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(54) **Title:** STABLE DOSAGE FORM OF AN ANTIDEPRESSANT

(57) **Abstract:** The present invention relates to a stable solid dosage form comprising an anti-depressant compound. More particularly, the present invention relates to a stable solid dosage form comprising paroxetine HCl hemihydrate prepared by wet granulation process comprising lactose.

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STABLE DOSAGE FORM OF AN ANTIDEPRESSANT

Field of the invention

The present invention relates to a stable solid dosage form comprising an anti-depressant compound. More particularly, the present invention relates to a stable solid dosage form comprising paroxetine HCl hemihydrate prepared by wet granulation process comprising lactose.

Background of the invention

Paroxetine, disclosed in U.S Pat. No 4,007,196, is a serotonin re-uptake inhibitor useful for the treatment of psychiatric problems including depression, parkinson's disease, anxiety disorders, obsessive-compulsive disorders, panic disorder and post-traumatic stress disorder.

Chemically, paroxetine is (-)-trans-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)piperidine and is commercially marketed under the trade name Paxil® in the US and Seroxat® in other countries by GlaxoSmithKline. Commercially available paroxetine tablets contain paroxetine HCl hemihydrate as active ingredient and excipients such as dibasic calcium phosphate dihydrate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

According to the disclosure given in U.S. Pat. No 6,113,944, the commercially available tablets are prepared by wet granulation using water as solvent, where in paroxetine HCl, dibasic calcium phosphate dihydrate, sodium starch glycolate/ magnesium stearate, and hydroxypropyl methyl cellulose were granulated with water and lubricated with sodium starch glycolate/ magnesium stearate and finally film coated with opadry. The tablets prepared by wet granulation using water exhibited a color change i.e., formation of pink hue, which is highly undesirable. To overcome this discoloration problem US '944 patent teaches the preparation of paroxetine

tablets using processes such as dry granulation and direct compression without using water. However, using these methods there is less flexibility in excipient selection and possibility of formation of hard tablets.

Apart from this patent, there are few other patents/publications, which describes dosage forms containing paroxetine.

The development of pink hue involves the formation of a coloring impurity identified, as dimer A, as disclosed in US 2004/0067254. It is further disclosed that oxygen and aqueous environment also apparently needed to allow the dimer reaction to proceed. To over come this problem, this application describes the use of paroxetine mesylate in the composition, which is less prone to coloration problem than paroxetine HCl salts. This is done by controlling the pH to 6.5 or less.

US 2003/0144324 describes oral pharmaceutical dosage form comprising paroxetine hydrochloride, a binder selected from the group consisting of povidone and copovidone, and filler that is HCl free or non-hygroscopic. It is disclosed that paroxetine hydrochloride tablets are particularly susceptible to becoming soft during storage, especially under accelerated aging conditions. In order to improve the hardness of the tablet povidone and copovidone are used as binders. It is further disclosed that an effective amount of povidone stabilizes the anhydrous form by preventing water molecules from incorporating into a paroxetine hydrochloride anhydrous crystal to yield a hemihydrate crystal. However, US '324 does not disclose about the stabilization of paroxetine hydrochloride hemihydrate with povidone.

WO 2005/034954 describes composition of paroxetine prepared by wet granulation, using microcrystalline cellulose and other excipients. However, WO 02/069969 discloses use of microcrystalline cellulose as a filler and copovidone as binder, and discloses that the microcrystalline cellulose is the perfect excipient.

The above prior art references discloses apart from dry granulation and direct compression, wet granulation process using water or organic solvent and using excipients such as microcrystalline cellulose, povidone, copovidone. Microcrystalline cellulose, povidone and copovidone being hygroscopic can absorb varying amounts of moisture at low relative humidities. Further, microcrystalline cellulose is an insoluble excipient where as lactose is a water-soluble excipient and is preferred over microcrystalline cellulose.

In view of the above problems associated with the paroxetine in the prior art described above, still there exists a need to develop stable dosage forms of paroxetine avoiding discoloration and softening problems. During our continuous efforts to develop stable dosage form of paroxetine, we found that pink hue formation can be minimized and the stability can be improved when aqueous or non-aqueous solvent is used in the granulation process using lactose as diluent without using microcrystalline cellulose, povidone, and copovidone as excipient.

Surprisingly, it was observed that the use of lactose as diluent provided tablets which have an excellent hardness and breaking load, with release properties similar to the marketed dosage form. Further, the problem of pink hue development as seen in the Paxil® tablets prepared by wet granulation process is surprisingly not observed.

Objective of the invention

Accordingly, the main objective of present invention is to provide a stable solid dosage form of paroxetine hydrochloride hemihydrate.

Yet another objective of the present invention is to provide a solid dosage form of paroxetine hydrochloride hemihydrate in such a way that it will comply with the reference product in terms of *in vivo* parameters like bioequivalence and *in vitro* parameters like dissolution, disintegration, and etc.

Yet another objective of the present invention is to provide process for preparing stable solid dosage form of paroxetine.

Summary of the invention

According to the main embodiment of the present invention, there is provided a stable solid dosage form comprising paroxetine hydrochloride hemihydrate, lactose, and one or more pharmaceutically acceptable excipients prepared by wet granulation process, wherein the excipients are not microcrystalline cellulose, povidone, and copovidone.

Detailed description of the invention

The present invention provides stable dosage form of paroxetine hydrochloride hemihydrate, which does not develop pink hue upon storage.

In an embodiment of the present invention, the excipients used are selected from diluents, binders, disintegrants, and lubricants.

The wet granulation is always preferred over dry or direct compression, since uniform distribution of the active substance within the bulk granulates is achieved without difficulty and also flexibility in selection of excipients.

In another embodiment, the stable dosage form of paroxetine hydrochloride hemihydrate comprises excipients selected from about 70% to about 95% of diluent, about 1.5% to about 5% of disintegrant, about 2.5% to about 7.5% of binder and about 0.5% to about 3% of lubricant wherein the tablet is prepared by wet granulation using, aqueous, non-aqueous solvents or mixture thereof.

Suitable diluents of the present invention include lactose, sucrose, calcium phosphate-dibasic, calcium silicate, starch, polyols such as mannitol, sorbitol, xylitol, maltitol, or combination thereof.

Suitable disintegrating agents used in accordance with the present invention are selected from crosscarmellose sodium, sodium starch glycolate, sodium carboxymethyl cellulose, hydroxypropyl cellulose,

alginic acid, alginates, polacrilin potassium, and the like or combination thereof.

Suitable binders of the present invention include hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, gelatin, alginates, methylcellulose or starch.

Suitable lubricants of the present invention include sodium stearyl fumarate, magnesium stearate, hydrogenated vegetable oil, stearic acid, calcium stearate, glyceryl behenate, sodium lauryl sulfate, talc and the like.

The paroxetine hydrochloride hemihydrate compositions of the present invention are stable and do not substantially loose its hardness after storage at a temperature of about 80°C and a relative humidity of at least about 75% for at least about 24 hours.

In another aspect, the dosage form of the present invention includes tablets, capsules and powder for oral suspension. The tablets may be uncoated or optionally coated with film forming materials such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, sodium lauryl sulfate, talc, colloidal silica, sodium stearyl fumarate and the like.

In another embodiment of the present invention, there is provided a process for preparing stable solid dosage form comprising paroxetine hydrochloride hemihydrate, lactose, and one or more pharmaceutically acceptable excipients prepared by wet granulation process, wherein the excipients are not microcrystalline cellulose, povidone, and copovidone, comprises the steps of:

i) blending paroxetine hydrochloride hemihydrate with lactose, filler, and disintegrant,

ii) granulating the blend of step (i) using aqueous or non-aqueous solvent or mixture thereof,

iii) drying the granules obtained in step (ii) at 40°C,

iv) blending the dried granules with extragranular excipients,

v) lubricating the blended granules of step (iv) and

vi) compressing the lubricated blend into tablets or filled into capsules.

The aqueous or non-aqueous solvents used according to the present invention are selected from water, isopropyl alcohol, ethanol, acetone, methylene chloride and the like or mixture thereof.

In yet another embodiment, the present invention also provides method of treating depression, mixed anxiety and depression, obsessive compulsive disorders, panic disorder, obesity, senile dementia, migraine, bulimia, anorexia, social phobia and the depression arising from premenstrual tension and adolescence by administering the stable solid dosage form of the present invention.

The following examples further exemplify the invention and are not intended to limit the scope of the invention. It is obvious to those skilled in the art to find out the composition for other dosage forms and substitute the equivalent excipients as described in this specification or with the one known to the industry.

Example 1

Ingredients	Qty / tab (mg)
Paroxetine HCl hemihydrate	6.43 %
Dibasic calcium phosphate	85.09 %
Lactose monohydrate	5.2 %
Sodium starch glycolate	2.28 %
Magnesium stearate	1.0 %
Purified Water	Qs

Example 2

Ingredients	Qty / tab (mg)
Paroxetine HCl hemihydrate	6.43 %
Dibasic calcium phosphate	84.09 %
Lactose monohydrate	6.2 %
Sodium starch glycolate	2.28 %
Magnesium stearate	1.0 %

Purified Water	Qs
Ethanol	Qs

The processing steps involved in manufacturing solid dosage forms of paroxetine HCl hemihydrate as per the compositions given in examples 1 and 2 are given below:

i) paroxetine hydrochloride, dibasic calcium phosphate, lactose, and sodium starch glycolate were sifted and blended,

ii) granulated the blended material of step (i) with water or water/ethanol mixture and dried the granulated mass at 40°C,

iii) dried granules were blended with extragranular dibasic calcium phosphate and sodium starch glycolate for 15 min,

iv) lubricated the blended granules of step (iv) with magnesium stearate for 5 min.,

v) compressed the lubricated blend into tablets, and

vi) finally the tablets were coated with film forming materials.

Example 3

Ingredients	Qty / tab (mg)
Paroxetine HCl hemihydrate	6.43 %
Dibasic calcium phosphate	84.09 %
Lactose monohydrate	5.2 %
Low viscosity Hydroxypropyl cellulose	1.0 %
Sodium starch glycolate	2.28 %
Magnesium stearate	1.0 %
Purified Water	Qs

Example 4

Ingredients	Qty / tab (mg)
Paroxetine HCl hemihydrate	6.43 %
Dibasic calcium phosphate	45.29 %
Lactose monohydrate	44.0 %
Sodium starch glycolate	2.28 %

Low viscosity Hydroxypropyl cellulose	1.0 %
Water	Qs
Ethanol	Qs
Magnesium Stearate	1.0 %

The processing steps involved in manufacturing solid dosage forms of paroxetine HCl hemihydrate as per the compositions given in examples 3 and 4 are given below:

i) paroxetine hydrochloride, dibasic calcium phosphate, lactose, and sodium starch glycolate were sifted and blended,

ii) binder solution of low viscosity hydroxypropyl cellulose in water or water/ethanol mixture was prepared,

iii) granulated the blended material of step (i) with binder solution of step (ii) and dried the granulated mass at 40°C,

iv) dried granules were blended with extragranular dibasic calcium phosphate and sodium starch glycolate for 15 min,

v) lubricated the blended granules of step (iv) with magnesium stearate for 5 min.,

vi) compressed the lubricated blend into tablets, and

vii) finally the tablets were coated with film forming materials.

Example 5

Ingredients	**mg**
Paroxetine HCl hemihydrate	44.4
Dibasic calcium phosphate	160
Lactose monohydrate	20
Sodium starch glycolate	8
Purified water	Qs
Extra granular	
Dibasic calcium phosphate	234.6
Sodium starch glycolate	8
Magnesium stearate	5

Example 6

Ingredients	mg
Paroxetine HCl hemihydrate	33.3
Dibasic calcium phosphate	120
Lactose monohydrate	15
Sodium starch glycolate	6
Purified water	Qs
Extra granular	
Dibasic calcium phosphate	175.95
Sodium starch glycolate	6
Magnesium stearate	3.75

The processing steps involved in manufacturing solid dosage forms of paroxetine HCl hemihydrate as per the compositions given in examples 5 and 6 are given below:

i) paroxetine hydrochloride, dibasic calcium phosphate, lactose, and sodium starch glycolate were sifted and blended,

ii) granulated the blended material of step (i) with water and dried the granulated mass at 40°C,

iii) dried granules were blended with extragranular dibasic calcium phosphate and sodium starch glycolate for 15 min,

iv) lubricated the blended granules of step (iv) with magnesium stearate for 5 min.,

v) compressed the lubricated blend into tablets, and

Table 1 given below shows the dissolution profile of paroxetine tablets carried out in Simulated gastric fluid without enzymes as medium according to the procedure described in the USP, Apparatus USP II/900 ml, Paddle, @ 60 rpm speed. The release profile (% of drug released in minutes) is given in table 1.

Table 1

Time (min)	% Drug dissolved	
	Example 5	Example 6
10	54	53
20	78	79
30	87	91
45	92	96
60	95	98

Stability Data: Tablets of examples 5 and 6 were stored at 40°C/75%RH, for one, two, three and six months and then tested by an HPLC method to determine the amount of paroxetine hydrochloride hemihydrate. The data is given in table 2.

Table 2

Example 5					Example 6				
(%) of paroxetine hydrochloride hemihydrate									
Initial	**1M**	**2M**	**3M**	**6M**	**Initial**	**1M**	**2M**	**3M**	**6M**
97.5	97.5	96.1	96.0	97.0	96.3	97.9	98.4	96.8	96.5

Claims:

1. A stable solid dosage form comprising paroxetine hydrochloride hemihydrate, lactose, and one or more pharmaceutically acceptable excipients prepared by wet granulation process, wherein the excipients are not microcrystalline cellulose, povidone and copovidone.

2. The dosage form as claimed in claim 1, wherein the excipients are selected from about 70% to about 95% of diluent, about 1.5% to about 5% of disintegrant, about 2.5% to about 7.5% of binder and about 0.5% to about 3% of lubricant.

3. The dosage form as claimed in claim 2, wherein the diluent is selected from sucrose, calcium phosphate-dibasic, calcium silicate, starch, polyols such as mannitol, sorbitol, xylitol, maltitol, or combination thereof.

4. The dosage form as claimed in claim 2, wherein the disintegrant is selected from crosscarmellose sodium, sodium starch glycolate, sodium carboxymethyl cellulose, hydroxypropyl cellulose, alginic acid, alginates, polacrilin potassium or combination thereof.

5. The dosage form as claimed in claim 2, wherein the binder is selected from hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxyethyl cellulose, gelatin, alginates, methylcellulose or starch.

6. The dosage form as claimed in claim 2, wherein the lubricant is selected from sodium stearyl fumarate, magnesium stearate, hydrogenated vegetable oil, stearic acid, calcium stearate, glyceryl behenate, sodium lauryl sulfate or talc.

7. A process for preparing stable solid dosage form comprising paroxetine hydrochloride hemihydrate, lactose, and one or more pharmaceutically acceptable excipients prepared by wet granulation process, wherein the excipients are not microcrystalline cellulose, povidone, and copovidone comprises the steps of:

i) blending paroxetine hydrochloride hemihydrate with lactose, filler, and disintegrant,

ii) granulating the blend of step (i) using aqueous, non-aqueous solvents or mixture thereof,

iii) drying the granules obtained in step (ii) at 40°C,

iv) blending the dried granules with extra granular excipients,

v) lubricating the blended granules of step (iv) and

vi) compressing the lubricated blend into tablets or filled into capsules.

8. The dosage form as claimed in claim 7, wherein the aqueous or non-aqueous solvents are selected from water, isopropyl alcohol, ethanol, acetone, methylene chloride or mixtures thereof.

9. A method of treating depression, mixed anxiety and depression, obsessive compulsive disorders, panic disorder, obesity, senile dementia, migraine, bulimia, anorexia, social phobia and the depression arising from premenstrual tension and adolescence by administering the stable solid dosage form of paroxetine hydrochloride hemihydrate of claim 1.