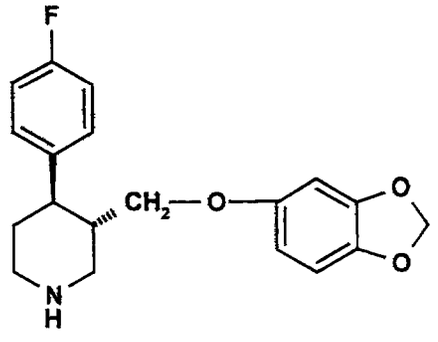
# NOVEL FORMULATION CONTAINING PAROXETINE

The present invention relates to novel formulations and to the use of the formulations in the treatment and/or prevention of certain disorders.

US Patent 4,007,196 describes certain compounds which possess anti-depressant activity. One specific compound mentioned in this patent is known as paroxetine and has the following formula:




This compound has been approved for human use and is marketed, in the form of its hydrochloride salt, in many countries around the world as an anti-depressant agent.

All paroxetine hydrochloride sold to date has been in the form of oral swallow tablets, containing the hemihydrate, which is described in EP-0 223 403. Paroxetine hydrochloride has been reported as also existing as an anhydrate. WO 96/24595 describes the preparation and physical properties of four different polymorphic forms (Forms A, B, C and D) of the anhydrate.

WO 95/16448 discloses that paroxetine is likely to develop a pink colour unless it is formulated into tablets using a formulation process in which water is absent, such as dry direct compression of paroxetine or dry granulation of paroxetine followed by compression into tablets. The term "dry" was used to denote substantially dry as opposed to the wholesale addition of water which had been previously employed in the wet granulation process.

It has now surprisingly been found that, even under these relatively dry conditions, paroxetine hydrochloride anhydrate has a tendency to convert at least partially to the hemihydrate during the tabletting process. Although not dangerous, this creates difficulties in establishing and maintaining a reference standard for regulatory and quality control purposes.

Accordingly, the present invention provides paroxetine hydrochloride, in a form other than the hemihydrate, which is formulated into tablets under conditions such there is no detectable conversion to hemihydrate during the tabletting process.

The paroxetine hydrochloride may, for example be amorphous or in the form of a crystalline anhydrate.

This can be achieved for example by the use of excipients which are essentially anhydrous. That is to say, they contain less than 2%, more especially less than 1.5%, preferably less than 1% water.

It has been found for example that dibasic calcium phosphate anhydrous can be used to form oral swallow tablets with paroxetine hydrochloride anhydrate without undesired conversion to hemihydrate during the tabletting process.

The tabletting process may for example comprise dry direct compression of paroxetine or dry granulation of paroxetine followed by compression into tablets. Preferably, the tablets are then packaged with a desiccant in order to prevent conversion of anhydrate to hemihydrate on storage.

Accordingly, the present invention also provides a process for the preparation of paroxetine hydrochloride anhydrate tablets free of detectable hemihydrate which is characterised by the use of conditions such there is no detectable conversion of the anhydrate to hemihydrate during the tabletting process. Such conditions can be achieved by the use of essentially anhydrous excipients. Advantageously, tabletting can also be carried out under conditions of low relative humidity

Examples of excipients with the necessary low moisture content suitable for direct compression include materials such as dibasic calcium phosphate anhydrous, anhydrous direct compression lactose, monosaccharide sugars eg mannitol, disaccharide sugars eg lactitol, powdered cellulose, pregelatinised starch and similar materials. Dibasic calcium phosphate anhydrous is commercially available in a pharmaceutically acceptable grade, eg A-TAB (Rhone Poulenc). Anhydrous direct compression lactose is commercially available in a pharmaceutically acceptable grade, eg anhydrous direct tabletting (Quest International Inc). Additionally, certain of the low moisture sugars available in direct compression grades eg mannitol and lactitol can improve the palatibility of the formulation by masking the bitter taste of paroxetine. Direct compression lactilol is commercially available in a pharmaceutically acceptable grade, eg Finlac DC (Xyrofin).

In a particular process of the invention, paroxetine hydrochloride anhydrate is mixed with dibasic calcium phosphate anhydrous, and/or anhydrous direct compression grade lactose(s), and/or microcrystalline cellulose (in particular A-TAB, lactose anhydrous direct tabletting, and Avicel PH112 dried to a moisture content of 0.8-1.5%) in a suitable blender. Other pharmaceutically acceptable excipients may also be added such as disintegrants eg sodium starch glycolate, croscarmellose sodium, and colloidal silicon dioxide (in particular Explotab (dried to a moisture content of < 2%), Ac-Di-Sol, and Syloid 244, respectively); lubricants such as magnesium stearate; and glidants such as colloidal silicon dioxide, and talc.

The composition is then mixed and compressed using standard pharmaceutical procedures. As an additional aid to the protection of this product from the deleterious affects of moisture the tablets can be film coated. Standard aqueous film coating is not appropiate for such a moisture sensitive product; however, the tablets can be coated with hydrophobic coating materials, such as glyceryl behenate, using a hot melt coating technique. In a particular process of the invention, tablet cores are coated with a 2% w/w of glyceryl behenate (in particular Compritol 888). 2% levels of glyceryl behenate do not adversely affect the dissolution of the dosage form in the gastric environment. Glyceryl behenate is commercially available in a pharmaceutically acceptable grade, eg Compritol 888 (Gattefosse). A modified aqueous film coating procedure using Opadry AMB (Aqueous Moisture Barrier) can also be utilised. In a particular process of the invention, tablet cores are coated with a 2% w/w of Opadry AMB. Opadry AMB is commercially available in a pharmaceutically acceptable grade, eg Opadry OY-B-31006 (Colorcon).

Coated tablets are then packaged in standard pharmaceutical container/closure presentations, optionally with a desiccant.

Typical compositional ranges of key excipients on a w/w basis are provided : Preferably the amounts of lubricants are in the range 0.5 to 2.0%, most preferably 0.5 to 1.0%. The disintegrants are controlled in the range 0.5 to 8.0%, most preferably 2.0 to 4.0%. Preferably the amounts of anhydrous diluents are controlled in the range 50.0 to 95.0%. Mixtures of the principal diluents can be used to assist in flow and compression properties of the formulation. Preferably the amounts of film coat are controlled in the range 1.0 to 3.0%, most preferably 2.0%.

The amount of paroxetine used is adjusted such that in a single unit dose there is a therapeutically effective amount of paroxetine. Preferably the unit dose contains from

10 to 100 mg paroxetine (as measured in terms of the free base). More preferable the amount of paroxetine in a unit dose is 10mg, 20mg, 30mg, 40mg or 50mg. The most preferred amount of paroxetine in a unit dose is 20mg.

Paroxetine used in the formulation is in the form of the hydrochloride anhydrate which may be prepared according to the procedures outlined in WO 96/24595. Suitable procedures for preparing paroxetine include those mentioned in US Patents 4,009,196, 4,902.801, 4,861,893 and 5,039.803 and PCT/GB 93/00721.

It has been mentioned that paroxetine has particular utility in the treatment of depression; paroxetine may also be used in the treatment of mixed anxiety and depression. obsessive compulsive disorders, panic, pain, obesity, senile dementia, migraine. bulimia. anorexia, social phobia and the depression arising from pre-menstrual tension and adolescence.

The present invention therefore also provides a method of treating or preventing any of the above disorders which comprises administering an effective or prophylactic amount of an oral swallow tablet prepared in accordance with the present invention.

The following examples illustrate the present invention:

**Example 1**

| | **mg** |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Dibasic Calcium Phosphate Anhydrous | 220.28 |
| Sodium Starch Glycolate | 5.00 |
| Magnesium Stearate | 2.50 |
| Tablet weight | 250.00 |

**Example 2**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Dibasic Calcium Phosphate Anhydrous | 171.78 |
| Sodium Starch Glycolate | 4.00 |
| Magnesium Stearate | 2.00 |
| Tablet weight | 200.00 |

**Example 3**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Dibasic Calcium Phosphate Anhydrous | 123.28 |
| Sodium Starch Glycolate | 3.00 |
| Magnesium Stearate | 1.50 |
| Tablet weight | 150.00 |

**Example 4**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Dibasic Calcium Phosphate Anhydrous | 224.03 |
| Croscarmellose Sodium | 1.25 |
| Magnesium Stearate | 2.50 |
| Tablet weight | 250.00 |

**Example 5**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Dibasic Calcium Phosphate Anhydrous | 225.28 |
| Magnesium Stearate | 2.50 |
| Tablet weight | 250.00 |

**Example 6**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Dibasic Calcium Phosphate Anhydrous | 224.03 |
| Colloidal Silicone Dioxide | 1.25 |
| Magnesium Stearate | 2.50 |
| Tablet weight | 250.00 |

**Example 7**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Dibasic Calcium Phosphate Anhydrous | 125.00 |
| Microcrystalline Cellulose | 95.28 |
| Sodium Starch Glycolate | 5.00 |
| Magnesium Stearate | 2.50 |
| Tablet weight | 250.00 |

**Example 8**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Dibasic Calcium Phosphate Anhydrous | 125.00 |
| Lactose Anhydrous | 95.28 |
| Sodium Starch Glycolate | 5.00 |
| Magnesium Stearate | 2.50 |
| Tablet weight | 250.00 |

**Example 9**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Lactose Anhydrous | 220.28 |
| Sodium Starch Glycolate | 5.00 |
| Magnesium Stearate | 2.50 |
| Tablet weight | 250.00 |

**Example 10**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Lactose Anhydrous | 171.78 |
| Sodium Starch Glycolate | 4.00 |
| Magnesium Stearate | 2.00 |
| Tablet weight | 200.00 |

**Example 11**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Lactose Anhydrous | 123.28 |
| Sodium Starch Glycolate | 3.00 |
| Magnesium Stearate | 1.50 |
| Tablet weight | 150.00 |

**Example 12**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Direct compression Lactitol | 220.28 |
| Sodium Starch Glycolate | 5.00 |
| Magnesium Stearate | 2.50 |
| Tablet weight | 250.00 |

**Example 13**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Lactose Anhydrous | 220.28 |
| Sodium Starch Glycolate | 5.00 |
| Magnesium Stearate | 2.50 |
| Compritol 888 | 2.50 |
| Tablet weight | 252.50 |

**Example 14**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Lactose Anhydrous | 171.78 |
| Sodium Starch Glycolate | 4.00 |
| Magnesium Stearate | 2.00 |
| Compritol 888 | 2.0 |
| Tablet weight | 202.00 |

**Example 15**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Lactose Anhydrous | 123.28 |
| Sodium Starch Glycolate | 3.00 |
| Magnesium Stearate | 1.50 |
| Compritol 888 | 1.50 |
| Tablet weight | 151.50 |

**Example 16**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Lactose Anhydrous | 220.28 |
| Sodium Starch Glycolate | 5.00 |
| Magnesium Stearate | 2.50 |
| Opadry AMB | 2.50 |
| Tablet weight | 252.50 |

**Example 17**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Lactose Anhydrous | 171.78 |
| Sodium Starch Glycolate | 4.00 |
| Magnesium Stearate | 2.00 |
| Opadry AMB | 2.0 |
| Tablet weight | 202.00 |

**Example 18**

| | mg |
|---|---|
| Paroxetine hydrochloride † | 22.22 |
| Lactose Anhydrous | 123.28 |
| Sodium Starch Glycolate | 3.00 |
| Magnesium Stearate | 1.50 |
| Opadry AMB | 1.5 |
| Tablet weight | 151.50 |

† Equivalent to 20 mg of Paroxetine on an anhydrous free base basis

**Claims**

1. Paroxetine hydrochloride, in a form other than the hemihydrate, which is formulated into tablets under conditions such there is no detectable conversion to hemihydrate during the tabletting process.

2. Paroxetine hydrochloride according to claim 1 which is amorphous or in the form of a crystalline anhydrate.

3. A process for the preparation of paroxetine hydrochloride tablets free of detectable hemihydrate which is characterised by the use of conditions such there is no detectable conversion to hemihydrate during the tabletting process.

4. A process according to claim 3 which comprises dry direct compression of paroxetine or dry granulation of paroxetine followed by compression into tablets.

5. A process according to claim 3 or 4 which is carried out using essentially anhydrous excipients.

6. A process according to claim 5 wherein the excipients are chosen from the group consisting of dibasic calcium phosphate anhydrous, anhydrous direct compression lactose, monosaccharide sugars, disaccharide sugars, powdered cellulose, and pregelatinised starch.

7. A process according to any one of claims 3 to 6 which is carried out under conditions of low relative humidity.

8. A process according to any one of claims 3 to 7, further comprising the application of a non-aqueous film coating.

9. A kit of parts comprising tablets according to claim 1or 2 or obtainable by the process of any one of claims 3 to 8, together with a desiccant.