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(54) **Title**: ORAL PHARMACEUTICAL COMPOSITION OF OLANZAPINE FORM 1

(57) **Abstract**: The present invention relates to a stable pharmaceutical composition for the oral administration of olanzapine that comprises olanzapine Form 1 or one of its pharmaceutically acceptable salts thereof, as active ingredient, which are stable to discoloration, degradation and exhibits dose uniformity.

ORAL PHARMACEUTICAL COMPOSITION OF OLANZAPINE FORM 1

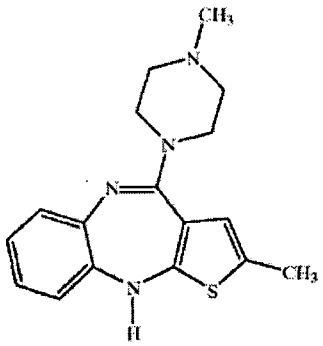
FILED OF THE INVENTION

The present invention relates to a new pharmaceutical composition for the oral administration of olanzapine or of one of its pharmaceutically acceptable salts.

In particular, the present invention relates to a stable pharmaceutical composition for the oral administration of olanzapine that comprises olanzapine Form 1 or one of its pharmaceutically acceptable salts thereof, as active ingredient, which are stable to discoloration, degradation and exhibits dose uniformity.

BACK GROUND

Olanzapine (2-mehtyl-4-(4-mehtly-1-piperazinyl)-10 H-thieno [2, 3 - b] [1, 5] benzodiazepine) belongs to the class of drugs known as thienobenzodiazepine of formula



that acts as an antagonist on dopamine receptors D1, D2, D3, D4 and D5; of serotonin 5-HT2 and 5-HT3; alpha-1-adrenergics, cholinergic and H1 histaminergics. It is indicated for the management of the manifestations of psychotic disorders and for the short-term treatment of acute manic episode associated with Bipolar I disorder. Olanzapine is market in several dosages (2.5, 5, 7.5, 10, 15 mg) for oral administration. The market final forms include coated tablets and quick dissolvable tablets.

Olanzapine and its application as a pharmaceutical have been suggested in **EP 454436** (herein after referred to as EP '436) and corresponding **US 5,229,382**. This patent does not refer to or identify any specific crystalline form of olanzapine.

Later, it became known through **EP 733635/US 5,736,541** (herein after referred to as EP '635) that olanzapine base may exist in various crystalline modifications and in hydrated/solvated forms that are stable at ambient conditions. The term 'olanzapine Form I' was later designated in EP '635 to the anhydrous olanzapine product that was stated to be obtainable according to the process of EP '436. EP '635 discloses olanzapine Form II which appears to be more stable than Form I, but is convertible to Form I.

EP '635 observes that olanzapine Form I is metastable in nature therefore prone to discoloration and degradation. Olanzapine Form I typically exhibit a colour which is undesirable for commercial pharmaceutical use, especially since the colour was found to change over time on exposure to air. Since olanzapine Form II is more stable than Form I, it is chemically stable and has satisfactory colour stability. However, Form II is rather difficult to prepare in substantially pure Form that is free from Form I or solvates.

The original olanzapine patent i.e., EP '436 describes that pharmaceutical compositions can be prepared by using conventional techniques. However, **EP 733367/US 5,919,485** (herein after referred to as EP '367) indicates that the known olanzapine tablets had the tendency to discolour, which can be especially problematic to a psychotic patient. In EP '367 applicants discovered that olanzapine undergoes discolouration when contacted with certain excipients including powder blends and discoloration enhances under ambient conditions of the air, at high temperatures and in wet environments. EP '367 attempts to address this problem by coating the solid oral formulation with a polymer. It is especially preferred that the formulation contain the most stable Form II of olanzapine. The process for the

preparation of the formulation comprises the steps of wet granulation, drying, blending with additional excipients and compression. The obtained cores are first sub-coated with hydroxypropyl methyl cellulose in order to avoid a direct contact of the active ingredient with polyethylene glycol and subsequently coated with a coating suspension. In the description it is pointed out that olanzapine may form an undesired crystal form in the presence of certain solvents and excipients, therefore it is desired to prepare the formulation using a method which does not require dissolution of the Olanzapine substance. They believe that a dry blend direct compression process or a dry granulation process for preparing solid oral formulations create a greater chance for poor dose uniformity to occur. In the light of the potent nature of olanzapine, consistent dose uniformity is imperative therefore they used high-shear aqueous wet granulation with fluid bed drying as the most effective method for preparing pharmaceutically elegant and stable oral olanzapine formulations. Though the presence of solvents can cause undesirable conversions they could not avoid the use of wet granulation.

EP 0830858 and published **US application 2001/0020032** also relates to solving the discoloration problem of olanzapine tablets. The formulation of the invention preferably contains the most stable Form II of olanzapine. Instead of the tablet being coated, however, here the olanzapine powder is coated with a polymer to protect it from discolouration. The technique is especially useful in making granules which can be compressed into tablets. The examples use wet granulation.

WO 2004/035027 recites an olanzapine pharmaceutical composition comprising a homogeneous mixture of (a) olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient, (b) a monosaccharide and/or oligosaccharide, and (c) a polysaccharide. The composition can additionally contain a binder, disintegrant, and a lubricant. Preferably the composition is an uncoated tablet which is preferably prepared by direct compression. The tablets are reported as being stable and not suffering from discoloration. According to this

publication, the discoloration is caused by the conversion of olanzapine into olanzapine hydrates but this could be prevented by homogenously mixing the olanzapine with certain excipients and then performing direct compression. The dose uniformity is stated to be excellent despite the use of direct compression.

WO 2005/0009407 discloses olanzapine pharmaceutical compositions that are also supposed to be stable against discoloration. The proposal involves coating olanzapine particles or powder with a coating that includes lactose and/or mannitol and optionally other excipients. The coated olanzapine particles can be formulated into granules or tablets. The examples use a number of excipients (seven or eight including typically two kinds of microcrystalline cellulose) and steps (a coating step and wet granulation step, etc) before obtaining granules ready for tabletting or filling into capsules.

WO 2007/134845 attempts stabilizing olanzapine pharmaceutical composition using anhydrous calcium hydrogen phosphate as the main excipient. It attempts to reduce the amount of the lactam impurity formed during prolonged storage of olanzapine compositions due to the presence of water in the composition and the micro environmental pH of the composition by using large amounts of anhydrous calcium hydrogen phosphate.

Therefore, there still remains a need for a stable pharmaceutical composition comprising olanzapine, particularly Form I olanzapine which efficiently address the colour stability and dose uniformity in a simple and effective way. It is desirable to form an olanzapine tablet that does not need a special coating or excipients to maintain an ambient environment for the tablet to remain stable and that preferably avoid significant discolouration upon storage and as well provides dose uniformity. The present invention successfully solves the problem of stabilizing Form I olanzapine and achieving dose uniformity.

SUMMARY

The present invention provides a pharmaceutical composition of olanzapine that has good stability to discoloration, degradation and has good dose uniformity.

Accordingly, a first aspect of the invention relates to a stable, scalable, homogenous solid oral pharmaceutical composition comprising 3 to 5% by weight of the total composition of olanzapine, preferably Form I olanzapine, or one of its pharmaceutically acceptable salts thereof and pharmaceutically acceptable excipients. The pharmaceutically acceptable excipients are selected from the group consisting of a diluent, glidant, binder, lubricant and mixtures thereof.

In particular, the pharmaceutical composition comprising 3 to 5% of Form I olanzapine, lactose anhydrous, mannitol, hydroxyl propyl cellulose, sodium starch glycolate and magnesium stearate.

The pharmaceutical composition can be formed into a film coated tablet having a weight of 50 mg, 100 mg, 150 mg, 200 mg, 300 mg and 400 mg or an orodispersible tablet having a weight of 100 mg, 200 mg, 300 mg and 400 mg.

In addition to development of the scalable and direct compression formulation across all strength, the present inventors have identified that the presence of sodium starch glycolate as one of the excipient is important to achieve a homogenous formulation having dose uniformity.

The present inventors have found surprising effect on the stability of the colouration and degradation of the olanzapine of Form I when the formulation contains 3 to 5% by weight of the total composition of olanzapine, in addition to improving the dose uniformity of said formulation by using sodium starch glycolate as one of the pharmaceutically acceptable excipients.

In another aspect of the invention there is provided a process for the preparation of the pharmaceutical composition that is stable to discoloration, degradation and has good dose uniformity. The process involves

(a) Co-sifting olanzapine, mannitol and sodium starch glycolate ;
(b) Separately sifting lactose and hydroxy propyl cellulose;
(c) Mixing the material of step (a) and (b);
(d) Lubricating the blend of step (c) and ;
(e) Compressing the blend of step (d) into tablets.

These and other aspects, features and advantages of the present invention will become better understood with reference to the following description and claims.

DESCRIPTION

The present invention has the object of solving the problem of colour stability, degradation and dose uniformity of formulation that contains Form I olanzapine by providing a particular drug to excipients proportion.

Number of attempts have been made, as evident in prior art, to avoid the degradation of olanzapine in the formulation. It has been studied that olanzapine Form I and pharmaceutical dosage Forms compounded with Form I were found to be sensitive to acid hydrolysis and oxidative degradation which are triggered specifically by temperature and light. Therefore formulating a pharmaceutical composition using Form I and stabilizing the same in order to control the degradation is a challenge.

Several experiments were carried out by the present inventors in order to achieve a stabilized pharmaceutical composition of olanzapine Form 1 wherein it

was surprisingly observed that the drug to excipients proportion played a vital role in stabilizing the formulation. It was found that composition having a particular drug to excipient ratio have low tendency to degrade and to change color.

It was studied that since olanzapine polymorphic form-1 is a metastable form and prone to oxidative degradation pathways along with discoloration, therefore compounding them into a tablet formulation containing excipients exacerbate the oxidative degradation of the compound. Therefore in order to minimize the effect of excipients on the stability of the formulation it becomes necessary to reduce the olanzapine particle to excipient particle contact which was found to be best achieved only in composition wherein olanzapine concentration was found to be 3 to 5% by weight of the total composition, owing to which the deaminated oxidative impurity concentration was found to be least.

It was further observed by the present inventors that the stable pharmaceutical composition of olanzapine, which does not show any degradation and undesired discoloration, can be prepared with an excellent dose uniformity in a simple direct compression process by using sodium starch glycolate as one of the excipients. In view of the fact that sodium starch glycolate is commonly used for the manufacturing of tablets, the finding that it allows the production of uniform dose of olanzapine formulation was totally unexpected.

The most obvious advantage of direct compression is economy. Savings can occur in a number of areas including reduced processing time and thus reduced labour costs, fewer manufacturing steps and pieces of equipment, less process validation, and a lower consumption power.

It has been studied that the commercially available olanzapine product (e.g., Zyprexa) is chemically stable due to olanzapine Form II been used in the formulation. As available in the prior art, olanzapine crystalline polymorphic Form

II is the stable polymorph compared to Form I which is metastable in nature therefore prone to discoloration and degradation.

It was been studied that in order to formulate Olanzapine tablets using Form 1 polymorphic Form it is necessary to stabilize the same so that they meet the quality standards of the commercially available products.

The present invention explains the vital role of the drug to excipient ratio for the stabilization of the formulation and minimizes the generation of the potential degradants formed during the stability studies of the drug product.

Accordingly, the first embodiment of the invention relates to a stable, scalable, homogenous solid oral pharmaceutical composition comprising olanzapine, preferably Form I olanzapine, or one of its pharmaceutically acceptable salts thereof and pharmaceutically acceptable excipients wherein the olanzapine constitute about 3 to 5% by weight of the total composition.

The pharmaceutically acceptable salts of olanzapine are those e.g. disclosed in EP 0454436.

The pharmaceutically acceptable excipients are selected from the group consisting of a diluent, glidant, binder, lubricant, bulk density modifier and mixtures thereof.

Suitable diluents are lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate and magnesium stearate. The diluent constitute 38-88% by weight of the total composition.

Suitable glidants / lubricants are colloidal silicon dioxide, talc, magnesium carbonate, magnesium stearate, cellulose, starch and calcium phosphate. The glidants/lubricant constitutes 1% by weight of the total composition.

Suitable binders are microcrystalline cellulose, hydroxy propyl cellulose, and copovidone. The binder constitutes 2.5% by weight of the total composition.

Suitable bulk density modifier is Sodium Starch Glycolate. The said excipient constitutes 1% by weight of the total composition.

In particular, the pharmaceutical composition comprising 3 to 5% by weight of the total composition of Form I olanzapine, lactose anhydrous, mannitol, hydroxyl propyl cellulose, sodium starch Glycolate and magnesium stearate.

In a preferred embodiment of the invention, the pharmaceutical composition comprises

3 to 5% of Form I olanzapine,
88 to 38% of lactose anhydrous,
5% of mannitol,
2.5% of hydroxyl propyl cellulose,
1% of sodium starch glycolate and
1% of magnesium stearate.

Tablets can be made from the final dosage Form of the composition. The tablet may either be a film coated tablet or an orodispersible. The term 'coated olanzapine' as used herein refers to olanzapine powder coated by at least one excipient. The coating can be achieved by conventional technique. Protective coating of the tablets is, in essence, not necessary. If desired, a tablet may be film-coated to improve its appearance and handling using conventional film-coating materials and techniques. This technique comprises mixing suitable film forming

polymer with water to form dispersion and spraying the dispersion over the compressed tablets using suitable tablet coating machine.

Olanzapine is effective over a wide dosage range, the actual dose administered depending on the condition treated. For example, in the treatment of adult humans, dosages of from 0.25 to 50 mg, preferably 1 to 30 mg and most preferably 1 to 20 mg per day may be used. The preferred weight of the tablets is 50 to 1000 mg, most preferably 100 to 500 mg.

In the state of art it is stressed that due to the potent nature of olanzapine, consistent dose uniformity is imperative and that such uniformity is hardly obtained by direct compression. Dose uniformity (i.e., homothetic blend formulations) is imperative, because the same blend can be compressed at different tablet weights to achieve tablets of different strength. In this way the manufacturing process time and cost is reduced and also the process becomes less tedious and simplified. Owing to all such advantages of development of homothetic blend for film coated tablets (herein after called as FCT) of strengths 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg and orodispersible tablets (hereafter called as ODT) of strengths 5 mg, 10 mg, 15 mg and 20 mg respectively it was a challenge to the present inventors to formulate a homothetic blend for 6 strengths of FCT range and 4 strength of ODT range. During this development the tablet attributes/parameters were never compromised.

The present inventors surprisingly observed that homothetic blend could be possible only by improving the flow properties of active ingredient by co sifting it by excipients especially sodium starch glycolate. The bulk density of this blend was found to 0.672 g/ml. This bulk density was found to matching with the cosifting blend of lactose anhydrous and Hydroxy Propyl Cellulose which was 0.610 g/ml.

Sodium starch glycolate has been conventionally know to exhibit the property of a super disintegrant, stabilizer, dissolution aid for tablets/capsules/pellets and/or suspending vehicle. The property of sodium starch glycolate to improve the flow property of the poorly flow active materials, found by the present inventors, is novel and is not be obvious to a person skilled in the art. This property helped in achieving a homogenous formulation.

In another embodiment of the invention there is provided a process for the preparation of a stable, scalable homogenous solid oral pharmaceutical composition comprising olanzapine, preferably Form I olanzapine that is stable to discoloration, degradation and has good dose uniformity. The process involves

(a) Co-sifting olanzapine, mannitol and sodium starch glycolate ;

(b) Separately sifting lactose and hydroxy propyl cellulose;

(c) Mixing the material of step (a) and (b);

(d) Lubricating the blend of step (c) and ;

(e) Compressing the blend of step (d) into tablets.

In particular, the process comprises the following steps:

STEP 1: Dispense all excipients in double lined clear polythene bags and Olanzapine (Form 1) in clear double lined polythene bags.

STEP 2: Co – sift Olanzapine, Sodium Starch Glycolate and Mannitol through BSS Sieve no. 36 [425 micron size] and collect in double lined polythene bags.

STEP 3: Co – sift Lactose Anhydrous & Hydroxy Propyl Cellulose and pass through BSS Sieve no. 36 [425 micron size] and collect in the same double lined polythene bags containing sifted materials of Step 2.

STEP 4: Sift Magnesium Stearate through BSS Sieve no. 60 [250 micron size] and collect in double lined polythene bags.

STEP 5: Charge Step 3 materials in 50 L capacity Intermediate bulk container [IBC] and fit in bin blender and blend for 25 min at 18 ± 1 rpm.

STEP 6: Add material of Step No. 4 to materials of Step 5 present in IBC.

STEP 7: Blend the Step 6 materials for 3 min at 18±1 rpm.

STEP 8: Compress the Step 7 lubricated blend on a tablet press.

STEP 9: Coat the Step 8 core tablets using film coating dispersion

STEP 10: Pack the tablets of step 8 in Alu / Alu blister pack.

The following examples, without limiting the scope of the claimed invention, illustrate the vital role of the drug to excipient ratio for the stabilization of the composition.

EXAMPLES

The stability of the composition is determined by the generation of the potential degradants formed during the stability studies of the drug product. The potential degradants like N-oxide and deaminated oxidative impurity formed was found to be controlled in the composition wherein the olanzapine concentration in the said composition was 3 to 5 % by weight of total composition. In addition it was studied that the discoloration of the olanzapine with concentration between 3-5 % by weight of total composition were found to be negligible in comparison to the drug product with 2.5 %.

The experiments been carried to stabilize the formulation reveals that the drug to excipient ratio is very critical and important in developing a stable dosage form, meeting the quality standards of reference product.

Example No. 1 - Analysis of impurities in a composition containing 2.5% by weight of the total composition of olanzapine by a stability indicating related substances method:

Raw Materials	% w/w	mg per tablet
Olanzapine Form 1	2.50	2.50
Lactose anhydrous	88.00	88.00
Mannitol	5.00	5.00
Hydroxy Propyl Cellulose	2.50	2.50
Sodium starch glycolate	1.00	1.00
Magnesium stearate	1.00	1.00
Tablet wt.	100%	100 mg

Procedure :

Olanzapine, mannitol, lactose anhydrous, hydroxy propyl cellulose, sodium starch glycolate and magnesium stearate were sifter through suitable mesh and compressed into tablets and charged for open exposure stress degradation studies and for 1 month and in finished alu/alu pack at accelerated stability conditions. Samples were withdrawn at definite time intervals and subjected for analysis of impurities by a stability indicating related substances method. The results of individual and total impurities are tabulated here underwith.

Table No. 1: Open Exposure stress degradation at 40°C 75% RH (relative humidity)

Olanzapine film coated tablets 10 mg			
Batch No. OLA-10/33			
Details: 2.5% by weight of total composition of olanzapine			
Relative retention time (RRT)	**Initial**	**15 days**	**30 days**
0.33 (N-Oxide impurity)	0.03%	0.07%	0.08
0.4 (Desmethyl Impurity)	0.01%	0.03%	Below detection limit
0.60 (Amide Impurity)	0.02%	0.09%	0.14
0.63	0.02%	0.01%	Below detection limit
Total Impurities	0.13%	0.27%	--

Table no. 2:

Period/ Condition Details: 2.5% by weight of total composition of olanzapine Batch No. OLA-10/45	Related Substances	
	Amide Impurity [%] (at RRT 0.6)	Total Impurities [%]
Initial	0.03%	0.17%
1 Month at 40°C & 75 % RH	0.17%	0.36%
2 Month at 40°C & 75 % RH	0.28%	0.55%
3 Month at 40°C & 75 % RH	*	*
6 Month at 40°C & 75 % RH	*	*

* Since impurities at 2nd month were observed to be high, therefore 3rd and 6th month sample were not analyzed.

Example No. 2 - Analysis of impurities in a composition containing 3.57% by weight of the total composition of olanzapine by a stability indicating related substances method:

Raw Materials	**% w/w**	**mg per tablet**
Olanzapine Form 1	3.57	2.50
Lactose anhydrous	58.00	58.00
Mannitol	5.00	5.00
Hydroxy propyl Cellulose	2.50	2.50
Sodium starch glycolate	1.00	1.00
Magnesium stearate	1.00	1.00
Tablet wt.	100%	70 mg

Procedure :

Olanzapine, mannitol, lactose anhydrous, hydroxy propyl cellulose, sodium starch glycolate and magnesium stearate were sifter through suitable mesh and compressed into tablets and charged for open exposure stress degradation studies and for 1 month and in finished alu/alu pack at accelerated stability conditions. Samples were withdrawn at definite time intervals and subjected for analysis of impurities by a stability indicating related substances method. The results of individual and total impurities are tabulated here underwith.

Table No. 3 : Open Exposure stress degradation at 40°C 75% RH

Olanzapine film coated tablets 2.5 mg			
Batch No. OLA-10/51			
Details: 3.75% by weight of total composition of olanzapine			
Relative Retention time (RRT)	**Initial**	**15 days**	**30 days**
0.35 (N-Oxide Impurity)	0.03	0.05	0.03
0.46 (Desmethyl Impurity)	Below detection limit	0.02	0.03
0.60 (Amide Impurity)	0.08	0.06	0.11
0.64	0.02	0.04	Below detection limit

Table No. 4:

Period/ Condition Details: 3.75% by weight of total composition of olanzapine Batch No. OLA-10/51	Related Substances	
	Amide Impurity [%] (at RRT~ 0.6)	Total Impurities [%]
Initial	0.07	0.31
1 Month at 40°C & 75 % RH	0.10	0.36
3 Month at 40°C & 75 % RH	0.14	--

Example 3 - Analysis of impurities in a composition containing 5% by weight of the total composition of olanzapine by a stability indicating related substances method:

Raw Materials	% w/w	mg per tablet
Olanzapine Form 1	5.0	2.50
Lactose anhydrous	38.00	38.00
Mannitol	5.00	5.00
Hydroxy propyl Cellulose	2.50	2.50
Sodium starch glycolate	1.00	1.00
Magnesium stearate	0.5	1.00
Tablet wt.	100 %	50 mg

Procedure:

Olanzapine, Mannitol, lactose anhydrous, hydroxy Propyl cellulose, sodium starch glycolate and magnesium stearate were sifter through suitable mesh and compressed into tablets and charged for open exposure stress degradation studies for 1 month and in finished alu/alu pack at accelerated stability conditions. Samples were withdrawn at definite time intervals and subjected for analysis of impurities by a stability indicating related substances method. The results of individual and total impurities are tabulated here under with.

Table No. 5: Open Exposure stress degradation at 40°C 75% RH

Olanzapine film coated tablets 10 mg			
Batch No. OLA-10/53			
Details : 5% by weight of total composition of olanzapine			
RRT	**Initial**	**At 15 days**	**At 30 days**
0.37	0.03	0.05	0.05
0.4	0.01	Not detected	Not detected
0.46	0.02	0.02	0.02
0.63	0.02	0.03	0.08
Total Impurities	0.25	0.3	0.32

Table No. 6

i) Olanzapine film coated tablets 10 mg

Batch No. 298002	At 40°C & 75% RH		At 25°C & 60% RH	
Period/ Condition	Amide Impurity [%] (at RRT 0.6)	Total Impurities [%]	Amide Impurity [%] (at RRT 0.6)	Total Impurities [%]
Specification limits (as per ICH Norms)	0.5%	N/AP	0.5%	N/AP
Initial	0.03	0.21	0.030	0.214
3 Month	0.22	0.63	0.082	0.409
6 Month	0.315	0.709	0.096	0.421
9 Month			0.131	0.446
12 Month			0.171	0.475
18 Month			0.181	0.503
24 Month			0.232	0.536

ii) Olanzapine Orodispersible tablets 10 mg

Batch No. 297001	At 40°C & 75% RH		At 25°C & 60% RH	
Period/ Condition	Amide Impurity [%] (at RRT 0.6)	Total Impurities [%]	Amide Impurity [%] (at RRT 0.6)	Total Impurities [%]
Specification limits (as per ICH Norms)	0.5%	N/AP	0.5%	N/AP
Initial	0.017	0.180	0.017	0.180
3 Month	0.128	0.339	0.032	0.275
6 Month	0.250	0.542	0.046	0.274
9 Month			0.055	0.286
12 Month			0.062	0.324
18 Month			0.098	0.395
24 Month			0.127	0.500

Example 4 – Analysis of the dose uniformity of the composition:

The pharmaceutical composition is produced according to the method of the present invention and analyzed for its dose uniformity.

Samples from 10 different locations of blend	**Blend Uniformity Results (% Label claim)** (Acceptance criteria: Between 90 – 110%, RSD: NMT 5.0%)	
	Batch No. 298001	
	Blending time: 03 Minutes	**Blending time: 05 Minutes**
1	98.9	98.1
2	106.1	99.2
3	102.4	97.5
4	100.7	97.7
5	101.4	99.4
6	103.6	98.8
7	101.3	96.9
8	100.8	100.0
9	98.3	96.2
10	101.9	98.9
Mean	**101.5**	**98.3**
RSD	**2.19**	**1.20**

The above example illustrates that drug to excipient ratio plays a vital role in the stabilization of the composition. The degradation and discoloration of the olanzapine with concentration between 3-5 % by weight of total composition were found to be negligible in comparison to the drug product with 2.5 %. Further, as illustrated above, a homothetic blend of the composition was obtained by using sodium starch glycolate.

Each of the patents, patent applications mentioned herein above are incorporated herein by reference. The invention having been described it will be obvious that the same may be varied in many ways and all such modifications are contemplated as being within the scope of the invention as defined by the following claims.

CLAIMS:

1. A stable, scalable, homogenous solid oral pharmaceutical composition comprising olanzapine or one of its pharmaceutically acceptable salts thereof and pharmaceutically acceptable excipients wherein the olanzapine constitute about 3 to 5% by weight of the total composition.

2. The pharmaceutical composition as claimed in claim 1, wherein the said olanzapine is Form I olanzapine.

3. The composition as claimed in claim 1 or 2, wherein the pharmaceutically acceptable excipients are selected from the group consisting of a diluent, glidant/lubricant, binder and mixtures thereof.

4. The pharmaceutical composition as claimed in claims 1 to 3, wherein said diluent is lactose anhydrous and mannitol

5. The pharmaceutical composition as claimed in claims 1 to 3, wherein said glidant/lubricant is magnesium stearate

6. The pharmaceutical composition as claimed in claims 1 to 3, wherein said binder is hydroxy propyl cellulose.

7. The pharmaceutical composition as claimed in claims 1 to 3, wherein said bulk density modifier is sodium starch glycolate.

8. The pharmaceutical composition as claimed in claims 1 to 7, comprising
   3 to 5% of Form I olanzapine,
   88 to 38% of lactose anhydrous,
   5% of mannitol,
   2.5% of hydroxyl propyl cellulose,
   1% of sodium starch glycolate and
   1% of magnesium stearate.

9. The pharmaceutical composition as claimed in claims 1 to 8, wherein said composition is a tablet.

10. The pharmaceutical composition as claimed in claims 1 to 9, wherein said tablet is a film coated tablet.

11. The pharmaceutical composition as claimed in claim 10, wherein in said tablet has weight of 50 mg, 100 mg, 150 mg, 200 mg, 300 mg and 400 mg.

12. A process for the preparation of a stable oral pharmaceutical composition comprising olanzapine Form I, which comprises the steps of:
   (a) Co-sifting olanzapine, mannitol and sodium starch glycolate;
   (b) Separately sifting lactose and hydroxy propyl cellulose;
   (c) Mixing the material of step (a) and (b);
   (d) Lubricating the blend of step (c) and ;
   (e) Compressing the blend of step (d) into tablets.

13. Use of sodium starch glycolate as an excipient in the preparation of a pharmaceutical composition comprising olanzapine.