Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2274389 C 2004/09/14

(11)(21) 2 274 389

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(22) Date de dépôt/Filing Date: 1994/12/14

(41) Mise à la disp. pub./Open to Public Insp.: 1995/06/22

(45) Date de délivrance/Issue Date: 2004/09/14

(62) Demande originale/Original Application: 2 214 575

(30) Priorité/Priority: 1993/12/15 (9325644.4) GB

(51) Cl.Int.^{6}/Int.Cl.^{6} A61K 31/445, A61K 9/20

(72) Inventeurs/Inventors:
PATHAK, RAM DUTTA, GB;
DOUGHTY, DAVID GEORGE, GB

(73) Propriétaire/Owner:
SMITHKLINE BEECHAM P.L.C., GB

(74) Agent: GOWLING LAFLEUR HENDERSON LLP

(54) Titre : COMPRIMES DE PAROXETINE ET PROCEDE DE PREPARATION
(54) Title: PAROXETINE TABLETS AND PROCESS TO PREPARE THEM

(57) Abrégé/Abstract:
Paroxetine which is formulated into tablets using a formulation process in which water is absent.

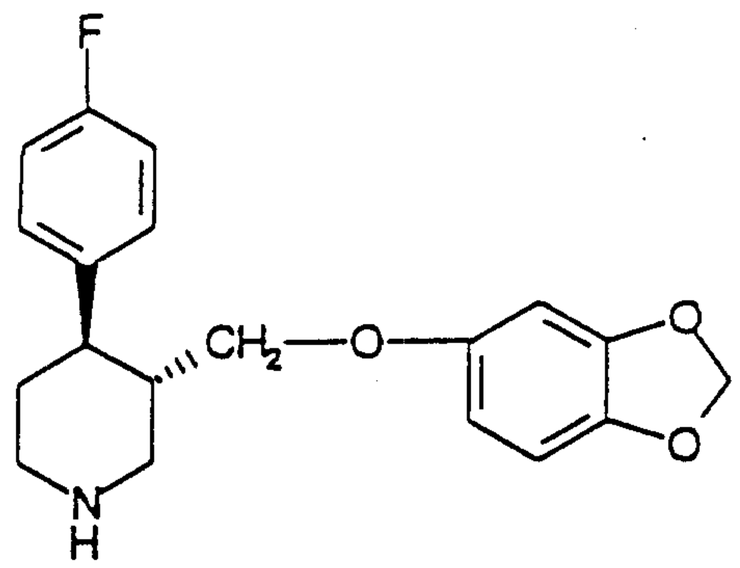
ABSTRACT

Paroxetine which is formulated into tablets using a formulation process in which water is absent.

Paroxetine tablets and process to prepare them

The present invention relates to novel formulations and to the use of the formulation 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 which has the following formula:



This compound has been approved for human use and is being sold in many countries around the world as an anti-depressant agent.

It has been noticed that tablets of paroxetine often develop a pink hue which is highly undesirable.

To date, all tablets which have been sold have been formulated using an aqueous granulation process. It has surprisingly been found that formulation of paroxetine into tablets can be carried out reliably and on a commercial scale using a formulation process in which water is absent, such as by direct compression or by dry granulation.

It has also been surprisingly found that paroxetine formulated into a tablet using a process in which water is absent, is much less likely to develop a pink hue.

Accordingly, the present invention provides paroxetine which is formulated into tablets using a formulation process in which water is absent.

Examples of such a formulation process are dry direct compression of paroxetine or dry granulation of paroxetine followed by compression into tablets. The present invention therefore provides a formulation comprising direct compressed paroxetine admixed with dry excipients in the form of a tablet and a formulation comprising dry granulated and compressed paroxetine admixed with dry excipients in the form of a tablet.

It should be appreciated that the term "dry" means substantially "dry" as opposed to the wholesale addition of water which was previously employed in the wet granulation process.

Direct compression techniques are generally known in the art of pharmaceutical science. For example, paroxetine is conventionally admixed with dry excipients and compressed into tablets.

Dry granulation techniques are generally also known in the art of pharmaceutical science. For example, paroxetine is conventionally admixed with dry excipients and compressed into large slugs or roller compacted into ribbon-like strands. The compacted material is then suitably milled to produce a free flowing powder which is then compressed into tablets.

Additional excipients may then be added and mixed with the free flowing powder before being compressed into tablets.

Examples of excipients include calcium phosphate, microcrystalline cellulose, sodium starch glycollate and magnesium stearate which may be admixed in appropriate ratios.

It should be appreciated that particularly good results are obtained when microcrystalline cellulose is absent from the formulation, this is surprising as tablets formulated in the absence of microcystalline cellulose are often prone to breaking up during manufacture or storage.

The paroxetine/excipient mixture may be compressed into an appropriate tablet shape. Preferred shapes include a pentagonal circumcircle, oval, round bi-convex or a tilt-tablet such as those described in US Patent 4,493,822.

Paroxetine when incorporated into the above-mentioned tablets is suitably, present as the hydrochloride hemi-hydrate form which may be prepared according to the procedures outlined in US Patent 4,721,723.

The amount of paroxetine present in the above-mentioned tablets is in the range of 10 to 100 mg of paroxetine as measured in terms of the "free base". Particularly preferred amounts include 10 mg, 20 mg, 30 mg, 40 mg and 50 mg of paroxetine as measured in terms of the "free base". Particularly preferred amounts include 20 mg, 30 mg and 40 mg of paroxetine as measured in terms of the "free base".

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 **WO 93/22284**.

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

prophylatic amount to a sufferer in need thereof of paroxetine which is formulated into a tablet using a process in which water is absent.

The present invention further provides a pharmaceutical composition comprising paroxetine which is formulated into a tablet using a process in which water is absent for use in treating or preventing of the above disorders.

The present invention further provides the use of paroxetine which is formulated into a tablet using a process in which water is absent in the manufacture of a medicament for treating or preventing the above disorders.

The following examples illustrate the present invention:

Example 1

INGREDIENTS	**20 mg Tablet**	**30mg Tablet**
Paroxetine hydrochloride hemihydrate	22.67 mg	34.0 mg
Dicalcium Phosphate (DCP)	83.34 mg	125.0 mg
Microcrystalline Cellulose	50.67 mg	76.0 mg
Sodium Starch Glycollate	8.34 mg	12.5 mg
Magnesium Stearate	1.67 mg	2.5 mg
Tablet Weight	**166.7 mg**	**250.0 mg**

Commercial source of the ingredients

Dicalcium Phosphate Dihydrate	-	Emcompress or Ditab*
Microcrystalline Cellulose	-	Avicel PH 102*
Sodium Starch Glycollate	-	Explotab.*

* Trademarks

Method

1. Pass DCP through a screen and weigh it into a Planetary mixer.

2. Add 30 mesh Paroxetine to the bowl.

3. Add 20 mesh Avicel and Explotab and mix all the powders for 10 minutes.

4. Add magnesium Stearate and mix for 5 minutes.

Tablet into Pentagonal Tablets using the following punches:

30 mg Tablet	9.5 mm	Circumcircle
20 mg Tablet	8.25 mm	Circumcircle

The tablets are made satisfactorily on a single punch or a Rotary press.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A paroxetine formulation which is prepared on a commercial scale into tablets using a formulation process in which water is absent and which is a dry direct compression of paroxetine or a dry granulation of paroxetine followed by compression into tablets and in which microcrystalline cellulose is absent from the formulation, wherein the paroxetine is admixed with dry excipients.

2. A formulation process according to claim 1 in which the paroxetine admixed with dry excipients is compressed into large slugs or roller compacted into ribbon-like strands.

3. A formulation process according to claim 2 in which the compressed or compacted material is milled to produce a free flowing powder and compressed into tablets.

4. A formulation process according to claim 1, 2 or 3 in which the excipients are selected from calcium phosphate, sodium starch glycollate and magnesium stearate which may be admixed in appropriate ratios.

5. A formulation process according to claim 3 in which the tablet is compressed into a pentagonal circumcircle, oval, round bi-convex, or tilt-tablet shape.

6. A formulation process according to any one of the claims 1 to 5 in which paroxetine is in the form of the hydrochloride hemi-hydate.

7. A formulation comprising direct compressed paroxetine admixed with any dry excipients in the form of a tablet.

8. A formulation comprising dry granulated and compressed paroxetine admixed with dry excipients in the form of a tablet.

9. A formulation according to claim 7 or 8 in which the excipients are selected from calcium phosphate, microcrystalline cellulose, sodium starch glycollate and magnesium stearate which may be admixed in appropriate ratios.

10. A formulation according to claim 7 or 8 in which microcrystalline cellulose is absent.

11. A formulation according to any one of claims 7 to 10 in which the tablet is compressed into a pentagonal circumcircle, oval, round bi-convex or tilt-tablet shape.

12. A formulation according to any one of claims 7 to 11 in which the paroxetine is in the form of the hydrochloride hemi-hydrate.