is non-toxic, that swells in a dimensionally unrestricted manner upon imbibition of water, and that provides for sustained release of incorporated quetiapine. Examples of suitable polymers include, for example, cellulose polymers and their derivatives (such as for example, hydroxyethylcellulose, hydroxypropylcellulose, carboxymethylcellulose, and microcrystalline cellulose, polysaccharides and their derivatives, polyalkylene oxides, polyethylene glycols, chitosan, poly(vinyl alcohol), xanthan gum, maleic anhydride copolymers, poly(vinyl pyrrolidone), starch and starch-based polymers, poly (2-ethyl-2-oxazoline), poly(ethyleneimine), polyurethane hydrogels, and crosslinked polyacrylic acids and their derivatives. Further examples are copolymers of the polymers listed in the preceding sentence, including block copolymers and grafted polymers. Specific examples of copolymers are PLURONIC and TECTONIC, which are polyethylene oxide-polypropylene oxide block copolymers available from BASF Corporation, Chemicals Div., Wyandotte, Mich., USA.

[0243] The terms "cellulose" and "cellulosic" denote a linear polymer of anhydroglucose. Cellulosic polymers include, for example, alkyl- substituted cellulosic polymers that ultimately dissolve in the gastrointestinal (GI) tract in a predictably delayed manner. Alkyl-substituted cellulose derivatives may be those substituted with alkyl groups of 1 to 3 carbon atoms each. Specific examples are methylcellulose, hydroxymethyl-cellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carboxymethylcellulose. In terms of their viscosities, one class of suitable alkyl-substituted celluloses includes those whose viscosity is about 100 to about 110,000 centipoise as a 2% aqueous solution at 20°C. Another class includes those whose viscosity is about 1,000 to about 4,000 centipoise as a 1% aqueous solution at 20°C. Exemplary alkyl-substituted celluloses are hydroxyethylcellulose and hydroxypropylmethylcellulose. A specific example of a hydroxyethylcellulose is NATRASOL 250HX NF (National Formulary), available from Aqualon Company, Wilmington, Del., USA.

[0244] Suitable polyalkylene oxides are those having the properties described above for alkyl-substituted cellulose polymers. An example of a polyalkylene oxide is poly(ethylene oxide), which term is used herein to denote a linear polymer of unsubstituted ethylene oxide. Poly(ethylene oxide) polymers having molecular weights of about 4,000,000 and higher are preferred. More preferred are those with molecular weights of about 4,500,000 to about 10,000,000, and even more preferred are polymers with molecular weights of about 5,000,000 to about 8,000,000. Preferred polyethylene oxides are those with a weight-average molecular weight within the range of about 1×10^5 to about 1×10^7, and preferably within the range of about 9×10^5 to about 8×10^6. Poly(ethylene oxide)s are often characterized by their viscosity in solution and may have a viscosity of about 50 to about 2,000,000 centipoise for a 2% aqueous solution at 20°C. Two specific example of poly(ethylene oxide)s are POLYOX NF, grade WSR Coagulant, molecular weight 5 million, and grade WSR 303, molecular weight 7 million, both products of Union Carbide Chemicals and Plastics Company Inc. of Danbury, Conn., USA.

[0245] Polysaccharide gums, both natural and modified (semi-synthetic) can be used. Examples are dextran, xanthan gum, gellan gum, welan gum and rhamsan gum.

[0246] Crosslinked polyacrylic acids of greatest utility are those whose properties are the same as those described above for alkyl-substituted cellulose and polyalkylene oxide polymers. Certain crosslinked polyacrylic acids useful in the invention are those with a viscosity of about 4,000 to about 40,000 centipoise for a 1% aqueous solution at 25°C. Three specific examples are CARBOPOL NF grades 971P, 974P and 934P (BFGoodrich Co., Specialty Polymers and Chemicals Div., Cleveland, Ohio, USA). Further examples include polymers known as WATER LOCK, which are starch/acrylates/acrylamide copolymers available from Grain Processing Corporation, Muscatine, Iowa, USA.

[0247] The hydrophilicity and water swellability of these polymers cause quetiapine-containing matrices to swell in size in the gastric cavity due to ingress of water in order to achieve a size that will be retained in the stomach when introduced during the fed mode. These qualities also cause the matrices to become slippery, which provides resistance to peristalsis and further promotes their retention in the stomach. The release rate of quetiapine from the matrix is primarily dependent upon the rate of water imbibition and the rate at which quetiapine dissolves and diffuses from the swollen polymer, which in turn is related to the

solubility and dissolution rate of quetiapine, quetiapine particle size and quetiapine concentration in the matrix. Also, because these polymers dissolve very slowly in gastric fluid, the matrix maintains its physical integrity over at least a substantial period of time, in many cases at least 90% and preferably over 100% of the dosing period. The particles will then slowly dissolve or decompose. Complete dissolution or decomposition may not occur until 24 hours or more after the intended dosing period ceases, although in most cases, complete dissolution or decomposition will occur within 10 to 24 hours after the dosing period.

[0248] The dosage forms may include additives that impart a small degree of hydrophobic character, to further retard the release rate of quetiapine into the gastric fluid. One example of such a release rate retardant is glyceryl monostearate. Other examples are fatty acids and salts of fatty acids, one example of which is sodium myristate. The quantities of these additives when present can vary; and in most cases, the weight ratio of additive to quetiapine will be about 1:20 to about 1:1, and preferably about 1:8 to about 1:2.

[0249] The amount of polymer relative to quetiapine can vary, depending on quetiapine release rate desired and on the polymer, its molecular weight, and excipients that may be present in the formulation. The amount of polymer will be sufficient however to retain at least about 40% of quetiapine within the matrix one hour after ingestion (or immersion in the gastric fluid). Preferably, the amount of polymer is such that at least 50% of quetiapine remains in the matrix one hour after ingestion. More preferably, at least 60%, and most preferably at least 80%, of quetiapine remains in the matrix one hour after ingestion. In all cases, however, quetiapine will be substantially all released from the matrix within about ten hours, and preferably within about eight hours, after ingestion, and the polymeric matrix will remain substantially intact until all of quetiapine is released. The term "substantially intact" is used herein to denote a polymeric matrix in which the polymer portion substantially retains its size and shape without deterioration due to becoming solubilized in the gastric fluid or due to breakage into fragments or small particles.

[0250] The water-swellable polymers can be used individually or in combination. Certain combinations will often provide a more controlled release of quetiapine than their components when used individually. An examplary combination is cellulose-based polymers

combined with gums, such as hydroxyethyl cellulose or hydroxypropyl cellulose combined with xanthan gum. Another example is poly(ethylene oxide) combined with xanthan gum.

[0251] The benefits of this dosage form will be achieved over a wide range of quetiapine loadings, with the weight ratio of quetiapine to polymer of 0.01:99.99 to about 80:20. Preferred loadings (expressed in terms of the weight percent of quetiapine relative to total quetiapine and polymer) are about 15% to about 80%, more preferably about 30% to about 80%, and in certain cases about 30% to about 70%. For certain applications, however, the benefits will be obtained with quetiapine loadings of 0.01% to 80%, and preferably 15% to 80%.

[0252] As indicated above, the dosage forms find their greatest utility when administered to a subject who is in the digestive state (also referred to as the postprandial or "fed" mode). The postprandial mode is distinguishable from the interdigestive (or "fasting") mode by their distinct patterns of gastroduodenal motor activity, which determine the gastric retention or gastric transit time of the stomach contents.

COMBINATIONS

[0253] In addition to the embodiments where quetiapine is the only active agent, the invention includes combination dosage forms that also contain other active agents useful in the treatment of conditions such as schizophrenia and bipolar mania, particularly the psychosis associated with schizophrenia, and acute episodes of bipolar mania, Alzheimer's dementia, and hyperactivity.

[0254] The invention include combinations that contain another neuroleptic agent such as trifluoperazine, pimozide, flupenthixol, clozepine, chlorpromazine, flupenthixol, fluphenazine decanoate, pipotiazine, or haloperidol decanoate, as an additional active agent.

[0255] The invention also includes combination dosage forms that contain one or more cognitive enhancer as the additional active agent. Such combinations are useful for treating both the psychosis and memory deficits of Alzheimer's dementia.

[0256] The invention pertains to combination dosage forms that contain an anti-parkinsonian agent as the additional active agent. Also called "side-effect medication" anti-parkinsonians are indicated when muscle side-effects of the neuroleptics make patients

uncomfortable. Anti=parkinsonian agents are usually anticholinergic drugs. Typical examples include benztropine mesylate, trihexyphenidyl, procyclidine, and amantadine.

[0257] The invention includes combination dosage forms that include a sedative, such as a benzodiazepine sedative or non-barbituate sedative as the additional active agent.

[0258] The invention also includes combination dosage forms that contain an anxiolytics as the additional active agent. Examples of frequently used anxiolytics include benzodiazepines such as lorazepam, chlordiazepoxide, oxazepam, clorazepate, diazepam, and alprazolam.

[0259] The invention further pertains to combination dosage forms that contain an antidepressant as the additional active agent. Antidepressents include tricyclic antidepressants such as amitriptyline, imipramine, doxepin, and clomipramine; monoamine oxidase inhibitors, such as phenelzine and tranylcypromine; tetracyclic antidepressants, such as maprotiline, and serontin re-uptake inhibitors such as fluoxetine and sertraline hydrochloride.

[0260] The invention includes combination dosage forms in which an antacid is included in the invention. Examples of antacids include acid neutralizers, such as aluminum hydroxide, magnesium hydroxide, calcium carbonate, and sodium bicarbonate; histamine-2 antagonists (H2-antagonists) examples of which include cimetidine, famotidine, nizatidine, ranitidine; and proton pump inhibitors, such as lansoprazole, omeprazole, pantoprazole, and rabeprazole.

DISSOLUTION PROFILES FOR QUETIAPINE DOSAGE FORMS

[0261] The invention provides the quetiapine dosage forms and dosage forms comprising quetiapine and one or more other active agent described herein formulated so that particular dissolution profiles are achieved.

[0262] The dissolution, or release, profile, of the quetiapine dosage form is obtained by immersing the dosage from in 750 ml of 0.1 N HCl for 2 hours at 37 °C at a speed of 100 rpm and then adding 250 ml of 0.2 M sodium phosphate buffer to the dissolution media to afford at pH of 6.2. Alternatively the quetiapine release rate data is obtained for a dosage form in USP Apparatus 2 at 50 rpm using 900 ml of either water or 0.1 N HCl as the

dissolution media. The dissolution profile can also be measured utilizing the Drug Release Test (724), which incorporates standard test USP (2002) (Test (711)).

[0263] In one embodiment the invention provides a dosage form that exhibits a dissolution profile that is substantially identical to that of SEROQUEL in the same dissolution media.

[0264] The invention includes a controlled release dosage form comprising a pharmaceutically effective amount of quetiapine or a pharmaceutically acceptable salt thereof and at least one excipient, exhibiting a dissolution profile in a dissolution media, e.g. 0.1 N HCl, such that at 4 hours after combining with the dissolution media 50 to 95% of the quetiapine or quetiapine salt is released.

[0265] The invention also includes a controlled release quetiapine dosage form dissolution profile such that at 1 hour after combining the dosage form with a dissolution media, e.g. 0.1 N HCl, 30% to 80% of the quetiapine or quetiapine salt is released, at 2 hours after combining the dosage form with a dissolution media 40% to 85% of the quetiapine or quetiapine salt is released, at 3 hours after combining the dosage form with a dissolution media 45% to 90% of the quetiapine or quetiapine salt is released, and at 4 hours after combining the dosage form with a dissolution media 50% to 95% of the quetiapine or quetiapine salt is released.

[0266] The invention includes a controlled release quetiapine dosage form comprising a pharmaceutically effective amount of quetiapine or a pharmaceutically acceptable salt thereof and at least one excipient, exhibiting a dissolution profile in 0.1 N HCl such that at 16 hours after combining the dosage form with a dissolution media less that 90 % of the quetiapine or the pharmaceutically acceptable salt thereof is released.

[0267] The invention also provides a controlled release dosage form comprising a pharmaceutically effective amount of quetiapine or a pharmaceutically acceptable salt thereof and at least one excipient, exhibiting a dissolution profile in 0.1 N HCl such that at 1 hour after combining the dosage form with a dissolution media 5% to 15% of the quetiapine or quetiapine salt is released, at 2 hours after combining the dosage form with a dissolution media 10% to 25% of the quetiapine or quetiapine salt is released, at 4 hours after combining the dosage form with a dissolution media 15% to 35% of the quetiapine or quetiapine salt is

released, at 8 hours after combining the dosage form with a dissolution media 25 to 50% of the quetiapine or quetiapine is released.

[0268] Preferably the quetiapine in the controlled release dosage form is in the form of quetiapine hemifumarate.

[0269] The invention also provides the novel quetiapine dosage forms, including the quetiapine wax formulations, press-coat dosage forms, and sprinkle dosage forms having a dissolution profile which substantially mimics that of SEROQUEL. The invention provides novel quetiapine dosage forms including the quetiapine wax formulations, press-coat dosage forms, and sprinkle dosage forms having a dissolution profile which substantially mimics that of the dosage form disclosed in U.S. patent no. 5,948,437 which is hereby incorporated by reference at Sheet 1 of 2, Figure 2, for its teachings regarding the dissolution of a quetiapine dosage form in 0.1 N HCl. Dosage forms that "substantially mimic" the dissolution profiles of SEROQUEL or the quetiapine dosage forms disclosed in U.S. patent no. 5,948,437 exhibit a release between 80% and 120% of the quetiapine released by these dosage forms at the same time point in the same dissolution media. For example the invention include novel dosage forms which exhibit dissolution profiles which are substantially similar to those of U.S. patent no. 5,948,437 such that at 1 hour after combining with 0.1 N HCl dissolution media between 15% and 25% of the quetiapine is released, at 2 hours after combining with 0.1 N HCl dissolution media between 35% and 45% of the quetiapine is released, at 4 hours after combining with 0.1 N HCl dissolution media between 35% and 50% of the quetiapine is released, and at 8 hours after combining with 0.1 N HCl dissolution media between 50% and 75% of the quetiapine is released.

PHARMACOKINETIC PROPERTIES OF QUETIAPINE DOSAGE FORMS

[0270] The invention provides the quetiapine dosage forms and dosage forms comprising quetiapine and one or more other active agent (combinations) described herein formulated so that particular plasma levels, Cmax, Tmax, and AUC values are achieved.

[0271] In one embodiment the invention provides a dosage form that exhibits a Cmax value and AUC from time of administration to 24 hours after administration that are from 80 % to 120 % of the C_{max} value and AUC from time of administration to 24 hours after administration exhibited by SEROQUEL (Astra Zeneca) under the same conditions.

[0272] The plasma concentration of quetiapine may be determined as follows: Blood samples are taken from patients immediately before dosing and at specified time intervals after administration. The concentration of quetiapine in the blood sample is quantified using liquid-liquid extraction and HPLC with UV detection.

[0273] The invention also comprises an oral dosage form comprising quetiapine or a pharmaceutically acceptable salt thereof in controlled release form which provides a maximum quetiapine plasma concentration (C_{max}) and an quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the ratio of C_{max} to C_{24} is less than about 4:1, or in certain embodiments less than about 2:1. Preferably the quetiapine is in the form of quetiapine hemifumarate.

[0274] The invention also provides a quetiapine oral dosage form in which the the ratio of C_{max} to C_{24} is less than about 4:1, or in certain embodiment less than about 2:1, and the ratio is achieved at steady-state.

[0275] The invention provides an oral dosage form comprising quetiapine or a pharmaceutically acceptable salt thereof in controlled release form, which, at steady-state, provides a maximum quetiapine plasma concentration (C_{max}), a quetiapine plasma concentration at about 12 hours after administration (C_{12}), and an quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the average quetiapine plasma concentration between C_{max} and C_{12} is substantially equal to the average quetiapine plasma concentration between C_{12} and C_{24}. Preferably the quetiapine in this quetiapine dosage form is in the form of quetiapine hemifumarate.

[0276] The invention provides a quetiapine oral dosage form, which provides a Cmax at between 5.5 and 12 hours after administration.

[0277] The invention also provides a quetiapine oral dosage form, which provides a C_{max} at between 2 and 3.5 hours after administration.

Pulsed release dosage forms

[0278] The invention also provides pulsed release quetiapine dosage forms, which exhibit characteristic plasma concentration profiles following administration.

[0279] Thus the invention provides an oral dosage form comprising quetiapine or a pharmaceutically acceptable salt thereof in sustained release form, which, at steady-state, provides a first maximum quetiapine plasma concentration (C_{max1}) between 0 hours and about

12 hours after administration, and a second maximum quetiapine plasma concentration (C_{max2}) between about 12 hours and about 24 hours after administration. Preferably the quetiapine in the pulsed release dosage forms is in the form of quetiapine hemifumarate.

[0280] The invention also provides a pulsed release quetiapine dosage form which, at steady-state, provides a first maximum quetiapine plasma concentration (C_{max1}) between 0 hours and about 12 hours after administration, a second maximum quetiapine plasma concentration (C_{max2}) between about 12 hours and about 24 hours after administration, and an quetiapine plasma concentration at about 24 hours after administration (C24), wherein the average quetiapine plasma concentration between about Cmax1 and about Cmax2 is substantially equal to the average quetiapine plasma concentration between about Cmax2 and about C24.

[0281] In another embodiment the invention provides a pulsed release quetiapine dosage form which, at steady-state, provides a first maximum quetiapine plasma concentration (C_{max1}) and a first minimum quetiapine plasma concentration (C_{min1}) between 0 hours and about 12 hours after administration, a second maximum quetiapine plasma concentration (C_{max2}), and an quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the ratio of C_{max1} to C_{min1} is less than about 4:1 or the ratio of C_{max2} to C_{24} is less than about 4:1.

[0282] In certain embodiments C_{max2} occurs about 12 to about 14 hours after administration.

[0283] For certain embodiments of the invention it is preferred that the ratio of Cmax1 to Cmin1 is less than about 8:5.

[0284] In certain embodiments of the invention the ratio of Cmax2 to C24 in the pulsed release quetiapine dosage form is less than about 2:1. The invention also includes a pulsed release quetiapine oral dosage form, which, at steady-state, wherein the difference between the ratio of C_{max1} to C_{min1} and the ratio of C_{max2} to C_{24} is less than about 30%, or in certain embodiments less than about 20%, or less than about 10%.

[0285] The invention further provides a pulsed release quetiapine sustained release oral dosage form comprising a first subunit and a second subunit, wherein the first subunit comprises quetiapine and a first release-retarding material and the second subunit comprises quetiapine and a second release-retarding material, wherein the first and second release-

retarding material can be the same or different, and wherein the dosage form, at steady-state, provides a maximum quetiapine plasma concentration (C_{max}) and an quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the ratio of C_{max} to C_{24} is less than about 4:1.

Semi - Delayed Release Dosage Forms

[0286] The invention also provides semi-delay release dosage forms, in which the peak quetiapine plasma concentration is attained significantly later after administration than the peak quetiapine plasma concentration is attained following administration of an immediate release form of quetiapine. The invention also provides semi-delayed release dosage froms which provide a moderate quetiapine concentration upon administration, followed by a larger "pulse" quetiapine plasma concentration some hours after administration. The purpose of such dosage forms is to provide a moderate quetiapine dosage following morning administration, followed by a larger dosage at night.

[0287] Thus the invention provides a quetiapine oral dosage form which, at steady-state, provides a first maximum quetiapine plasma concentration (C_{max1}) between 0 hours and about 12 hours after administration, and a second maximum quetiapine plasma concentration (C_{max2}) between about 12 hours and about 24 hours after administration, wherein the ratio of C_{maxI} to C_{max2} is greater than 1:1.5 and less than about 1:4, or in certain embodiments wherein the ratio of C_{maxI} to C_{max2} is greater than about 1:3 and less than about 1:4.

[0288] In certain embodiments the invention provides a quetiapine oral dosage form of in which C_{maxI} occurs between 0 and about 2.5 hours after administration and Cmax2 occurs between about 10 and about 15 hours after administration.

[0289] The invention also provides a quetiapine oral dosage form of in which CmaxI occurs between about 2.5 and about 3.5 hours after administration and Cmax2 occurs between about 10 and about 15 hours after administration.

[0290] The invention provides a quetiapine oral dosage form wherein CmaxI occurs between 5.5 and about 10 hours after administration and Cmax2 occurs between about 10 and about 16 hours after administration.

[0291] The invention also pertains to a method of treating psychosis, the method comprising orally administering to a human on a once-daily basis an oral sustained release dosage form comprising quetiapine or a pharmaceutically acceptable salt thereof which, at

steady-state, provides a maximum quetiapine plasma concentration (C_{max}) and an quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the ratio of C_{max} to C_{24} is less than about 4:1.

Dosage Forms Characterized by AUC

[0292] Quetiapine dosage forms of the invention exhibit characteristic plasma concentrations over time. When integrated the graph of plasma concentration over time provides a characteristic "area under the curve" or AUC.

[0293] In addition to providing an oral dosage form that provides an AUC between 0 and 24 hours after administration that is more than 80 percent and less than 120 percent of the AUC provided by an equivalent weight of SEROQUEL between 0 and 24 hours after administration, the invention also provides the following sustained release quetiapine dosage forms having a characteristic AUC.

[0294] The invention also provides a controlled release dosage form which provides a maximum quetiapine plasma concentration (C_{max}) and an quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the ratio of C_{max} to C_{24} is less than about 4:1 in which the AUC between 0 and 24 hours after administration is more than 80 percent and less than 120 percent of the AUC provided by 2 times the equivalent weight of SEROQUEL between 0 and 24 hours after administration.

[0295] In other embodiments the invention provides an oral quetiapine dosage form comprising quetiapine or a pharmaceutically acceptable salt thereof in sustained release form, which, at steady-state, provides a first AUC (AUC_1) between 0 and about 12 hours and a second AUC (AUC_2) between about 12 hours and about 24 hours, wherein difference between AUC_2 and AUC_1 is less than about 50%, or in certain embodiments wherein AUC_1 and AUC_2 are about equal.

[0296] The invention provides the particular dosage forms described herein, e.g. quetiapine wax formulations, press-coat dosage formulation, taste masked formulations, and the like, formulated to provide the quetiapine plasma concentration profiles and characteristic AUC ratios described above.

MANUFACTURE OF QUETIAPINE DOSAGE FORMS

AMORPHOUS TECHNOLOGY

[0297] Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Quetiapine may be prepared in such a way that substantially all of quetiapine is present in amorphous form.

[0298] A process for preparing solid, amorphous quetiapine comprising mixing quetiapine or a salt thereof with water and pharmaceutically acceptable polymeric carrier; and drying to form a composition comprising amorphous quetiapine and polymeric carrier.

[0299] In another aspect, a pharmaceutical composition comprises quetiapine salt in amorphous, solid form, and polymeric carrier, prepared by the aforementioned process.

[0300] Suitable pharmaceutically acceptable polymeric carriers include, for example, hydroxypropyl cellulose, methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, cellulose acetate phthalate, cellulose acetate butyrate, hydroxyethyl cellulose, ethyl cellulose, polyvinyl alcohol, polypropylene, dextrans, dextrins, hydroxypropyl-beta-cyclodextrin, chitosan, co(lactic/glycolid) copolymers, poly(orthoester), poly(anhydrate), polyvinyl chloride, polyvinyl acetate, ethylene vinyl acetate, lectins, carbopols, silicon elastomers, polyacrylic polymers, maltodextrins, lactose, fructose, inositol, trehalose, maltose, raffinose, polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), and alpha-, beta-, and gamma-cyclodextrins, and combinations comprising one or more of the foregoing carriers.

[0301] Preferred polymeric carriers are one or more of polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, block co-polymers of ethylene oxide and propylene oxide, and polyethylene glycol, wherein a more preferred polymeric carrier is polyvinylpyrrolidone (PVP) having an average molecular weight of about 2,500 to about 3,000,000. A most preferred polymeric carrier is polyvinylpyrrolidone having an average molecular weight of from about 10,000 to about 450,000.

[0302] The polymeric carrier is preferably miscible with both quetiapine free base and the salt, capable of keeping the salt in a homogeneous noncrystalline solid state dispersion after the water has been removed by evaporation and chemically inert with respect to the free base of the active ingredient, the salt of the free base, and the aqueous acid

solution. The polymeric carrier is preferably at least partially water soluble, and more preferably is fully water soluble.

[0303] Quetiapine may be added in either free base or salt form. When quetiapine is added in free base form, the process comprises adding an acid corresponding to a salt of quetiapine to the mixture or solution of the free base. The free base is then converted to a salt *in situ*, for example by addition of an inorganic or an organic acid. The acid may be added either as a gas, a liquid or as a solid dissolved into water. A preferred acid is fumaric acid and the molar quantity of acid added to the solution of quetiapine free base and carrier may either be in stoichiometric proportion to quetiapine free base or be in excess of the molar quantity of quetiapine free base, especially when added as a gas.

[0304] The preferred range of fumaric acid added is about 1.0 to about 1.8 times the molar quantity of quetiapine free base. Preferred molar ratios of quetiapine to fumaric acid are about 2:1. It is understood that upon addition of the acid, the formed free base salt remains dissolved in solution with the polymeric carrier.

[0305] Quetiapine, polymeric carrier, and water may be combined in any order. It is preferred that they be combined in a manner so as to form a solution of quetiapine salt and the polymeric carrier.

[0306] In forming a solution of polymeric carrier and water, heating the solution is not necessary at lower concentrations but is strongly preferred at higher concentrations, provided that the temperature does not result in decomposition or degradation of any materials. It is preferred to add quetiapine free base or salt after dissolving the polymeric carrier in water, suitably at about 25° to about 100°C, preferably at about 45° to about 80°C. When quetiapine is added as a free base, it is preferred to form a salt at a temperature at which the final solution is clear. For the most preferred embodiments, a temperature of at least about 60°C may result in a clear solution of quetiapine salt being formed, although for other concentrations and embodiments, clear solutions are formed at other temperatures. It is preferred to only add enough heat to form a clear solution.

[0307] The ratio of quetiapine to the polymeric carrier can be varied over a wide range and depends on the concentration of quetiapine required in the pharmaceutical dosage form ultimately administered. The ratio by weight of polymeric carrier to quetiapine salt is

about 20:1 to about 0.5:1; preferably about 4:1 to about 1:1; more preferably about 3:1 to about 1.5:1; most preferably about 2:1.

[0308] Preferably a clear solution is formed. Upon formation of the clear solution, the process proceeds by recovering the water to form a solid state dispersion of the free base salt in the polymeric carrier. Any method of removal of the water which renders a homogeneous solid state dispersion is intended, although preferred are methods of evaporation under vacuum or spray drying. Methods of evaporation under vacuum include rotary evaporation, static vacuum drying and the combination thereof. It is understood that one skilled in the art of pharmaceutical formulations can determine a reasonable temperature at which water can be removed, provided the temperature is not so high as to cause degradation or decomposition of the materials; however, it is preferred that evaporation occurs at about 25 °C to about 100 °C. Evaporation of water should render a solid state dispersion which is homogeneous and substantially free of water. By substantially free it is meant that the solid state dispersion contains less than 20% by weight of residual water, preferably less than 10%, more preferably less than 5%, most preferably less than 1%.

[0309] The ratio of quetiapine free base to the polymeric carrier can be varied over a wide range and depends on the quetiapine concentration required in the pharmaceutical dosage form ultimately administered. However, the preferred range of quetiapine in the solid dispersion is about 16% to about 50% of the total solid dispersion weight, more in some embodiments is about 20% to about 50%, and in certain embodiments is about 25% to about 40%, in one embodiment the quetiapine is about 33% of the total dispersion weight. The weight ratio of polymeric carrier to quetiapine, in some embodiments is about 0.4:1 to 20:1.

[0310] Suitable pharmaceutically acceptable excipients can be added in the process. Examples of pharmaceutically acceptable excipients include diluents, binders, disintegrants, coloring agents, flavoring agents, lubricants and/or preservatives. The pharmaceutical composition may be formulated by conventional methods of admixture such as blending, filling, granulation and compressing. These agents may be utilized in conventional manner.

OPTIONAL ADDITIONAL ADDITIVE FOR QUETIAPINE FORMULATIONS

EXCIPIENTS

[0311] Excipients are components added to a pharmaceutical formulation other than quetiapine, and include inert substances used as a diluent or vehicle for quetiapine. Excipients may be added to facilitate manufacture, enhance stability, control release, enhance product characteristics, enhance bioavailability, enhance patient acceptability, etc. Pharmaceutical excipients include binders, disintegrants, lubricants, glidants, compression aids, colors, sweeteners, preservatives, suspending agents, dispersing agents, film formers, flavors, printing inks, etc. Binders hold the ingredients in the dosage form together. Exemplary binders include, for example, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose and hydroxyethyl cellulose, sugars, and combinations comprising one or more of the foregoing binders. Disintegrants expand when wet causing a tablet to break apart. Exemplary disintegrants include croscarmellose sodium. Lubricants, for example, aid in the processing of powder materials. Exemplary lubricants include calcium stearate, glycerol behenate, magnesium stearate, mineral oil, polyethylene glycol, sodium stearyl fumarate, stearic acid, talc, vegetable oil, zinc stearate, and combinations comprising one or more of the foregoing lubricants. Glidants include, for example, silicon dioxide.

FILLERS

[0312] Certain dosage forms described herein contain a filler, such as a water insoluble filler, water soluble filler, and combinations thereof. The filler may be a water insoluble filler, such as silicon dioxide, titanium dioxide, talc, alumina, starch, kaolin, polacrilin potassium, powdered cellulose, microcrystalline cellulose, and combinations comprising one or more of the foregoing fillers. Exemplary water-soluble fillers include water soluble sugars and sugar alcohols, preferably lactose, glucose, fructose, sucrose, mannose, dextrose, galactose, the corresponding sugar alcohols and other sugar alcohols, such as mannitol, sorbitol, xylitol, and combinations comprising one or more of the foregoing fillers.

PREPARATION OF QUETIAPINE-CONTAINING SUBUNITS

[0313] Quetiapine and any optional additives may be prepared in many different ways, for example as subunits. Pellets comprising an active ingredient can be prepared, for example, by a melt pelletization technique. In this technique, the active ingredient in finely divided form is combined with a binder and other optional inert ingredients, and thereafter the mixture is pelletized, e.g., by mechanically working the mixture in a high shear mixer to form the pellets (e.g., pellets, granules, spheres, beads, etc., collectively referred to herein as "pellets"). Thereafter, the pellets can be sieved in order to obtain pellets of the requisite size. The binder material may also be in particulate form and has a melting point above about 40 °C. Suitable binder substances include, for example, hydrogenated castor oil, hydrogenated vegetable oil, other hydrogenated fats, fatty alcohols, fatty acid esters, fatty acid glycerides, and the like, and combinations comprising one or more of the foregoing binders.

[0314] Oral dosage forms may be prepared to include an effective amount of melt-extruded subunits containing quetiapine or other active agents in the form of multiparticles within a capsule. For example, a plurality of the melt-extruded muliparticulates can be placed in a gelatin capsule in an amount sufficient to provide an effective release dose when ingested and contacting by gastric fluid.

[0315] Subunits, e.g., in the form of multiparticulates, can be compressed into an oral tablet using conventional tableting equipment using standard techniques. The tablet formulation may include excipients such as, for example, an inert diluent such as lactose, granulating and disintegrating agents such as cornstarch, binding agents such as starch, and lubricating agents such as magnesium stearate.

[0316] Alternatively, the subunits containing quetiapine and optionally containing additional active agents are added during the extrusion process and the extrudate can be shaped into tablets by methods know in the art. The diameter of the extruder aperture or exit port can also be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

[0317] A melt-extruded multiparticulate system can be, for example, in the form of granules, spheroids, pellets, or the like, depending upon the extruder exit orifice. The terms "melt-extruded multiparticulate(s)" and "melt-extruded multiparticulate system(s)" and

"melt-extruded particles" are used interchangeably herein and include a plurality of subunits, preferably within a range of similar size and/or shape. The melt-extruded multiparticulates can be about 0.1 to about 12 mm in length and have a diameter of about 0.1 to about 5 mm. In addition, the melt-extruded multiparticulates can be any geometrical shape within this size range. Alternatively, the extrudate can simply be cut into desired lengths and divided into unit doses of quetiapine without the need of a spheronization step.

[0318] The melt-extruded dosage forms can further include combinations of melt-extruded multiparticulates containing one or more of the therapeutically active agents before being encapsulated. Furthermore, the dosage forms can also include an amount of quetiapine formulated for immediate release for prompt therapeutic effect. Quetiapine formulated for immediate release can be incorporated or coated on the surface of the subunits after preparation of the dosage forms (e.g., controlled release coating or matrix-based). The dosage forms can also contain a combination of controlled release beads and matrix multiparticulates to achieve a desired effect.

[0319] A melt-extruded material may be prepared without the inclusion of subunits containing quetiapine, which are added thereafter to the extrudate. Such formulations have the subunits and other active agents blended together with the extruded matrix material. The mixture is then tableted in order to provide release of quetiapine or other active agents. Such formulations can be particularly advantageous, for example, when an active agent included in the formulation is sensitive to temperatures needed for softening the hydrophobic material and/or the retardant material.

[0320] The oral dosage form containing quetiapine may be in the form of micro-tablets enclosed inside a capsule, e.g. a gelatin capsule. For this, a gelatin capsule as is employed in pharmaceutical formulations can be used, such as the hard gelatin capsule known as CAPSUGEL, available from Eli Lilly.

QUETIAPINE PARTICLES

[0321] Many of the oral dosage forms described herein contain quetiapine and optionally additional active agents in the form of particles. Such particles may be compressed into a tablet, present in a core element of a coated dosage form, such as a taste

masked dosage form, a press coated dosage form, or an enteric coated dosage form, or may be contained in a capsule, osmotic pump dosage form, or other dosage form.

[0322] For particles, such as powder particles, present in the core element of a coated dosage form, the core element may have a particle size distribution with a median of about 100 μm. The particles in the distribution may vary from about 1 μm to about 250 μm, more preferably from 25 μm to about 250 μm, most preferably about 35 μm to about 125 μm. If the median of the distribution is close to either extreme of the distribution, the taste masking or sustained release characteristics may be affected. In a particle size range of about 25 μm to about 250 μm, no more than about 25% of particles can be less than about 25 μm, and no more than about 25% can be over about 250 μm.

[0323] Another parameter to consider is particle shape. Particle shape can influence the coverage and stability of the coat. Both the crystallinity of quetiapine and the aspect ratio of the particles are related to particle shape. It is preferred that quetiapine of the coated dosage forms has a crystalline morphology, however, sharp angles on a crystal can cause weaknesses in the coat. These sharp corners may lead to stress points on the coat and cause weaknesses in the structure possibly leading to premature release of quetiapine from the dosage form. Furthermore, areas of thin coating are susceptible to breaking and cracking and hence ineffective for sustained release and taste masking.

[0324] Regarding the aspect ratio, a low aspect ratio is preferred. The aspect ratio is a measure of the length to breadth. For example, a low aspect ratio of about 1 would be a box or sphere. Crystals with a high aspect ratio are more pointed with needle-like crystals. Crystals with a high aspect ratio may result in a relatively thin coat at the crystal needle tips leading to a more rapid release rate of quetiapine than is preferred. A low aspect ratio spherical shape of the particle is advantageous for both solubility of the coat and high payload of quetiapine. Therefore, it is most preferable that the aspect ratio is less than about 3, more preferably about 1 to about 2, and most preferably approximately 1 providing a substantially rounded shape.

[0325] Inconsistencies in size and shape can lead to inconsistent coating. Where the particles containing quetiapine are of different size and shape, polymeric coating materials such as ethyl cellulose may deposit differently on each particle. It is therefore preferable for

coated dosage forms that substantially all particles of the dosage form have substantially the same size and shape so that the coating process is better controlled and maintained.

COATINGS

[0326] The formulations described herein may be coated with a functional or non-functional coating. The coating may comprise about 0 to about 40 weight percent of the composition. The coating material may include a polymer, preferably a film-forming polymer, for example, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate (lower, medium or higher molecular weight), cellulose acetate propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, cellulose triacetate, cellulose sulphate sodium salt, poly(methyl methacrylate), poly (ethyl methacrylate), poly (butyl methacrylate), poly (isobutyl methacrylate), poly (hexyl methacrylate), poly (phenyl methacrylate), poly (methyl acrylate), poly (isopropyl acrylate), poly (isobutyl acrylate), poly (octadecyl acrylate), poly (ethylene), poly (ethylene) low density, poly (ethylene)high density, (poly propylene), poly (ethylene glycol poly (ethylene oxide), poly (ethylene terephthalate), poly(vinyl alcohol), poly(vinyl isobutyl ether), poly(viny acetate), poly (vinyl chloride), polyvinyl pyrrolidone, and combinations comprising one or more of the foregoing polymers.

[0327] In applications such as taste-masking, the polymer can be a water-insoluble polymer. Water insoluble polymers include ethyl cellulose or dispersions of ethyl cellulose acrylic and/or methacrylic ester polymers, cellulose acetates, butyrates or propionates or copolymers of acrylates or methacrylates having a low quaternary ammonium content, and the like, and combinations comprising one or more of the foregoing polymers.

[0328] In controlled release applications, for example, the coating can be a hydrophobic polymer that modifies the release properties of quetiapine from the formulation. Suitable hydrophobic or water insoluble polymers for controlled release include, for example, methacrylic acid esters, ethyl cellulose, cellulose acetate, polyvinyl alcohol-maleic anhydride copolymers, β-pinene polymers, glyceryl esters of wood resins, and combinations comprising one or more of the foregoing polymers.

[0329] The inclusion of an effective amount of a plasticizer in the coating composition may improve the physical properties of the film. For example, because ethyl cellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it may be advantageous to add plasticizer to the ethyl cellulose before using the same as a coating material. Generally, the amount of plasticizer included in a coating solution is based on the concentration of the polymer, e.g., most often from about 1 to about 50 percent by weight of the polymer. Concentrations of the plasticizer, however, can be determined by routine experimentation.

[0330] Examples of plasticizers for ethyl cellulose and other celluloses include plasticizers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, triacetin, and combinations comprising one or more of the foregoing plasticizers, although it is possible that other water-insoluble plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) can be used.

[0331] Examples of plasticizers for acrylic polymers include citric acid esters such as triethyl citrate 21, tributyl citrate, dibutyl phthalate, 1,2-propylene glycol, polyethylene glycols, propylene glycol, diethyl phthalate, castor oil, triacetin, and combinations comprising one or more of the foregoing plasticizers, although it is possible that other plasticizers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) can be used.

[0332] An example of a functional coating comprises a coating agent comprising a poorly water-permeable component (a) such as, an alkyl cellulose, for example an ethylcellulose, such as AQUACOAT (a 30% solution available from FMC, Philadelphia, PA) or SURELEASE (a 25% solution available from Colorcon, West Point, PA) and a water-soluble component (b), e.g., an agent that can form channels through the poorly water-permeable component upon the hydration or dissolution of the soluble component. Preferably, the water-soluble component is a low molecular weight, polymeric material, e.g., a hydroxyalkylcellulose, hydroxyalkyl(alkylcellulose), carboxymethylcellulose, or salts thereof. Particular examples of these water soluble polymeric materials include hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, and combinations comprising one or more of the foregoing materials. The water-soluble

component can comprise hydroxypropylmethylcellulose, such as METHOCEL. The water-soluble component is preferably of relatively low molecular weight, preferably less than or equal to about 25,000 molecular weight, or preferably less than or equal to about 21,000 molecular weight.

[0333] In the functional coating, the total of the water soluble portion (b) and poorly water permeable portion (a) are present in weight ratios (b):(a) of about 1:4 to about 2:1, preferably about 1:2 to about 1:1, and more preferably in a ratio of about 2:3. While the ratios disclosed herein are preferred for duplicating target release rates of presently marketed dosage forms, other ratios can be used to modify the speed with which the coating permits release of quetiapine. The functional coating in certain embodiments comprises from about 2 % to about 20%, about 5% to about 10%, or about 6% of the total formulation.

[0334] In certain embodiments, particularly where the coating provides taste masking, it the coating may be a substantially continuous coat and substantially hole-free. By "substantially continuous coating" is meant a coating, which retains a smooth and continuous appearance when magnified 1000 times under a scanning electron microscope and wherein no holes or breakage of the coating are evident.

[0335] Suitable methods can be used to apply the coating to quetiapine. Processes such as simple or complex coacervation, interfacial polymerization, liquid drying, thermal, and ionic gelation, spray drying, spray chilling, fluidized bed coating, pan coating, electrostatic deposition, may be used. A substantially continuous nature of the coating may be achieved, for example, by spray drying from a suspension or dispersion of quetiapine in a solution of the coating composition including a polymer in a solvent in a drying gas having a low dew point.

[0336] When a solvent is used to apply the coating, the solvent is preferably an organic solvent that constitutes a good solvent for the coating material, but is substantially a non-solvent or poor solvent for of quetiapine. While quetiapine may partially dissolve in the solvent, it is preferred that the active ingredient will precipitate out of the solvent during the spray drying process more rapidly than the coating material. The solvent may be selected from alcohols such as methanol, ethanol, halogenated hydrocarbons such as dichloromethane (methylene chloride), hydrocarbons such as cyclohexane, and combinations comprising one

or more of the foregoing solvents. Dichloromethane (methylene chloride) has been found to be particularly suitable.

[0337] The concentration of polymer in the solvent will normally be less than about 75% by weight, and typically about 10 to about 30% by weight. After coating, the coated dosage forms may be allowed to cure for at least about 1 to about 2 hours at a temperature of about 50 °C to about 60 °C, and in certain embodiments of about 55 °C.

[0338] The coatings may be about 0.005 micrometers to about 25 micrometers thick, preferably about 0.05 micrometers to about 5 micrometers.

PREPARATION OF QUETIAPINE DOSAGE FORMS

[0339] The term "dosage form" denotes a form of a formulation that contains an amount sufficient to achieve a therapeutic effect with a single administration. When the formulation is a tablet or capsule, the dosage form is usually one such tablet or capsule. The frequency of administration that will provide the most effective results in an efficient manner without overdosing will vary with the characteristics of the particular quetiapine formulation, including both its pharmacological characteristics and its physical characteristics such as solubility, and with the characteristics of the swellable matrix such as its permeability, and the relative amounts of the drug and polymer. In most cases, the dosage form will be such that effective results will be achieved with administration no more frequently than once every eight hours or more, preferably once every twelve hours or more, and even more preferably once every twenty- four hours or more.

[0340] The dosage form can be prepared by various conventional mixing, comminution and fabrication techniques readily apparent to those skilled in the chemistry of drug formulations. Examples of such techniques are as follows:

(1) Direct compression, using appropriate punches and dies; the punches and dies are fitted to a suitable rotary tableting press;

(2) Injection or compression molding using suitable molds fitted to a compression unit

(3) Granulation followed by compression; and

(4) Extrusion in the form of a paste, into a mold or to an extrudate to be cut into lengths.

[0341] When particles are made by direct compression, the addition of lubricants may be helpful and sometimes important to promote powder flow and to prevent capping of the particle (breaking off of a portion of the particle) when the pressure is relieved. Useful lubricants are magnesium stearate (in a concentration of from about 0.25% to about 3% by weight, in some embodiments less than about 1% by weight, in the powder mix), and hydrogenated vegetable oil (frequently hydrogenated and refined triglycerides of stearic and palmitic acids are used at about 1% to about 5% by weight, and in some embodiments about 2% by weight. Additional excipients may be added to enhance powder flowability and reduce adherence.

QUETIAPINE-CONTAINING PELLETS IN CAPSULES

[0342] Oral dosage forms may be prepared to include an effective amount of melt-extruded subunits in the form of multiparticles within a capsule. For example, a plurality of the melt-extruded muliparticulates can be placed in a gelatin capsule in an amount sufficient to provide an effective release dose when ingested and contacted by gastric fluid.

QUETIAPINE-CONTAINING TABLETS IN CAPSULES

[0343] The composition may be in the form of micro-tablets enclosed inside a capsule, e.g. a gelatin capsule. For this, a gelatin capsule employed in the pharmaceutical formulation field can be used, such as the CAPSUGEL hard gelatin capsule, available from Eli Lilly.

EXAMPLES

[0344] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLE 1. QUETIAPINE HEMIFUMARATE WAX FORMULATION IN TABLET FORM

[0345] Quetiapine hemifumarate tablet cores of the following formulation are prepared as follows (the Table I presents the formulas in % by weight, while Table II presents the same formulas in mg amounts per 500 mg Quetiapine hemifumarate dosage form):

TABLE I

Component	Formula 1 (wt. %)	Formula 2 (wt. %)	Formula 3 (wt. %)	Formula 4 (wt. %)	Formula 5 (wt. %)
Matrix					
Quetiapine hemifumarate	81.97	73.86	70.72	66.00	67.68
Carnauba wax	16.39	24.67	28.29	33.00	27.07
Glyceryl Dibehenate					4.06
Processing aids					
Hydrophobic colloidal silicon dioxide (CAB-O-SIL M5)					0.11
Magnesium Stearate	1.64	1.47	0.99	1.00	1.08
Total Core	100.00	100.00	100.00	100.00	100.00

TABLE II					
Component	Formula 1 wt. (mg)	Formula 2 wt. (mg)	Formula 3 wt. (mg)	Formula 4 wt. (mg)	Formula 5 wt. (mg)
Matrix					
Quetiapine hemifumarate	500	500	500	500	500
Carnauba wax	100	170	200	250	200
Glyceryl Dibehenate					30
Processing aids					
Hydrophobic colloidal silicon dioxide (CAB-O-SIL M5)					0.8
Magnesium Stearate	10	10	7	7.5	8
Total Core	610	680	707	757.5	738.8

[0346] Quetiapine hemifumarate is mixed with carnauba wax and hot melt granulated. The granulate is then milled and the magnesium stearate and colloidal silicon dioxide processing aids are added and blended. The blend is then compressed.

EXAMPLE 2. QUETIAPINE HEMIFUMARATE COATED WAX FORMULATION

[0347] Cores of Formula 3 in Example 1 above are coated at 35°C to 40°C with a functional coating solution comprising 5% OPADRY II Yellow (Colorcon), 20% SURELEASE (Colorcon), and 75% deionized water. The coating is applied so that the coating comprises 2%, 4%, or 6% of the total formulation.

EXAMPLE 3. QUETIAPINE HEMIFUMARATE COATED WAX FORMULATION (CURED)

[0348] Cores of Formula 2 above (approximately 170 mg of carnauba wax/core) are coated with a functional coating solution comprising 5% OPADRY II Yellow (Colorcon,

West Point, PA), 20% SURELEASE (Colorcon, West Point, PA), and 75% deionized water as in Example 2. The coating is applied so that the coating is 6% of the final formulation. A portion of the coated cores is cured for 1 hour at 55 °C. The coated and cured cores are compared for release characteristics with the uncured coat, the uncoated cores, and SEROQUEL.

EXAMPLE 4. COATED QUETIAPINE HEMIFUMARATE WAX PREPARATION CONTAINING A PROCESSING AID

[0349] A further example of the invention includes the formulation set forth below.

TABLE III

Component		
Matrix	% total formulation	weight (mg)
Quetiapine Hemifumarate	69.58	100
Carnauba wax	23.66	35
Processing aids		
Hydrophobic colloidal silicon dioxide (CAB-O-SIL M5)	0.14	0.2
Magnesium Stearate	0.97	1.40
Coating		
Opadry clear	2.26	3.24
Surelease Coat	3.39	4.86
Total coating	5.65	8.10
Total Tablet	100.00	152.8

[0350] Quetiapine hemifumarate is mixed with the carnauba wax and hot melt granulated. The granulate is then milled and magnesium stearate and colloidal silicon dioxide processing aids are added and blended. The mixture is compressed. The compressed (as yet uncoated) tablets are then coated with a blend of the coating ingredients at 35 °C to 40 °C and the tablets are cured for 1 to 2 hours at 55 °C.

[0351] Tablets of the invention are tested when freshly prepared and after storage at 40°C for 1, 2 or 3 months.

EXAMPLE 5. PRESS-COATED TABLETS

[0352] Press-coated tablets are prepared from cores of the following formulation:

Component (mg/ tablet)	
Quetiapine hemifumarate	50.0
Dicalcium Phosphate	14.4
Carnauba Wax	25.0
CAB-O-SIL (silica)	0.2
Magnesium Stearate	0.4
Total Core	90.0

[0353] The components are blended together and compressed to form a core composition. The core composition is then press-coated with the composition below:

Component (mg/ tablet)	
Quetiapine hemifumarate	50.0
Lactose monohydrate	170.0
METHOCEL K4M	96.0
CAB-O-SIL (silica)	1.0
Magnesium Stearate	3.0
Total Press Coat	320.0

[0354] The press-coat composition components are blended together and about one half of the blend (about 160 mg) is placed in a die and lightly pressed. A core composition, as prepared above, is placed at approximately the center of the die and covered with the other half of the press-coat composition and pressed in the die to form a tablet. Some tablets are then given a further immediate release "loading dose" of an additional 10 mg of quetiapine hemifumarate per tablet.

[0355] Quetiapine hemifumarate release rate data is obtained for these tablets in USP Apparatus 2 at 50 rpm using 900 ml of either water or 0.1 N HCl as the dissolution media.

EXAMPLE 6. PRESS COATED FORMULATION CONTAINING HPMC

[0356] The cores of Example 5 are used with a press-coat composition containing (per tablet):

TABLE IV			
	15% HPMC	20% HPMC	40% HPMC
Component	mg per tablet	mg per tablet	mg per tablet
Quetiapine hemifumarate	50	50	50
Lactose Monohydrate	218	192.0	128
METHOCEL K4M	48	64.0	128
CAB-O-SIL (silica)	1	1.0	1
Magnesium Stearate	3	3.0	3
Total Press-coat	320	320.0	320

[0357] Tablets are prepared as in Example 5 (except that no loading dose was added) and dissolution profiles are measured as in Example 5.

EXAMPLE 7. PRESS COATED TABLETS HAVING FIXED CORE: COAT RATIOS

[0358] The cores of Example 5 are used with a press-coat composition comprising 12 mg of quetiapine hemifumarate to provide a $Core_{AA}$:$Coat_{AA}$ ratio of 4:3 (Example 7A). Additional quetiapine hemifumarate formulations are prepared as set forth below to provide $Core_{AA}$:$Coat_{AA}$ ratio of 1:3 (Example 7B) and 3:1 (Example 7C). Quetiapine dissolution is tested in 0.1 N HCl.

TABLE V			
Core (mg/ tablet):			
Component	Example 7A (4:3)	Example 7B (1:3)	Example 7C (3:1)
Quetiapine hemifumarate	28	12.5	37.5
Dicalcium Phosphate	27.4	42.9	17.9
Carnauba Wax	24.0	24.0	24.0
CAB-O-SIL (silica)	0.2	0.2	0.2
Magnesium Stearate	0.4	0.4	0.4
Total Core	80.0	80.0	80.0
Press-coating (mgs/ tablet):			
Quetiapine hemifumarate	22	37.5	12.5
Lactose Monohydrate	238.0	222.5	247.5
METHOCEL K4M	56.0	56.0	56.0
CAB-O-SIL (silica)	1.0	1.0	1.0
Magnesium Stearate	3.0	3.0	3.0
Total Press-coat	320.0	320.0	320.0

EXAMPLE 8. PRESS COATED FORMULATION CONTAINING METHOCEL K100M

[0359] A press coated quetiapine hemifumarate formulation is prepared utilizing METHOCEL K100M mannitol and a $Core_{AA}$: $Coat_{AA}$ ratio of 4:1. Dissolution data is obtained using two rotation speeds.

Core Component (mg/tablet)	
Quetiapine hemifumarate	40.0
Dicalcium Phosphate	15.5
Carnauba Wax	14.0
Magnesium Stearate	0.5
Total Core	70.0

Press Coat Component (mg/ tablet)	
Quetiapine hemifumarate	10.0
Mannitol granules (Pearlitol SD 200)	233.5
METHOCEL K100M	82.5
CAB-O-SIL (silica)	1.0
Magnesium Stearate	3.0
Total Press-coat	330.0

EXAMPLE 9. TASTE-MASKED QUETIOAPINE HEMIFUMARATE SOLID DOSAGE FORM

[0360] A slurry is produced with the following composition: Quetiapine hemifumarate (50 grams), EUDRAGIT IRS100 (50 grams), ethanol (500 ml), and sodium lauryl sulfate (2 grams). The slurry is spray dried at a gas inlet temperature of 101 °C to produce a free flowing fine powder which has satisfactory sustained release properties and adequate taste masking of the quetiapine hemifumarate.

EXAMPLE 10. DELAYED RELEASE FORM OF QUETIAPINE HEMIFUMARATE

Core:

Ingredients	Amount (mg)
Quetiapine hemifumarate	150.00
Kollidon 90F (povidone USP)	9.00
Purified Water	171.00
Stearic Acid	3.20
Total (dry weight)	162.20

[0361] Povidone is first dissolved in water. Quetiapine hemifumarate is placed in the top spraying chamber of a Glatt GPCG1 fluidized bed apparatus. The solution of povidone is sprayed onto the active ingredient, using the following conditions:

Air flow (m^3/h)	100-110 m^3/hour
Liquid flow (g/min)	6-7 g/minute
Inlet temperature	65 °C
Spraying pressure	2.8 bar

[0362] Once the granulation is complete, the granules are passed through a sieve (1 mm mesh). The stearic acid is weighed, added and blended in a drum mixer (TURBULA T2C, Bachoffen, Switzerland). The resulting mixture is pressed into tablets (7 mm diameter and 7 mm curvature) with average hardness being between about 6.0 and about 120 kP.

[0363] The tablet cores are then coated with the following formulation.

Ingredients	Amount (mg)
Tablet cores	162.20
ETHOCEL PR100 (ethylcellulose)	7.05
Kollidon 90F (povidone USP)	7.05
PEG 1450	2.10
Denatured alcohol	210.00
Total (dry weight)	178.40

[0364] Ethocel, povidone, and PEG 1450 are first dissolved in denatured alcohol. The coating solution is then sprayed onto the tablet cores in a coating pan (Vector LCDS), with the following spraying parameters:

Air flow (m^3 /h)	100-110 m^3 /h
Liquid flow (g/min)	6-7 g/min
Inlet temperature	65 °C.
Spraying pressure	2.8 bar

EXAMPLE 11. QUETIAPINE HEMIFUMARATE DELAYED RELEASE DOSAGE FORM WITH MODIFIED COATING

[0365] Tablet cores are prepared as in Example 10. The coating is modified by the addition of 0.60 mg of a red iron oxide pigment, to permit identification of the tablets. The total tablet weight is 179 mg. The coating and coating process are as in Example 10.

EXAMPLE 12. COMBINED IMMEDIATE RELEASE AND CONTROLLED RELEASE QUETIAPINE HEMIFUMARATE TABLETS

[0366] In this formulation, one part of quetiapine hemifumarate mixed with a binder is sprayed onto the coated tablet of Example 11. This produces immediate release of quetiapine from the coating, while maintaining controlled release of quetiapine from the core.

Core:

Ingredients	Amount (mg)
Quetiapine Hemifumarate	135.00
Kollidon 90F (povidone USP)	9.00
Purified Water	160.00
Stearic Acid	3.20
Total (dry weight)	147.20

[0367] The core is prepared by the procedure given in Example 10. These tablet cores are then coated with the following formulation.

First Coating:

Ingredients	Amount (mg)
Ethocel PR100 (ethylcellulose)	7.05
Kollidon 90F (povidone USP)	7.05
PEG 1450	2.10
Denatured alcohol	210.00

[0368] The first coating is applied by the spraying process given in Example 11. The coated tablet core is then sprayed with a second coating containing the remaining quetiapine.

Second Coating

Ingredients	Amount (mg)
Coated Tablet Core	163.40
Quetiapine Hemifumarate	15.00
ETHOCEL (ethylcellulose)	5.00
Denatured alcohol	30.00
Total (dry weight)	183.40

[0369] The second coating is applied by the process used to apply the first coating.

[0370] The dissolution profile of this tablet is a combination of two profiles, the first one is an immediate release profile and the second a controlled release profile.

EXAMPLE 13. SOLVENT FREE DELAYED RELEASE QUETIAPINE HEMIFUMARATE FORMULATION

Core:

Ingredients	Amount (mg)
Quetiapine Hemifumarate	150.00
Stearic Acid	5.00
AVICEL (Microcrystalline cellulose)	20.00
No solvent required	
Total (dry weight)	185.00

[0371] Quetiapine hemifumarate and stearic acid are placed in the chamber of a GLATT GPCG1 fluidized bed apparatus. The powders are fluidized with hot air. The powders are heated until the product temperature reaches 50-55 °C; at which point granulation occurs. The product is then cooled to room temperature. Avicel is sprayed onto the granules using the following parameters:

Air flow (m^3 /h)	100-110 m^3/h
Inlet temperature	60-65 °C

[0372] Once the granulation is complete, the granules are passed through a sieve (1 mm) and microcrystalline cellulose is weighted, added and blended in a drum mixer (TURBULA T2C, Bachoffen, Switzerland). The resulting mixture is pressed into tablets (7 mm diameter and 7 mm curvature) with average hardness being between about 5.0 and about 12.0 kP (kilopond). These tablet cores are then coated with the following formulation.

Coating:

Ingredients	Amount (mg)
Tablet cores	172.00
ETHOCEL (ethylcellulose)	5.00
KOLLIDON 90F (povidone USP)	5.00
PEG 1450	1.50
Denatured alcohol	210.00
Total (dry weight)	183.50

[0373] The coating process is as given in Example 11.

[0374] Alternatively the core is coated with the following coating; the same coating procedure is used.

Example 13a. Alternate Coating

Ingredients	Amount (mg)
Tablet cores	172.00
ETHOCEL (ethylcellulose)	8.00
KOLLIDON 90F (povidone USP)	3.00
PEG 1450	2.00
Denatured alcohol	300.00
Total (dry weight)	190.00

EXAMPLE 14. DELAYED RELEASE QUETIAPINE HEMIFUMARATE FORMULATION, ALTERNATE CORE FORMULATION

[0375] One of the two coatings set forth in Example 13 is applied to the following core formulation.

Core:

Ingredients	Amount (mg)
Quetiapine Hemifumarate	150.00
Glyceryl behenate	10.00
Avicel (microcrystalline Cellulose)	20.00
No solvent required	
Total (dry weight)	190.00

[0376] The core manufacturing process is identical to the one provided in Example 14, except that the powder mixture is heated to 65 °C.

EXAMPLE 15. DELAYED RELEASE QUETIAPINE HEMIFUMARATE FORMULATION

Core

Ingredients	Amount (mg)
Quetiapine Hemifumarate	150.00
Polyethylene Glycol 8000	22.50
Mineral oil	3.00
Purified Water	120.00
Total (dry weight)	175.50

[0377] Polyethylene glycol 8000 is first dissolved in water. Mineral oil is then suspended in the PEG solution. Quetiapine hemifumarate is placed in the top spraying chamber of Glatt GPCG1 fluidized bed apparatus. The solution of PEG and mineral oil is sprayed onto the active ingredient, with the following parameters:

Air flow (m^3/h)	100-110 m^3/h
Liquid flow (g/min)	6-7 g/min
Inlet temperature	65 °C
Spraying pressure	2.2 bar

[0378] Once granulation is complete, the granules are passed through a sieve (1 mm mesh) and pressed into tablets (7 mm diameter and 7 mm curvature) with average hardness of about 5.0 to about 12.0 kP. These tablet cores are then coated with the following formulation.

Coating:

Ingredients	Amount (mg)
Tablet cores	175.50
ETHOCEL (ethylcellulose)	5.00
KOLLIDON 90F (povidone USP)	5.00
PEG 1450	1.50
Denatured alcohol	210.00
Total (dry weight)	187.00

[0379] The coating process is as provided in Example 11.

[0380] Alternatively, the Core formulation of this example can be coated with the following coating formulation.

Coating

Ingredients Amount (mg)	
Tablet cores	175.50
ETHOCEL (ethylcellulose)	8.00
KOLLIDON 90F (povidone USP)	3.00
PEG 1450	2.00
Denatured alcohol	300.00
Total (dry weight)	188.50

EXAMPLE 16. DELAYED RELEASE QUETIAPINE HEMIFUMARATE FORMULATION

Core:

Ingredients	Amount (mg)
Quetiapine Hemifumarate	150.00
PVA (Polyvinyl Acetate USP)	5.30
Purified Water	110.00
Glyceryl behenate	4.70
Total (dry weight)	160.00

[0381] The PVA is first dissolved in water. Quetiapine hemifumarate is placed in the top spraying chamber of a GLATT GPCG1 fluidized bed apparatus. The solution of PVA is sprayed onto the active ingredient, with the following parameters:

Air flow (m^3/h)	100-110 m^3/h
Liquid flow (g/min)	6-7 g/min
Inlet temperature	65 °C
Spraying pressure	2.8 bar

[0382] Once the granulation is completed, granules are passed through a sieve (1 mm mesh) and glyceryl behenate is weighed, added and blended in a drum mixer (Turbula T2C, Bachoffen, Switzerland). The resulting mixture is pressed into tablets (7 mm diameter and 7 mm curvature) with average hardness being between about 6.0 and 12.0 kP. These tablet cores are then coated with the following formulation.

First coating

Ingredients	Amount (mg)
Tablet cores	160.00
Ethocel PR100 (ethylcellulose)	7.00
Kollidon 90F (povidone USP)	3.00
PEG 1450	1.50
Denatured alcohol	210.00
Total (dry weight)	171.50

[0383] ETHOCEL, povidone, and PEG 1450 are first dissolved in denatured alcohol. The coating solution is then sprayed onto the tablet cores in a coating pan (Vector LCDS), with the following spraying parameters:

Air flow (m^3/h)	100-110 m^3/h
Liquid flow (g/min)	6-7 g/min
Inlet temperature	65 °C
Spraying pressure	2.8 bar

Second coating:

Ingredients	Amount (mg)
Coated tablets	171.50
EUDRAGIT L30 D-55	7.00
Silicon dioxide	2.10
PEG 1450	1.40
Triethyl citrate	0.70
Water	40.00
Total (dry weight)	182.70

[0384] PEG and triethyl citrate 1450 are first dissolved in half the quantity of water. EUDRAGIT is then added and the solution is stirred for 45 minutes. Silicon dioxide is suspended in the remaining quantity of water and homogenized. The silicon dioxide suspension is then added to the EUDRAGIT dispersion. The tablets are coated in a coating pan (VECTOR LCDS), with the following spraying parameters:

Air flow (m^3/h)	100-110 m^3/h
Liquid flow (g/min)	6-7 g/min
Inlet temperature	55 °C
Spraying pressure	2.8 bar

EXAMPLE 17. POLYVINYLPYROLIDONE (PVP) 29/32K: QUETIAPINE, 2:1 WEIGHT BASIS, OVEN DRYING (AMORPHOUS QUETIAPINE FORMULATION)

[0385] Quetiapine hemifumarate (4.62 g) and hot purified water (60°C, 48 mL) is added to a 125 mL Erlenmeyer flask is added PVP 29/32K (8.1210 g). The Erlenmeyer flask is immersed in water bath at 60 °C. Hot 1.0 N HCl (60 °C., 13.6 mL) is added to the 125 mL Erlenmeyer flask and stirred for approximately 5 minutes. Approximately 5 mL of the hot solution is transferred using a pipette to a pre-heated crystallization dish (60 °C) and dried in a tray oven at 60 °C for 71 hours to yield a solid product containing amorphous quetiapine hemifumarate.

EXAMPLE 18. PVP 29/32K/QUETIAPINE HEMIFUMARATE, 2:1 WEIGHT BASIS, VACUUM DRYING

[0386] Approximately 5 mL of the hot solution prepared in Example 18 is transferred using a pipette to a pre-heated 50 mL round bottom flask (60°C). The sample is dried under static vacuum at 60°C for 29 hours to yield a solid product containing amorphous quetiapine hemifumarate.

EXAMPLE 19. PVP 29/32K/ QUETIAPINE HEMIFUMARATE, 1:1 WEIGHT BASIS, VACUUM DRYING

[0387] PVP having a molecular weight distribution corresponding to 29/32K (22.24 g), quetiapine hemifumarate (22.21 g) and purified water (278 g) is added to a 250 mL flask (equipped with a magnetic stir bar). The contents of the flask are stirred and heated to a temperature of approximately 60 °C with a stirring hotplate to obtain a clear solution. The hot solution is spray dried onto dibasic calcium phosphate dihydrate (187. 344 g) using a bench top fluid bed dryer.

[0388] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[0389] Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

CLAIMS

What is claimed is:

1. A solid dosage formulation comprising a matrix, wherein the matrix comprises:

a therapeutically effective amount of quetiapine or a pharmaceutically acceptable salt thereof; and

a wax material.

2. The solid dosage form of Claim 1 wherein the matrix comprises a therapeutically effective amount of quetiapine hemifumarate.

3. The solid dosage form of Claim 1 or 2, wherein the wax material includes carnauba wax, glyceryl behenate, castor wax, or any combination thereof.

4. The solid dosage form of any one of Claim 1 to 3 wherein the dosage is formulated as a sustained release dosage formulation.

5. The solid dosage form of any one of Claim 1 to 4, wherein the matrix is coated with a coating composition.

6. The solid dosage form of Claim 5, wherein the coating composition is a functional coating composition.

7. The solid dosage form of Claim 6, wherein the functional coating composition comprises:

a water-insoluble component; and

a water-soluble component.

8. The solid dosage form of Claim 5, wherein the coating composition is a non-functional coating composition.

9. The solid dosage form of Claim 8, wherein the non-functional coating composition comprises a water-soluble component in the substantial absence of a water-insoluble component.

10. The solid dosage form of Claim 9, wherein the non-functional coating composition comprises pharmaceutically acceptable dyes, pigments, or mixtures thereof.

11. The solid dosage form of any one of Claims 1 to 10, wherein the matrix further comprises a processing aid.

12. The solid dosage form of any one of Claims 1 to 11, wherein the matrix further comprises an additional active agent.

13. A method of making a solid dosage form comprising a matrix, which comprises a therapeutically effective amount of quetiapine or a pharmaceutically acceptable salt thereof and a wax material;

the method comprising: hot melting the wax material to form a melt,

granulating the quetiapine or pharmaceutically acceptable salt thereof with the melt to form a granulate;

milling the granulate; and

compressing the granulate to form the matrix.

14. The method of Claim 13, further comprising blending the granulate with a processing aid; prior to compressing the granulate to form the matrix.

15. The method of Claim 13 or 14, further comprising coating the matrix with a functional and/ or a non-functional coating.

16. The solid dosage form resulting from the method of claim 13.

17. The solid dosage form of Claim 2, having a size which is substantially smaller than the size of a same strength dosage form of a quetiapine hemifumarate dosage form containing

povidone in a weight: weight ratio of about 0.072: 1 to quetiapine hemifumarate,

dibasic dicalcium phosphate dihydrate in a weight: weight ratio of about 0.087: 1 to quetiapine hemifumarate,

microcrystalline cellulose in a weight: weight ratio of about 0.286: 1 to quetiapine hemifumarate,

sodium starch glycolate in a weight: weight ratio of about 0.072: 1 to quetiapine hemifumarate,

lactose monohydrate in a weight: weight ratio of about 0.194: 1 to quetiapine hemifumarate,

magnesium stearate in a weight: weight ratio of about 0.026: 1 to quetiapine hemifumarate,

hydroxypropyl methyl cellulose in a weight: weight ratio of about 0.043: 1 to quetiapine hemifumarate,

polyethyleneglycol in a weight: weight ratio of about 0.009: 1 to quetiapine hemifumarate, and

titanium dioxide in a weight: weight ratio of about 0.016: 1 to quetiapine hemifumarate.

18. A press-coat dosage form comprising

a core composition comprising an active agent, which active agent is quetiapine or a pharmaceutically acceptable salt thereof, a wax material; and

a coating composition comprising a hydrophilic polymer, wherein the coating composition is press-coated onto the core composition.

19. The press-coat dosage form of Claim 18 wherein the active agent is quetiapine hemifumarate.

20. The press-coat dosage form of Claim 18 or 19 wherein the coating composition further comprises quetiapine or a pharmaceutically acceptable salt thereof.

21. The press-coat dosage form of Claim 20 wherein the coating composition further comprises quetiapine hemifumarate.

22. The press-coat dosage form of Claim 20 or 21 wherein the ratio of quetiapine in the core composition to quetiapine in the coating composition is about 1:99 to about 99:1.

23. The press-coat dosage form of Claim 22, wherein the ratio of quetiapine in the core composition to quetiapine in the coating composition is greater than about 5:3.

24. The press-coat dosage form of any one of Claims 18 to 23, wherein the wax material is carnauba wax, tribehenin, fatty alcohols, lauryl alcohol, myristyl alcohol, stearyl alcohol, palmityl alcohol, fatty acids, lauric acid, myristic acid, stearic acid, palmitic acid, polyethylenes, castor wax, C_{16-30} fatty acid triglycerides, beeswax, or any combination thereof.

25. The press-coat dosage form of any one of Claims 18 to 24, wherein the hydrophilic polymer comprises a hydrophilic cellulose polymer.

26. The press-coat dosage form of Claim 25 comprising
a core composition comprising an active agent which is quetiapine hemifumarate and wherein the hydrophilic cellulose polymer is hydroxypropylmethyl cellulose (HPMC).

27. The press-coat dosage form of Claim 18 comprising
a core composition comprising an active agent which is quetiapine or quetiapine hemifumarate,
carnauba wax; and
a coating composition comprising the active agent and hydroxypropylmethyl cellulose (HPMC),
wherein the coating composition is press-coated onto the core.

28. The press-coat dosage form of Claim 27 comprising
a core composition comprising quetiapine hemifumarate and carnauba wax,
a coating composition comprising quetiapine hemifumarate and hydroxypropylmethyl cellulose (HPMC), wherein the coating composition is press-coated onto the core, and
an additional coating composition comprising quetiapine hemifumarate.

29. The press-coat dosage form of Claim 28, wherein the additional coating composition is an immediate release coating composition.

30. The press-coat dosage form of any one of Claims 27 to 29, wherein the quetiapine in the core composition and the quetiapine in the coating composition are present in amounts effective to provide a substantially zero order release profile.

31. The press-coat dosage form of any one of Claims 27 to 29, wherein the quetiapine in the core composition and the quetiapine in the coating composition are present in amounts effective to provide a substantially first order release profile.

32. The press-coat dosage form of any one of Claims 27 to 29, wherein the quetiapine in the core composition and the quetiapine in the coating composition are present in amounts effective to provide a substantially second order release profile.

33. A method for preparing a press-coat dosage form, the method comprising providing a core composition comprising quetiapine or a pharmaceutically acceptable salt thereof and a wax material,
providing a coating composition comprising quetiapine or a pharmaceutically acceptable salt thereof and a hydrophilic polymer, and
press-coating the coating composition onto the core composition to provide the press-coat dosage form.

34. A dosage form of quetiapine comprising an easily openable capsule enclosing a plurality of micropellets, where each of the micropellets comprises a seed coated with a first coating mixture of quetiapine or a pharmaceutically acceptable salt thereof and a water soluble polymer and coated thereon with a second coating mixture of about 90% to about 70% by weight of a non-hydrophilic polymer and about 10% to about 30% of a hydrophilic polymer.

35. The dosage form of Claim 34 wherein the first coating mixture comprises quetiapine or a pharmaceutically acceptable salt thereof and polyvinylpyrrolidone.

36. The dosage form of Claim 34 or 35 wherein the non-hydrophilic polymer is ethyl cellulose.

37. The dosage form of any one of Claims 34 to 36 wherein the hydrophilic polymer is hydroxypropyl methyl cellulose.

38. The dosage form of Claim 34, wherein the dosage form is formulated as a sustained release dosage form.

39. The dosage form of Claim 34 wherein the weight of the second coating mixture is about 5-10% of the weight of the micropellets before the second coating is applied.

40. The dosage form of Claim 34 wherein the second coating mixture comprises about 3 parts ethylcellulose to 1 about part hydroxypropylcellulose.

41. The dosage form of Claim 35 wherein the polyvinylpyrrolidone has a molecular weight of about 30,000 to about 50,000.

42. The dosage form of Claim 41 wherein the polyvinylpyrrolidone has a molecular weight of about 40,000.

43. The dosage form of any one of Claims 34 to 42 wherein the seed is sugar having a mesh size of 60/80.

44. The dosage form of Claim 34 wherein the micropellets have a mean diameter of about 0.5 to about 0.7 mm.

45. A controlled release dosage form comprising a pharmaceutically effective amount of quetiapine or a pharmaceutically acceptable salt thereof and at least one excipient,

exhibiting a dissolution profile such that

at 4 hours after combining the dosage form with a dissolution media 50 to 95% of the quetiapine or the pharmaceutically acceptable salt thereof is released.

46. The controlled release dosage form of Claim 45 exhibiting a dissolution profile such that

at 1 hour after combining the dosage form with a dissolution media 30 to 80% of the quetiapine or the pharmaceutically acceptable salt thereof is released,

at 2 hours after combining the dosage form with a dissolution media 40 to 85% of the quetiapine or pharmaceutically acceptable salt thereof is released,

at 3 hours after combining the dosage form with a dissolution media 45 to 90% of the quetiapine or pharmaceutically acceptable salt thereof is released, and

at 4 hours after combining the dosage form with a dissolution media 50 to 95% of the quetiapine or pharmaceutically acceptable salt thereof is released.

47. A controlled release dosage form comprising a pharmaceutically effective amount of quetiapine or a pharmaceutically acceptable salt thereof and at least one excipient,

exhibiting a dissolution profile such that

at 1 hour after combining the dosage form with a dissolution media 5 to 15% of the quetiapine or pharmaceutically acceptable salt thereof is released,

at 2 hours after combining the dosage form with a dissolution media 10 to 25% of the quetiapine or pharmaceutically acceptable salt thereof is released,

at 4 hours after combining the dosage form with a dissolution media 15 to 35% of the quetiapine or pharmaceutically acceptable salt thereof is released, and

at 8 hours after combining the dosage form with a dissolution media 25 to 50% of the quetiapine or pharmaceutically acceptable salt thereof is released.

48. The controlled release dosage form of Claim 47 comprising a pharmaceutically effective amount of quetiapine or a pharmaceutically acceptable salt thereof and at least one excipient,

exhibiting a dissolution profile such that at 16 hours after combining the dosage form with a dissolution media less that 90 % of the quetiapine or the pharmaceutically acceptable salt thereof is released.

49. A controlled release dosage form of Claim 1 or Claim 18 comprising a pharmaceutically effective amount of quetiapine or a pharmaceutically acceptable salt thereof and at least one excipient,

exhibiting a dissolution profile such that

at 1 hour after combining the dosage form with a dissolution media 0 to 25% of the quetiapine or pharmaceutically acceptable salt thereof is released,

at 2 hours after combining the dosage form with a dissolution media 25 to 50% of the quetiapine or pharmaceutically acceptable salt thereof is released,

at 4 hours after combining the dosage form with a dissolution media 50 to 100% of the quetiapine or pharmaceutically acceptable salt thereof is released, and

at 8 hours after combining the dosage form with a dissolution media not less than 80% of the quetiapine or pharmaceutically acceptable salt thereof is released.

50. The controlled release dosage form of any one of Claims 45 to 49 comprising a pharmaceutically effective amount of quetiapine hemifumarate.

51. The controlled release dosage form of any one of Claims 45 to 50 wherein the dissolution media is 0.1 N HCl.

52. A method for providing a dissolution profile comprising combining a controlled release dosage from of quetiapine or a pharmaceutically acceptable salt thereof with a dissolution media such that at 4 hours after combining the controlled release dosage form with the dissolution media 50 to 95% of the quetiapine or pharmaceutically acceptable salt thereof is released.

53. The method of providing a dissolution profile of Claim 52 such that

at 1 hour after combining the dosage form with the dissolution media 30 to 80% of the quetiapine or pharmaceutically acceptable salt thereof is released,

at 2 hours after combining the dosage form with the dissolution media 40 to 85% of the quetiapine or pharmaceutically acceptable salt thereof is released,

at 3 hours after combining the dosage form with the dissolution media 45 to 90% of the quetiapine or pharmaceutically acceptable salt thereof released, and

at 4 hours after combining the dosage form with the dissolution media 50 to 95% of the quetiapine or pharmaceutically acceptable salt thereof is released.

54. A method of providing a dissolution profile comprising combining a controlled release dosage from of quetiapine or pharmaceutically acceptable salt thereof with a dissolution media such that

at 1 hour after combining the dosage form with the dissolution media 5 to 15% of the quetiapine or pharmaceutically acceptable salt thereof is released,

at 2 hours after combining the dosage form with the dissolution media 10 to 25% of the quetiapine or pharmaceutically acceptable salt thereof is released,

at 4 hours after combining the dosage form with the dissolution media 15 to 35% of the quetiapine or pharmaceutically acceptable salt thereof is released, and

at 8 hours after combining the dosage form with the dissolution media 25 to 50% of the quetiapine or pharmaceutically acceptable salt thereof is released.

55. The method of Claim 54 of providing a dissolution profile such that at 16 hours after combining the dosage form with the dissolution media less that 90 % of the quetiapine or the pharmaceutically acceptable salt thereof is released.

56. A method of providing a dissolution profile comprising combining a controlled release dosage form of Claim 1 or Claim 18 with a dissolution media such that

at 1 hour after combining the dosage form with the dissolution media 0 to 25% of the quetiapine or pharmaceutically acceptable salt thereof is released,

at 2 hours after combining the dosage form with the dissolution media 25 to 50% of the quetiapine or pharmaceutically acceptable salt thereof is released,

at 4 hours after combining the dosage form with the dissolution media 50 to 100% of the quetiapine or pharmaceutically acceptable salt thereof is released, and

at 8 hours after combining the dosage form with the dissolution media not less than 80% of the quetiapine or pharmaceutically acceptable salt thereof is released.

57. The method of any one of Claims 52 to 56 wherein the dissolution media is 0.1 N HCl.

58. An oral dosage form comprising quetiapine or a pharmaceutically acceptable salt thereof in controlled release form which provides a maximum quetiapine plasma concentration (C_{max}) and an quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the ratio of C_{max} to C_{24} is less than about 4:1.

59. The oral dosage form of Claim 58 comprising quetiapine hemifumarate.

60. The oral dosage form of Claim 58 or 59, wherein the ratio is achieved at steady-state.

61. The oral dosage form of Claim 58 or 59, wherein the ratio of C_{max} to C_{24} is less than about 2:1.

62. An oral dosage form comprising quetiapine or a pharmaceutically acceptable salt thereof in controlled release form, which, at steady-state, provides a maximum quetiapine plasma concentration (C_{max}), a quetiapine plasma concentration at about 12 hours after administration (C_{12}), and an quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the average quetiapine plasma concentration between C_{max} and C_{12} is substantially equal to the average quetiapine plasma concentration between C_{12} and C_{24}.

63. The oral dosage form of claim 62 comprising quetiapine hemifumarate.

64. The oral dosage form of Claim 58 or 59, which provides a C_{max} at between 5.5 and 12 hours after administration.

65. The oral dosage form of Claim 58 or 59, which provides a C_{max} at between 2 and 3.5 hours after administration.

66. An oral dosage form comprising quetiapine or a pharmaceutically acceptable salt thereof in sustained release form, which, at steady-state, provides a first maximum quetiapine plasma concentration (C_{max1}) between 0 hours and about 12 hours after administration, and a second maximum quetiapine plasma concentration (C_{max2}) between about 12 hours and about 24 hours after administration.

67. The oral dosage form of Claim 66 comprising quetiapine hemifumarate.

68. The oral dosage form of Claim 66 or 67 which, at steady-state, provides a first maximum quetiapine plasma concentration (C_{max1}) between 0 hours and about 12 hours after administration, a second maximum quetiapine plasma concentration (C_{max2}) between about 12 hours and about 24 hours after administration, and an quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the average quetiapine plasma concentration between about C_{max1} and about C_{max2} is substantially equal to the average quetiapine plasma concentration between about C_{max2} and about C_{24}.

69. The oral dosage form of Claim 66 or 67, which, at steady-state, provides a first maximum quetiapine plasma concentration (C_{max1}) and a first minimum quetiapine plasma concentration (C_{min1}) between 0 hours and about 12 hours after administration, a second maximum quetiapine plasma concentration (C_{max2}), and a quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the ratio of C_{max1} to C_{min1} is less than about 4:1 or the ratio of C_{max2} to C_{24} is less than about 4:1.

70. The oral dosage form of Claim 69, wherein C_{max2} occurs about 12 to about 14 hours after administration.

71. The oral dosage form of Claim 69, wherein the ratio of C_{max1} to C_{min1} is less than about 8:5.

72. The oral dosage form of Claim 69, wherein the ratio of C_{max2} to C_{24} is less than about 2:1.

73. The oral dosage form of Claim 72 or 73, wherein at steady-state, the difference between the ratio of C_{max1} to C_{min1} and the ratio of C_{max2} to C_{24} is less than about 30%.

74. The oral dosage form of Claim 73, wherein the difference between the ratio of C_{max1} to C_{min1} and the ratio of C_{max2} to C_{24} is less than about 20%.

75. The oral dosage form of Claim 73, wherein the difference between the ratio of C_{max1} to C_{min1} and the ratio of C_{max2} to C_{24} is less than about 10%.

76. A sustained release oral dosage form comprising a first subunit and a second subunit,

wherein the first subunit comprises quetiapine or a pharmaceutically acceptable salt thereof, and a first release-retarding material and

the second subunit comprises quetiapine or a pharmaceutically acceptable salt thereof and a second release-retarding material,

wherein the first and second release-retarding material can be the same or different, and wherein the dosage form, at steady-state, provides a maximum quetiapine plasma concentration (C_{max}) and an quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the ratio of C_{max} to C_{24} is less than about 4:1.

77. The controlled release dosage form of Claim 58 or 59 which provides an AUC between 0 and 24 hours after administration that is more than 80 percent and less than 120 percent of the AUC provided between 0 and 24 hours after administration by the same strength dosage form of quetiapine hemifumarate,

wherein the same strength dosage form of quetiapine hemifumarate comprises

povidone in a weight: weight ratio of about 0.072: 1 to quetiapine hemifumarate,

dibasic dicalcium phosphate dihydrate in a weight: weight ratio of about 0.087: 1 to quetiapine hemifumarate,

microcrystalline cellulose in a weight: weight ratio of about 0.286: 1 to quetiapine hemifumarate,

sodium starch glycolate in a weight: weight ratio of about 0.072: 1 to quetiapine hemifumarate,

lactose monohydrate in a weight: weight ratio of about 0.194: 1 to quetiapine hemifumarate,

magnesium stearate in a weight: weight ratio of about 0.026: 1 to quetiapine hemifumarate,

hydroxypropyl methyl cellulose in a weight: weight ratio of about 0.043: 1 to quetiapine hemifumarate,

polyethyleneglycol in a weight: weight ratio of about 0.009: 1 to quetiapine hemifumarate, and

titanium dioxide in a weight: weight ratio of about 0.016: 1 to quetiapine hemifumarate.

78. The controlled release dosage form of Claim 58 or 59 which provides an AUC between 0 and 24 hours after administration that is more than 80 percent and less than 120 percent of the AUC provided between 0 and 24 hours after administration by a dosage form containing 2 times the equivalent weight of quetiapine hemifumarate, wherein the dosage form containing 2 times the equivalent weight of quetiapine hemifumate contains

povidone in a weight: weight ratio of about 0.072: 1 to quetiapine hemifumarate,

dibasic dicalcium phosphate dihydrate in a weight: weight ratio of about 0.087: 1 to quetiapine hemifumarate,

microcrystalline cellulose in a weight: weight ratio of about 0.286: 1 to quetiapine hemifumarate,

sodium starch glycolate in a weight: weight ratio of about 0.072: 1 to quetiapine hemifumarate,

lactose monohydrate in a weight: weight ratio of about 0.194: 1 to quetiapine hemifumarate,

magnesium stearate in a weight: weight ratio of about 0.026: 1 to quetiapine hemifumarate,

hydroxypropyl methyl cellulose in a weight: weight ratio of about 0.043: 1 to quetiapine hemifumarate,

polyethyleneglycol in a weight: weight ratio of about 0.009: 1 to quetiapine hemifumarate, and

titanium dioxide in a weight: weight ratio of about 0.016: 1 to quetiapine hemifumarate.

79. An oral dosage form comprising quetiapine or a pharmaceutically acceptable salt thereof in sustained release form, which, at steady-state, provides a first AUC (AUC_1) between 0 and about 12 hours and a second AUC (AUC_2) between about 12 hours and about 24 hours, wherein difference between AUC_2 and AUC_1 is less than about 50%.

80. The oral dosage form of Claim 79, wherein AUC_1 and AUC_2 are about equal.

81. The oral dosage form of Claim 66 or 67 herein the ratio of C_{maxI} to C_{max2} is greater than 1:1.5 and less than about 1:4.

82. The oral dosage form of Claim 81 wherein the ratio of C_{maxI} to C_{max2} is greater than 1:3.

83. The oral dosage form of Claim 81 wherein C_{maxI} occurs between 0 and about 2.5 hours after administration and C_{max2} occurs between about 10 and about 15 hours after administration.

84. The oral dosage form of Claim 81 wherein C_{maxI} occurs between about 2.5 and about 3.5 hours after administration and C_{max2} occurs between about 10 and about 15 hours after administration.

85. The oral dosage form of Claim 81 wherein C_{maxI} occurs between 5.5 and about 12 hours after administration and C_{max2} occurs between about 12 and about 16 hours after administration.

86. The manufacture of a medicament for the treatment of psychosis or bipolar mania, the medicament comprising a matrix,
wherein the matrix comprises:
a therapeutically effective amount of quetiapine or a pharmaceutically acceptable salt thereof; and
a wax material.

87. A controlled release dosage form of any one of Claims 1, 18, or 28 comprising a pharmaceutically effective amount of quetiapine or quetiapine hemifumarate and at least one excipient,

exhibiting a dissolution profile such that

at 4 hours after administration 50 to 95% of the quetiapine or quetiapine hemifumarate is released.

88. The controlled release dosage form of Claim 87 exhibiting a dissolution profile such that

at 1 hour after administration 30 to 80% of the quetiapine or quetiapine hemifumarate is released,

at 2 hours after administration 40 to 85% of the quetiapine or quetiapine hemifumarate is released,

at 3 hours after administration 45 to 90% of the quetiapine or quetiapine hemifumarate is released, and

at 4 hours after administration 50 to 95% of the quetiapine or quetiapine hemifumarate is released.

89. A controlled release dosage form of any one of Claims 1, 18, or 28 comprising a pharmaceutically effective amount of quetiapine or a quetiapine hemifumarate and at least one excipient,

exhibiting a dissolution profile such that

at 1 hour after administration 5 to 15% of the quetiapine or quetiapine hemifumarate is released,

at 2 hours after administration 10 to 25% of the quetiapine or quetiapine hemifumarate is released,

at 4 hours after administration 15 to 35% of the quetiapine or quetiapine hemifumarate is released, and

at 8 hours after administration 25 to 50% of the quetiapine or quetiapine hemifumarate is released.

90. An oral dosage form of any one of Claims 1, 18, or 28 comprising quetiapine or a pharmaceutically acceptable salt thereof in controlled release form which provides a maximum quetiapine plasma concentration (C_{max}) and an quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the ratio of C_{max} to C_{24} is less than about 4:1.

91. An oral dosage form of any one of Claims 1, 18, or 28 comprising quetiapine or a pharmaceutically acceptable salt thereof in controlled release form, which, at steady-state, provides a maximum quetiapine plasma concentration (C_{max}), a quetiapine plasma concentration at about 12 hours after administration (C_{12}), and an quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the average quetiapine plasma concentration between C_{max} and C_{12} is substantially equal to the average quetiapine plasma concentration between C_{12} and C_{24}.

92. An oral dosage form of any one of Claims 1, 18, or 28 comprising quetiapine or a pharmaceutically acceptable salt thereof in sustained release form, which, at steady-state, provides a first maximum quetiapine plasma concentration (C_{max1}) between 0 hours and about 12 hours after administration, and a second maximum quetiapine plasma concentration (C_{max2}) between about 12 hours and about 24 hours after administration.

93. A sustained release oral dosage form of any one of Claims 1, 18, or 28 comprising a first subunit and a second subunit, wherein the first subunit comprises quetiapine or a pharmaceutically acceptable salt thereof and a first release-retarding material and the second subunit comprises quetiapine or a pharmaceutically acceptable salt thereof and a second release-retarding material, wherein the first release-retarding material and second release-retarding material can be the same or different, and wherein the dosage form, at steady-state, provides a maximum quetiapine plasma concentration (C_{max}) and an quetiapine plasma concentration at about 24 hours after administration (C_{24}), wherein the ratio of C_{max} to C_{24} is less than about 4:1.

94. A controlled release dosage form of any one of Claims 1, 18, or 28 which provides an AUC between 0 and 24 hours after administration that is more than 80 percent and less than 120 percent of the AUC provided between 0 and 24 hours after administration by a same strength dosage form of quetiapine hemifumate;

wherein the same strength dosage form contains

povidone in a weight: weight ratio of about 0.072: 1 to quetiapine hemifumarate,

dibasic dicalcium phosphate dihydrate in a weight: weight ratio of about 0.087: 1 to quetiapine hemifumarate,

microcrystalline cellulose in a weight: weight ratio of about 0.286: 1 to quetiapine hemifumarate,

sodium starch glycolate in a weight: weight ratio of about 0.072: 1 to quetiapine hemifumarate,

lactose monohydrate in a weight: weight ratio of about 0.194: 1 to quetiapine hemifumarate,

magnesium stearate in a weight: weight ratio of about 0.026: 1 to quetiapine hemifumarate,

hydroxypropyl methyl cellulose in a weight: weight ratio of about 0.043: 1 to quetiapine hemifumarate,

polyethyleneglycol in a weight: weight ratio of about 0.009: 1 to quetiapine hemifumarate, and

titanium dioxide in a weight: weight ratio of about 0.016: 1 to quetiapine hemifumarate.

95. An oral dosage form of any one of Claims 1, 18, or 28 comprising quetiapine or a pharmaceutically acceptable salt thereof in sustained release form, which, at steady-state, provides a first AUC (AUC_1) between 0 and about 12 hours and a second AUC (AUC_2) between about 12 hours and about 24 hours, wherein difference between AUC_2 and AUC_1 is less than about 50%.

96. A tablet comprising a dosage form of any one of Claims 1, 2, and 52 to 85.

97. The tablet of Claim 96, further comprising a functional or non-functional coating.

98. A capsule comprising the solid dosage form of any one of Claims 1, 2, and 52 to 85.

99. The controlled release dosage form of any of Claims 52 to 85 wherein the controlled release dosage form does not contain a gelling agent.

100. The controlled release dosage form of Claim 99 wherein the controlled release dosage form is a tablet or capsule.

INTERNATIONAL SEARCH REPORT

PCT/US2004/034743

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K9/48 A61K9/50 A61K31/554

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)
IPC 7 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/039514 A (VERION INC; VAGHEFI, FARID; SAVITZKY, MARTIN, F) 15 May 2003 (2003-05-15) claims 1-46 page 8, line 12 - page 25, line 2	1-6, 8-16, 18-25, 45-100
X	US 2003/059471 A1 (COMPTON BRUCE JON ET AL) 27 March 2003 (2003-03-27) paragraph '0012! - paragraph '0015! paragraph '0044! - paragraph '0060! paragraph '0072! - paragraph '0074! paragraph '0292!	1-6,8, 10-16, 45-100

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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Date of the actual completion of the international search	Date of mailing of the international search report
16 March 2005	06/04/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schifferer, H

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C.(Continuation) 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	US 2001/036472 A1 (WONG PATRICK S.-L ET AL) 1 November 2001 (2001-11-01) paragraphs '0032!, '0038! - paragraph '0079! claims 1-11	1-6,8, 10-16, 45-100

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