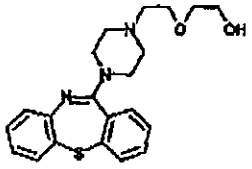
CONTROLLED RELEASE DOSAGE FORM COMPRISING QUETIAPINE

FIELD OF THE INVENTION

The present invention relates to a novel dosage form and a process for the manufacturing the same. More specifically, the present invention relates to a controlled release oral dosage form comprising an antipsychotic agent.

BACKGROUND OF THE INVENTION

Quetiapine, chemically designated as 2-[2-(4-dibenzo[*b,f*][1,4]thiazepin-11-yl-1-piperazinyl) ethoxy]ethanol (also known as 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4] thiazepine), is a compound of formula (I):



(I)

Quetiapine has been employed as an antipsychotic or neuroleptic agent in the treatment of schizophrenia and bipolar mania, due to its antidopaminergic activity, as well as depressive episodes associated with bipolar disorder. As a combined serotonin ($5HT_2$) and dopamine (D_2) receptor antagonist, quetiapine, including its fumarate salt, is also known for the effective treatment of psychiatric conditions. Quetiapine is a drug of the dibenzothiazepine class and belongs to a group of drugs known as "atypical" or second generation antipsychotics which have become increasingly popular alternatives to "typical" antipsychotics.

When administered orally, quetiapine is rapidly absorbed and generally reaches a peak plasma level within about 1.5 hours. Quetiapine is highly metabolized, with elimination occurring mainly through hepatic metabolism in the liver. The plasma half-life of quetiapine is typically about 5 to about 7 hours. Quetiapine is currently marketed as a

hemifumarate salt in the form of tablets of several doses, including 25 mg, 100 mg, 150 mg, 200 mg and 300 mg, 400 mg for administration two or three times per day.

One of the first preparations of quetiapine is described in United States Patent No. 4,879,288 (corresponds to European Patent No. 0 240 228), which issued November 7, 1989. Since then, many references have been published describing various formulations of quetiapine in which certain drawbacks exist in light of the poor dissolution properties of this medicament and the uncontrolled release profile provided by said formulations. For example, International Patent Application WO2005/041935 describes quetiapine formulations which do not provide a constant or substantially constant level of quetiapine, such that the patient can, at certain time intervals, receive therapeutic amounts of quetiapine exceeding the recommended doses, whereas at other times the amount may be below the therapeutically effective limits.

International Patent Applications WO1997/45124 and WO2005/041935 describe modified-release pharmaceutical compositions containing quetiapine. More specifically, International Patent Application WO2005/041935 (corresponds to Canadian Patent Application No. 2,542,836) describes a solid dosage pharmaceutical composition comprising a matrix formed by means of melted waxes, whereas International Patent Application WO1997/45124 (corresponds to Canadian Patent No. 2,251,944) describes the use of matrices with a gelling agent. However, in the latter application, the use of water-soluble active ingredients, such as quetiapine or its pharmaceutically acceptable salts, combined with gelling agents such as hydroxypropyl-methylcelluloses, can give rise to a phenomenon known as dumping in which the release of the active ingredient is delayed, but once initiated the release occurs at very high rates.

European Patent No. 1 218 009 describes the preparation of granules containing quetiapine and a freely or very water-soluble binder for their use in suspensions or solutions. International Patent Application WO2003/039516 describes methods for improving the dissolution of poorly dispersible medicaments, including, for example, quetiapine. The dissolution is improved by means of preparing granules in which a

floating agent is added to the medicament. Unfortunately, there is no indication about the release profile of these medicaments in the granulate formulations.

United States Patent Application 2007/0244093 describes a controlled release dosage form comprising quetiapine 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. Examples 10, 12 and 13 are formulations of quetiapine where stearic acid is used as a lubricant and wherein the tablets may further be coated with ethylcellulose.

International Patent Application WO2008/152434 relates to a novel process for the synthesis of quetipaine.

United States Patent Application 2008/0287418 describes a formulation comprising quetiapine or a pharmaceutically acceptable salt thereof wherein the quetiapine content is about 9.6% to about 10.4% by weight and wherein the formulation comprises about 30% hydroxypropyl methylcellulose by weight and about 7.2% sodium citrate dehydrate by weight. The formulation further comprises 25.1% lactose monohydrate by weight, about 25.1% microcrystalline cellulose and about 1% magnesium stearate by weight.

United States Patent Application 2009/0035370 describes an orally deliverable pharmaceutical dosage form comprising quetiapine and at least one pharmaceutically acceptable excipient, wherein quetiapine is in a form of free base and/or pharmaceutically acceptable salt thereof and comprising a major component in immediate release form and one or more minor components in delayed extended release or delayed pulsed-release form.

International Patent Application WO2007/058593 relates to the a method of treating a patient suffering from or susceptible to a mood disorder or an anxiety disorder comprising administering a sustained release pharmaceutical composition comprising a pharmaceutically effective amount ofquetiapine, or a pharmaceutically acceptable salt

thereof, to the patient in need thereof. The compositions claimed display a particular mean C_{max} characteristics. The proposed method to obtain controlled release of the active ingredient uses the conventional Methocel® excipients.

International Patent Application WO2008/098969 describes a granule for the preparation of pharmaceutical compositions comprising a core that contains quetiapine or pharmaceutically acceptable salt thereof as active ingredient and a binder, and a coating layer comprising a lubricant. It is said that the presence of a lubricant in an amount ranging from 5 to 10 % would be sufficient to achieve the goal of the invention. The application suggests the use of lubricants from the glyceryl behenate, glyceryl palmitostearate and macrogol groups.

For the reasons set out above, there is still a need to develop pharmaceutical compositions which incorporate quetiapine, or one of its pharmaceutically acceptable salts, and which provide desired release rates of the pharmaceutically active agent and a robust manufacturing process. The formulations according to the present invention overcome the drawbacks of the prior art by providing a novel approach by the using at least one hydrophobic controlled release agent in achieving an extended release dosage form.

SUMMARY OF THE INVENTION

Thus, the present invention provides a novel controlled release pharmaceutical dosage form comprising:

- intragranular excipients comprising:
  - quetiapine or a pharmaceutically acceptable salt thereof;
  - at least one hydrophobic controlled release agent,
  - at least one pH dependent polymer; and
- extragranular excipients comprising at least one pharmaceutically acceptable excipient.

In a more preferred embodiment, the present invention provides a novel controlled release pharmaceutical dosage form wherein the content (in % by weight) of the at least one hydrophobic controlled release agent is in the range of about 4.5 to about 35% and

the content of the at least one pH dependent polymer is in the range from about 15 to about 35%.

In a further embodiment of the present invention there is provided a novel controlled release pharmaceutical dosage form, wherein the ratio of the % by weight content between the at least one hydrophobic controlled release agent and the at least one pH dependent polymer ranges from about 1:3 to about 1:7. Preferably, the ratio of the % by weight content between the at least one hydrophobic controlled release agent and the at least one pH dependent polymer ranges from about 1:4 to about 1:6. More preferably, the ratio of the % by weight content between the at least one hydrophobic controlled release agent and the at least one pH dependent polymer ranges from about 1:4.5 to about 1:5.5.

The novel controlled release pharmaceutical dosage form can be optionally coated with a water insoluble/non gelling polymer.

Another aspect of the present invention is to provide a controlled release pharmaceutical dosage form that allows a single daily administration with a prolonged effect, simplified production and is cost effective.

Another aspect of the present invention is to provide a novel stable controlled release pharmaceutical dosage form comprising quetiapine or a pharmaceutically acceptable salt thereof, wherein said dosage form provides a dissolution of quetiapine or pharmaceutically acceptable salt thereof between about 30% and about 45% within 1 hour, between about 45 and about 70 % within 6 hours and between about 75 and about 95 % within 16 hours as measured by Apparatus I USP (baskets) at 100 rpm, in 1000mL of 0.1N HCl (1.2 pH) for the first hour, in 1000mL of 4.5 pH acetate buffer for the 2 hour and subsequently in 1000mL of 6.8 pH phosphate buffer.

One can also measure the *in vitro* dissolution rate of the dosage form, according to the present invention, by the following USP Basket (Apparatus I) Method: at 200 rpm at

1000 ml aqueous buffer (pH 1.2 from 0 to 2 hours and 6.8 from 4 to 20 hours) at 37°C. Preferably, the dissolution rates for dosage forms of the present invention, obtained by using the above method is between about 50% and about 60% (by wt) of quetiapine or pharmaceutically acceptable salt thereof released after 2 hours; between about 60% and about 70% (by wt) after 4 hours; between about 65% and about 80% (by wt) of quetiapine or pharmaceutically acceptable salt thereof released after 8 hours; between about 70% and about 80% (by wt) of quetiapine or pharmaceutically acceptable salt thereof released after 12 hours; and over about 75% (by wt) of quetiapine or pharmaceutically acceptable salt thereof released after 16 hours.

Yet another aspect of the present invention is to provide a process for manufacturing the novel dosage form.

Other embodiments and further scope of applicability of the present invention will become apparent from the detailed description and examples given hereinafter. It should be understood, however, that this detailed description and examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art.

DETAILED DESCRIPTION OF THE INVENTION

Before the present formulations and methods of use are disclosed and described, it is to be understood by a person skilled in the art that unless otherwise indicated this invention is not limited to specific pharmaceutical carriers, or to particular administration regimens, as such may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an" and "the" include plural references unless the context clearly dictates

otherwise. Thus, for example, reference to "an active agent" includes mixtures of active agents, reference to "a pharmaceutical carrier" includes combinations of two or more carriers, and the like.

"Optional" or "optionally" means that the subsequently described circumstance may or may not occur, so that the description includes instances where the circumstance occurs and instances where it does not.

The terms or expressions "active agent", "active ingredient", "active pharmaceutical ingredient", "drug", "pharmacologically active agent", "pharmaceutically acceptable active agent" and/or "pharmaceutically acceptable active substance" are used interchangeably herein to refer to a chemical material or compound which, when administered to an organism (human or animal, generally human) induces a desired pharmacologic effect. In the context of the present invention, the terms or expressions refer to a compound that is capable of being delivered orally.

According to the present invention, the pharmaceutically active substance is quetiapine (marketed as Seroquel®) or a pharmaceutically acceptable salt, ester or solvate thereof. The term "quetiapine" as used herein includes all optical isomers, racemic mixtures and the like of the compound and all pharmaceutically acceptable salts, esters, amides, prodrugs and analogs thereof.

Similarly, a "pharmaceutically acceptable salt" or a "pharmaceutically acceptable ester" of the compound as provided herein is a salt or ester which is not biologically or otherwise undesirable.

By the terms "effective amount" or "pharmaceutically effective amount" of an agent as provided herein are meant a nontoxic but sufficient amount of the agent to provide the desired therapeutic effect. The exact amount required will vary from subject to subject, depending on age, general condition of the subject, the severity of the condition being treated, and the particular active agent administered, and the like. Thus, it is not

possible to specify an exact "effective amount." However, an appropriate "effective" amount in any individual case may be determined by a person of ordinary skill in the art using routine experimentation.

The term "excipient" refers to a generally pharmaceutically inactive or inert substance used as a diluent or vehicle for a drug. Different forms of drug administration may require a different excipient and a "pharmaceutically acceptable excipient" includes a "pharmaceutically acceptable carrier." For example, tablets, troches, pills, capsules, and the like, may contain excipients including binders, such as gum tragacanth, acacia, corn starch or gelatin; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate. Capsules may contain additional excipients such as a liquid carrier.

By "pharmaceutically acceptable carrier" is meant a carrier comprised of a material that is not biologically or otherwise undesirable, i.e., the material may be administered to an individual along with the selected active agent without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained. The term "carrier" is used generically herein to refer to any components present in the pharmaceutical formulations other than the active agent or agents, and thus includes diluents, binders, lubricants, disintegrants, fillers, colouring agents, wetting or emulsifying agents, pH buffering agents, preservatives, and the like.

According to the present invention, the expression "dosage form" may consist of granules, spheroids, beads, pellets, capsules, tablets or any other suitable unit. In the present invention, the dosage form is preferably a tablet.

The novel delayed release dosage form comprising a pharmaceutically acceptable active substance is characterized in the following way. Individual units, for example granules, containing a pharmaceutically acceptable active substance are mixed with other pharmaceutically acceptable excipients and compressed into a final dosage form,

preferably a tablet. By the expression "individual units" is meant small beads, particles, granules or pellets. In the present invention, the preferred individual units are granules.

The compaction process (or compression process) must not significantly affect the chemical, i.e. degradation and/or mechanical properties of the individual unit or the final dosage form, even if it were to be further layered with a coating layer.

Of course, other components, such as fillers, binders, disintegrants, and other pharmaceutically acceptable additives can be envisaged, and compressed into tablets. The compressed tablet is optionally covered with one or more coating layers to obtain a smooth surface of the tablet and further enhances the stability of the tablet during packaging and transport.

Furthermore, the granules or tablets may be covered with one or more coating layer(s). The coating layer(s) can be applied onto the tablets by coating or layering procedures in suitable equipments such as coating pan, coating granulator or in a fluidized bed apparatus using water and/or organic solvents for the coating or layering process. The materials for coating layers are chosen among pharmaceutically acceptable compounds such as, for instance methacrylic acid copolymer, ethylcellulose, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide, talc and other additives may also be included into the coating layer(s). The coating layer may further protect the tablet from environmental conditions.

According to the present invention, the coating layer is preferably made up of an aqueous dispersion of, for example, Eudragit® (i.e. methacrylic acid copolymer) or OPadry®, a plasticizer (i.e. triethyl citrate) and a diluent (i.e. colloidal silicon dioxide), which can be applied onto the final dosage form.

The novel drug dosage forms are to be administered orally to a mammal and can be used to administer the pharmaceutically acceptable active substance (i.e. quetiapine or a

pharmaceutically acceptable salt or solvate thereof) to treat or prevent a variety of disorders, conditions and diseases. In accordance with the present invention, administration of quetiapine or a pharmaceutically acceptable salt or solvate thereof may be carried out in order to treat any disorder, condition or disease for which quetiapine is generally indicated. Such disorders, conditions and diseases include, for example:

- treat the symptoms of schizophrenia, such as hallucinations (hearing or seeing things which are not there), fixed false beliefs, unusual suspiciousness, or emotional withdrawal. Patients may also feel depressed, anxious or tense.
- treat the symptoms of mania associated with bipolar disorder, such as racing thoughts, irritability, aggressiveness, agitation, impulsive behaviour or excessively elevated mood; and
- treat the symptoms of depression associated with bipolar disorder, such as sadness, feeling guilty, lack of energy, loss of appetite and/or sleep disturbance.

The novel controlled release pharmaceutical dosage form of the present invention provide a controlled release pharmaceutical dosage form that allows a single daily administration with a prolonged effect, simplified production, and is cost effective. The dosage forms of the present invention comprise a matrix comprising:

- o intragranular excipients, comprising:
  - quetiapine or a pharmaceutically acceptable salt thereof;
  - at least one hydrophobic controlled release agent,
  - at least one pH dependent polymer; and
- o extragranular excipients comprising:
  - at least one pharmaceutically acceptable excipient.

The content (in % by weight) of the hydrophobic controlled release agent is in the range of about 4.5 to about 35 % and the content of the pH dependent polymer is in the range from about 15 to about 35 %. Preferably, the ratio of the % by weight content between the at least one hydrophobic controlled release agent and the at least one pH dependent polymer ranges from about 1:3 to about 1:7. More preferably, the ratio of the % by

weight content between the at least one hydrophobic controlled release agent and the at least one pH dependent polymer ranges from about 1:4 to about 1:6. More preferably, the ratio of the % by weight content between the at least one hydrophobic controlled release agent and the at least one pH dependent polymer ranges from about 1:4.5 to about 1:5.5.

The dosage forms, for example a tablet, of the present invention were subjected to dissolution studies, using either Method 1 where the conditions are as follows:

Apparatus 1 (USP baskets)
Speed: 100 rpm
1st hour in 1000mL of 0.1N HCl (1.2 pH)
2nd hour in 1000mL of 4.5 pH acetate buffer
Then in 1000mL of 6.8 pH phosphate buffer

or by using Method 2 where the conditions are as follows:

Apparatus 1 (USP baskets)
Speed: 200 rpm
Initial 2 hours in 1000mL of 0.1N HCl (1.2 pH)
Then in 1000mL of 6.8 pH phosphate buffer (for 4 to 20 hours)

Preferably, the dosage forms of the present invention provide a dissolution of quetiapine, or pharmaceutically acceptable salt thereof, when determined via Method 1, between about 30% and about 45% within 1 hour, between about 45% and about 70% within 6 hours and between about 75% and about 95% within 16 hours.

Preferably, the dosage forms of the present invention also have an *in vitro* dissolution rate, when determined by Method 2, of between about 50% and about 60% (by wt) of quetiapine or pharmaceutically acceptable salt thereof released after 2 hours; between about 60% and about 70% (by wt) after 4 hours; between about 65% and about 80% (by wt) of quetiapine or pharmaceutically acceptable salt thereof released after 8 hours; between about 70% and about 80% (by wt) of quetiapine or pharmaceutically acceptable salt thereof released after 12 hours; and over about 75% (by wt) of quetiapine or pharmaceutically acceptable salt thereof released after 16 hours.

The process for manufacturing the novel dosage form according to the present invention generally comprises the following steps:

(a) providing quetiapine or a pharmaceutically acceptable salt thereof,

(b) adding to the quetiapine or to the mixture obtained in step (a) a hydrophobic controlled release agent or sodium starch glycolate, and at least one diluent and a pH dependent polymer; and

(c) adding a solvent mixture, comprising a binder to the mixture obtained step (b);

(d) wet granulating the mixture obtained in step (c);

(e) drying the granules in step (d); and

(f) sieving the dried granules with a lubricant; and

(g) blending the granules of step (f) with extragranular excipients in a suitable non shear blender;

(h) compressing the blend of step (g) into a tableted dosage form; and

(i) optionally coating the granules/tablets with an aqueous dispersion.

Preferably, the at least one hydrophobic controlled release agent is stearic acid or Cutina® HR PH (i.e. hydrogenated castor oil). Preferably, the pH dependent polymer is Eudragit® (i.e. a methacrylic acid copolymer), and more preferably, the pH dependent polymer is selected from Eudragit L 30 D-55, Eudragit L100-55, and mixtures thereof.
For the avoidance of doubt, Eudragit L 30 D-55 and Eudragit L100-55 are both poly(methacrylic acid-co-ethyl acrylate) 1:1 - see the following web pages:
http://eudragit.evonik.com/product/eudragit/en/products-services/eudragit-products/enteric-formulations/l-30-d-55/pages/default.aspx &
http://eudragit.evonik.com/product/eudragit/en/products-services/eudragit-products/enteric-formulations/l-100-55/pages/default.aspx

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the description above as well as the examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains. Although any method and material whether similar or equivalent to those described herein can be used in the practice for testing the present invention, the preferred methods and materials as described.

EXAMPLES

All of the percentages given hereinabove and below are percentages by weight. Examples of various formulations and/or dosage forms, i.e. tablets, containing quetiapine as choice of pharmaceutically active ingredient, are provided herein below.

For the pharmaceutical compositions of the present invention, the preferred manufacturing technique is direct compression. Tablets are the preferred dosage form of the present invention, however, other dosage forms can be envisaged. The dosage strength in the dosage forms can be any desired strength, for example, 50, 150, 200, 300, or 400 mg per tablet..

Examples 1 to 5

Table 1 **List of ingredients for the formulation of quetiapine tablets (Example 1)**

S.N.	Formulation	mg/tablet	% w/w
	INTRAGRANULAR		
1	Quetiapine Fumarate	230.26*	38.38
2	Lactose Monohydrate 200M	60.00	10.00
3	Sodium Citrate	60.00	10.00
4	Cutina HR PH	90.00	15.00
5	Povidone K-90	9.00	1.50
6	Purified Water	—	—
	EXTRAGRANULAR		
7	Cutina HR PH	138.00	23.00
8	Lactose Monohydrate Flowlac 100	6.74	1.12
9	Magnesium Stearate	6.00	1.00
	Total	600.00	100.00

* 230.26 mg Quetiapine Fumarate is equivalent to 200 mg Quetiapine

Manufacturing Process:

1. Sift Quetiapine fumarate, lactose monohydrate 200M, sodium citrate and cutina HR PH and mix in a high shear granulator.
2. Dissolve Povidone K 90 to get the binder solution.
3. Granulate the mixture of step 1 using binder solution of step 2.
4. Dry the granules and size.

5. Blend the granules of step 4 and extragranular ingredients in suitable non shear blender.
6. Compress the blend to tablets using suitable tooling.

Dissolution Profile of Example 1 and Seroquel XR (Lot No. TM0047)

Conditions: Apparatus 1 (USP baskets)
Speed: 200 rpm
Time 2 hours in 1000mL of 0.1N HCl (1.2 pH)
Time 4-16 hours in 1000mL of 6.8 pH phosphate buffer

Innovator Lot#: TM0047

Time (Hour)	Average Percentage Release (%)		Apparatus I Baskets 200 rpm
	Seroquel XR TM0047	Example 1	
0	0	0	0.1 N HCl
1	23	28	
2	42	45	
6	63	62	6.8 pH phosphate buffer
12	95	83	
16	100	94	

Table 2 List of ingredients for the formulation of quetiapine tablets (Example 2)

S.N.	Formulation	mg/tablet	% w/w
	INTRAGRANULAR		
1	Quetiapine Fumarate	230.26	38.38
2	Lactose Monohydrate 200M	30.00	5.00
3	Sodium Citrate dihydrate	60.00	10.00
4	Cutina HR PH	135.00	22.50
5	Eudragit L 30 D-55	30.00	5.00
	EXTRAGRANULAR		
7	Lactose Monohydrate Flowlac 100	108.74	18.12
8	Magnesium Stearate	6.00	1.00
	Total	600.00	100.00

Manufacturing Process:

1 Sift Quetiapine fumarate, lactose monohydrate 200M, sodium citrate and cutina HR PH and mix in a high shear granulator.

2 Granulate the mix of step 1 using the Eudragit L 30 D-55 dispersion in high shear granulator.

3 Dry the granules and size.

4 Blend the granules of step 3 and extragranular ingredients in suitable non shear blender.

5 Compress the blend to tablets using suitable tooling.

Table 3 List of ingredients for the formulation of quetiapine tablets (Example 3)

S.N.	Formulation	mg/tablet	% w/w
	INTRAGRANULAR		
1	Quetiapine Fumarate	230.26	38.38
2	Lactose Monohydrate 200M	60.00	10.00
3	Citric Acid Monohydrate	30.00	5.00
4	Cutina HR PH	45.00	7.50
5	Eudragit L100-55	72.00	12.00
6	Eudragit L 30 D-55	24.00	4.00
	EXTRAGRANULAR		
7	Lactose Monohydrate Flowlac 100	132.74	22.12
8	Magnesium Stearate	6.000	1.00
	Core Tablet Total	600.00	100.00
9	Opadry Yellow	18.00	3.00
10	Water	q.s.	
	Total	618.00	103.00

Manufacturing Process:

1 Sift Quetiapine fumarate, lactose monohydrate 200M, citric acid, cutina HR PH, Eudragit L100-55 and mix in a high shear granulator.

2 Granulate the mix of step 1 using the Eudragit L 30 D-55 dispersion in high shear granulator.

3 Dry the granules and size.

4 Blend the granules of step 3 and extragranular ingredients in suitable non shear blender.

5 Compress the blend to tablets using suitable tooling.

6 Prepare aqueous dispersion of Opadry Yellow.

7 Coat the tablets of step 5 using the dispersion of step 6.

Table 4 List of ingredients for the formulation of quetiapine tablets (Example 4)

S.N.	Formulation	mg/tablet	% w/w
	INTRAGRANULAR		
1	Quetiapine Fumarate	230.26	38.38
2	Mircocyrstalline Cellulose PH101	114.00	19.00
3	Citric Acid Monohydrate	30.00	5.00
4	Cutina HR PH	45.00	7.50
5	Eudragit L100-55	36.00	6.00
6	Eudragit L 30 D-55	24.00	4.00
	EXTRAGRANULAR		
7	Mircocyrstalline Cellulose PH102	114.74	19.12
8	Magnesium Stearate	6.000	1.00
	Core Tablet Total	600.00	100.00

Manufacturing Process:

1. Sift Quetiapine fumarate, microcrystalline cellulose PH 101, citric acid, cutina HR PH, Eudragit L100-55 and mix in a high shear granulator.
2. Granulate the mix of step 1 using the Eudragit L 30 D-55 dispersion in high shear granulator.
3. Dry the granules and size.
4. Blend the granules of step 3 and extragranular ingredients in suitable non shear blender.
5. Compress the blend to tablets using suitable tooling.

Table 5 List of ingredients for the formulation of quetiapine tablets according to a preferred embodiment (Example 5)

S.N.	Formulation	mg/tablet	% w/w
	INTRAGRANULAR		
1	Quetiapine Fumarate	230.26	38.38
2	Lactose Monohydrate (Flowlac 100)	165.74	27.62
3	Cutina HR PH	30.00	5.00
4	Eudragit L100-55	54.00	9.00
5	Eudragit L 30 D-55	60.00	10.00
	EXTRAGRANULAR		
6	Lactose Monohydrate (Flowlac 100)	42.00	7.00
7	Talc	12.00	2.00
8	Magnesium Stearate	6.00	1.00
	Core Tablet Total	600.00	100.000
8	Opadry Yellow 03B92736	18.00	3.00
	Coated Tablet Total	618.00	103.000

Manufacturing Process:

1 Sift Quetiapine fumarate, lactose monohydrate, cutina HR PH, Eudragit L100-55 and mix in a high shear granulator.

2 Granulate the mix of step 1 using the Eudragit L 30 D-55 dispersion in high shear granulator.

3 Dry the granules and size.

4 Blend the granules of step 3 and extragranular ingredients in suitable non shear blender.

5 Compress the blend to tablets using suitable tooling.

6 Prepare aqueous dispersion of Opadry Yellow.

7 Coat the tablets of step 5 using the dispersion of step 6.

<u>Dissolution Profiles of Examples 1 to 5</u>

Conditions:

Apparatus 1 (USP baskets)
Speed: 100 rpm
Time 1 hour in 1000mL of 0.1N HCl (1.2 pH)
Time 2 hour in 1000mL of 4.5 pH acetate buffer
Time 4-20 hours in 1000mL of 6.8 pH phosphate buffer

Time (Hour)	Average Percentage Release (%)					Apparatus I Baskets at 100 rpm
	Example 1	Example 2	Example 3	Example 4	Example 5	
0	0	0	0	0	0	0.1 N HCl
1	22	31	27	33	28	
2	24	33	31	39	32	4.5 pH acetate buffer
4	25	34	36	42	38	6.8 pH phosphate buffer
5	25	35	39	44	42	
6	25	36	42	46	45	
8	26	37	48	48	51	
12	26	38	58	51	62	
16	–	–	–	54	72	
20	–	–	–	56	82	

Examples 6 to 12

Table 6 List of ingredients for the formulation of quetiapine tablets according to a preferred embodiment (Example 6)

S.N.	Formulation	mg/tablet	% w/w
	INTRAGRANULAR		
1	Quetiapine Fumarate	230.26	38.38
2	Lactose Monohydrate (Flowlac 100)	165.74	27.62
3	Cutina HR PH	30.00	5.00
4	Eudragit L100-55	54.00	9.00
5	Eudragit L 30 D-55	60.00	10.00
	EXTRAGRANULAR		
6	Lactose Monohydrate (Flowlac 100)	42.00	7.00
7	Talc	12.00	2.00
8	Magnesium Stearate	6.00	1.00
	Core Tablet Total	**600.00**	**100.000**
9	Opadry Yellow 03B92736	18.00	3.00
	Coated Tablet Total	**618.00**	**103.000**

Manufacturing Process:

1. Sift Quetiapine fumarate, lactose monohydrate, cutina HR PH, eudragit L100-55 and mix in a high shear granulator.
2. Granulate the mix of step 1 using the Eudragit L 30 D-55 dispersion in high shear granulator.
3. Dry the granules and size.
4. Blend the granules of step 3 and extragranular ingredients in suitable non shear blender.
5. Compress the blend to tablets using suitable tooling.
6. Prepare aqueous dispersion of Opadry Yellow.
7. Coat the tablets of step 5 using the dispersion of step 6

Table 7 List of ingredients for the formulation of quetiapine tablets (Example 7)

S.N.	Formulation	mg/tablet	% w/w
	INTRAGRANULAR		
1	Quetiapine Fumarate	230.26	38.38
2	Lactose Monohydrate 200M	90.00	15.00
3	Cutina HR PH	45.00	7.50
4	Eudragit L100-55	60.00	10.00
5	Eudragit L 30 D-55	36.00	6.00

	EXTRAGRANULAR		
6	Lactose Monohydrate (Flowlac 100)	132.74	22.12
7	Magnesium Stearate	6.00	1.00
	Core Tablet Total	**600.00**	**100.000**

Manufacturing Process:

1 Sift Quetiapine fumarate, lactose monohydrate, cutina HR PH, Eudragit L100-55 and mix in a high shear granulator.

2 Granulate the mix of step 1 using the Eudragit L 30 D-55 dispersion in high shear granulator.

3 Dry the granules and size.

4 Blend the granules of step 3 and extragranular ingredients in suitable non shear blender.

5 Compress the blend to tablets using suitable tooling.

Table 8 **List of ingredients for the formulation of quetiapine tablets according to a preferred embodiment (Example 8)**

S.N.	Formulation	mg/tablet	% w/w
	INTRAGRANULAR		
1	Quetiapine Fumarate	230.26	38.38
2	Lactose Monohydrate 200M	72.00	12.00
3	Cutina HR PH	45.00	7.50
4	Eudragit L100-55	96.00	16.00
5	Eudragit L 30 D-55	36.00	6.00
	EXTRAGRANULAR		
6	Lactose Monohydrate (Flowlac 100)	114.74	19.12
7	Magnesium Stearate	6.00	1.00
	Core Tablet Total	**600.00**	**100.000**

Manufacturing Process:

1 Sift Quetiapine fumarate, lactose monohydrate, cutina HR PH, Eudragit L100-55 and mix in a high shear granulator.

2 Granulate the mix of step 1 using the Eudragit L 30 D-55 dispersion in high shear granulator.

3 Dry the granules and size.

4 Blend the granules of step 3 and extragranular ingredients in suitable non shear blender.

5 Compress the blend to tablets using suitable tooling.

Table 9 List of ingredients for the formulation of quetiapine tablets according to a preferred embodiment (Example 9)

S.N.	Formulation	mg/tablet	% w/w
	INTRAGRANULAR		
1	Quetiapine Fumarate	230.26	38.38
2	Lactose Monohydrate 200M	105.00	17.50
3	Cutina HR PH	30.00	5.00
4	Eudragit L100-55	90.00	15.00
5	Eudragit L 30 D-55	24.00	4.00
	EXTRAGRANULAR		
6	Lactose Monohydrate (Flowlac 100)	114.74	19.12
7	Magnesium Stearate	6.00	1.00
	Core Tablet Total	**600.00**	**100.000**

Manufacturing Process:

1 Sift Quetiapine fumarate, lactose monohydrate, cutina HR PH, Eudragit L100-55 and mix in a high shear granulator.

2 Granulate the mix of step 1 using the Eudragit L 30 D-55 dispersion in high shear granulator.

3 Dry the granules and size.

4 Blend the granules of step 3 and extragranular ingredients in suitable non shear blender.

5 Compress the blend to tablets using suitable tooling.

Table 10 List of ingredients for the formulation of quetiapine tablets according to a preferred embodiment (Example 10)

S.N.	Formulation	mg/tablet	% w/w
	INTRAGRANULAR		
1	Quetiapine Fumarate	230.26	38.38
2	Lactose Monohydrate 200M	84.00	14.00
3	Cutina HR PH	30.00	5.00
4	Eudragit L100-55	120.00	20.00
5	Eudragit L 30 D-55	24.00	4.00
	EXTRAGRANULAR		
6	Lactose Monohydrate (Flowlac 100)	105.74	17.62
7	Magnesium Stearate	6.00	1.00
	Core Tablet Total	**600.00**	**100.000**

Manufacturing Process:

1 Sift Quetiapine fumarate, lactose monohydrate, cutina HR PH, Eudragit L100-55 and mix in a high shear granulator.

2 Granulate the mix of step 1 using the Eudragit L 30 D-55 dispersion in high shear granulator.

3 Dry the granules and size.

4 Blend the granules of step 3 and extragranular ingredients in suitable non shear blender.

5 Compress the blend to tablets using suitable tooling.

Table 11 ***List of ingredients for the formulation of quetiapine tablets according to a preferred embodiment (Example 11)***

S.N.	Formulation	mg/tablet	% w/w
	INTRAGRANULAR		
1	Quetiapine Fumarate	230.26	38.38
2	Lactose Monohydrate 200M	105.00	17.50
3	Cutina HR PH	30.00	5.00
4	Eudragit L100-55	96.00	16.00
5	Eudragit L 30 D-55	48.00	8.00
	EXTRAGRANULAR		
6	Lactose Monohydrate (Flowlac 100)	72.74	12.12
7	Talc	12.00	2.00
8	Magnesium Stearate	6.00	1.00
	Core Tablet Total	**600.00**	**100.000**

Manufacturing Process:

1 Sift Quetiapine fumarate, lactose monohydrate, cutina HR PH, Eudragit L100-55 and mix in a high shear granulator.

2 Granulate the mix of step 1 using the Eudragit L 30 D-55 dispersion in high shear granulator.

3 Dry the granules and size.

4 Blend the granules of step 3 and extragranular ingredients in suitable non shear blender.

5 Compress the blend to tablets using suitable tooling.

Table 12 List of ingredients for the formulation of quetiapine tablets according to a preferred embodiment (Example 12)

S.N.	Formulation	mg/tablet	% w/w
	INTRAGRANULAR		
1	Quetiapine Fumarate	230.26	38.38
2	Lactose Monohydrate 200M	225.74	37.62
3	Cutina HR PH	30.00	5.00
4	Eudragit L100-55	36.00	6.00
5	Eudragit L 30 D-55	60.00	10.00
	EXTRAGRANULAR		
6	Talc	12.00	2.00
7	Magnesium Stearate	6.00	1.00
	Core Tablet Total	**600.00**	**100.000**

Manufacturing Process:

1 Sift Quetiapine fumarate, lactose monohydrate, cutina HR PH, Eudragit L100-55 and mix in a high shear granulator.

2 Granulate the mix of step 1 using the Eudragit L 30 D-55 dispersion in high shear granulator.

3 Dry the granules and size.

4 Blend the granules of step 3 and extragranular ingredients in suitable non shear blender.

5 Compress the blend to tablets using suitable tooling.

Dissolution Profiles of Examples 6 to 12 and Seroquel XR (Lot No. TM0047)
Conditions:

Apparatus 1 (USP baskets)
Speed: 100 rpm
Time 1 hours in 1000mL of 0.1N HCl (1.2 pH)
Time 2 hours in 1000mL of 4.5 pH acetate buffer
Time 4-20 hours in 1000mL of 6.8 pH phosphate buffer

Time (Hr)	Average Percentage Release (%)								Apparatus I Baskets at 100 rpm
	Seroquel XR TM0047	Ex. 6	Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11	Ex. 12	
0	0	0	0	0	0	0	0	0	0.1 N HCl
1	21	28	41	34	47	35	31	33	
2	27	32	47	40	55	42	36	37	4.5 pH acetate buffer
4	34	38	53	46	61	47	41	44	6.8 pH phosphate buffer
5	30	42	56	49	65	51	45	47	
6	47	45	59	52	68	55	49	50	
8	59	51	65	59	74	62	55	57	
12	80	62	75	70	84	73	68	69	
16	94	72	–	79	91	83	79	79	
20	100	82	–	86	97	91	88	87	

Examples 5, 6 and 8 to 12 are examples of the preferred embodiments of the present invention, wherein the at least one hydrophobic controlled release agent and at least on pH dependent polymer are present at a weight % ratio of about 1:3 to about 1:7, and the dosage forms provide a dissolution of quetiapine or a pharmaceutically acceptable salt thereof, that is within the preferred dissolution profile as discussed above.

CLAIMS

1. A stable controlled release pharmaceutical dosage form comprising:

- intragranular excipients comprising:

- quetiapine or a pharmaceutically acceptable salt thereof,

- at least one hydrophobic controlled release agent,

- at least one pH dependent polymer, and

- extragranular excipients comprising at least one pharmaceutically acceptable excipient, wherein the hydrophobic controlled release agent is hydrogenated castor oil.

2. The controlled release pharmaceutical dosage form according to claim 1, wherein the content (in % by weight) of the hydrogenated castor oil is in the range from 4.5% to 35% and the content of the at least one pH dependent polymer is in the range from 15% to 35%.

3. The controlled release pharmaceutical dosage form according to claim 1 or 2, wherein the ratio of the % by weight content between the at least one hydrophobic controlled release agent and the at least one pH dependent polymer ranges from 1:3 to 1:7.

4. The controlled release pharmaceutical dosage form according to claim 1 or 2, wherein the ratio of the % by weight content between the at least one hydrophobic controlled release agent and the at least one pH dependent polymer ranges from 1:4 to 1:6.

5. The controlled release pharmaceutical dosage form according to claim 1 or 2, wherein the ratio of the % by weight content between the at least one hydrophobic controlled release agent and the at least one pH dependent polymer ranges from 1:4.5 to 1:5.5.

6. The controlled release pharmaceutical dosage form according to any one of claims 1 to 5, wherein the at least one hydrophobic controlled release agent further comprises stearic acid.

7. The controlled release pharmaceutical dosage form according to any one of claims 1 to 6, wherein the pH dependent polymer is a methacrylic acid copolymer and is present in an amount ranging from 15% to 35 % w/w of the total pharmaceutical composition.

8. The controlled release pharmaceutical dosage form according to any one of claims 1 to 6, wherein the pH dependent polymer is a Poly(methacrylic acid-co-ethyl acrylate) 1:1 and is present in an amount ranging from 15% to 35 % w/w of the total pharmaceutical composition.

9. The stable controlled release pharmaceutical dosage form according to any one of claims 1 to 8, wherein said dosage form provides a dissolution of quetiapine or pharmaceutically acceptable salt thereof from 30% to 45 % within 1 hour, from 45% to 70 % within 6 hours; from 75% to 95 % within 16 hours as measured by USP Apparatus I (basket) at 100 rpm, in 1000 mL of 0.1N HCl (1.2 pH) for the first hour, in 1000 mL of 4.5 pH acetate buffer for the 2 hours and subsequently in 1000 mL of 6.8 pH phosphate buffer.

10. The stable controlled release pharmaceutical dosage form according to any one of claims 1 to 8, wherein said dosage form provides a dissolution of quetiapine or pharmaceutically acceptable salt thereof from 50% to 60 % (by wt) of quetiapine or pharmaceutically acceptable salt thereof released after 2 hours, from 60% to 70 % (by wt) after 4 hours; from 65% to 80 % (by wt) of quetiapine or pharmaceutically acceptable salt thereof released after 8 hours, from 70% to 80 % (by wt) of quetiapine or pharmaceutically acceptable salt thereof released after 12 hours, and over 75 % (by wt) of quetiapine or pharmaceutically acceptable salt thereof released after 16 hours, as measured by USP Apparatus I (basket) method at 200 rpm, at 1000 ml aqueous buffer pH 1.2 from 0 to 2 hours and pH 6.8 from 4 to 20 hours at 37°C.