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(54) Title: EFFERVESCENT ANTIPSYCHOTIC FORMULATIONS

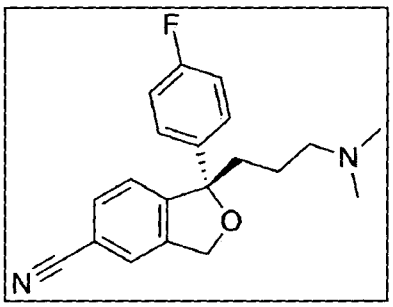
(57) Abstract: The present invention relates to effervescent formulations comprising escitalopram as active agent at least at 0.1% and to the fields of use thereof.

EFFERVESCENT ANTIPSYCHOTIC FORMULATIONS

The present invention relates to effervescent formulations comprising escitalopram as active agent at least at 0.1% and to the fields of use thereof.

Citalopram is a selective serotonin reuptake inhibitor, which was firstly disclosed in the patent numbered DE2657 013. Average daily dose of citalopram is 20 mg and it is marketed as hydrobromide and hydrochloride salts.

Pharmaceutically more effective (S)-enantiomer of citalopram is escitalopram, which was firstly disclosed in the patent numbered US 4 943 590 and has the molecule formula (S)-l-[3-(dimethylamino)propyl]-l-(4-fluorophenyl)-l,3-dihydroisobenzofurane-5-carbonitrile.



Formula (I)

The active agent is sold on the market in 10 and 20 mg film-coated tablet or oral solution dosage forms. The drug is used in the treatment of acute and major depressive diseases in adults and adolescents aged in the range of 12 to 17.

However, escitalopram is a substance with a highly low solubility rate; and this low solubility of the active agent leads to a decrease in the amount of therapeutic dose taken by the patient.

In this case, patients increase the dose of the drug to be able to obtain the required therapeutic effect. Increased dose of drug also increases the possibility of side effects and thus it is not preferred.

On the other hand, the commercial dosage forms of the active agent pose disadvantages both for the producer and the patients in terms of short shelf-lives, high costs of production, problems in using and carrying, problems in physical and chemical stability of suspension forms; and in terms of swallowing problems and low bioavailability in tablet forms.

As a result of the studies conducted, the inventor has achieved to produce new, easy-to-use effervescent formulations with high bioavailability that can provide the required bioavailability without any need to use high amounts of active agent.

An important advantage of the effervescent formulations of the invention is that they eliminate the need for using high amounts of active agent to provide an effective treatment. When formulations comprising high amounts of active agent by weight are formulated

together with pharmaceutically acceptable excipients, they become pretty large by weight and this case extends the time for the final dosage form to dissolve in water. On the other hand, a tablet high in volume is also disadvantageous in terms of storage and carrying.

Another important advantage of the effervescent formulations of the invention is that said formulations appeal to a wide range of patients as they are easy to use.

Another important advantage of the effervescent formulations of the invention is that said formulations provide a higher bioavailability as compared to the other pharmaceutical dosage forms.

In this respect, the present invention relates to effervescent formulations comprising escitalopram as active agent at least at 0.1% by weight.

The term "escitalopram" used herein refers to pharmaceutically acceptable salts, enantiomers, racemates, solvates, hydrates, various polymorphic forms, amorphous and crystalline forms of said active agent or combinations thereof; though the active agent used in the formulations of the invention is preferably escitalopram oxalate salt.

The effervescent formulations of the invention comprising escitalopram at least at 0.1% by weight can be produced in effervescent tablet or effervescent sachet forms.

A characteristic of the formulations of the invention comprising escitalopram at least at 0.1% by weight is that said formulations comprise at least one pharmaceutically acceptable excipient in addition to the active agent.

Another characteristic of the formulations of the invention comprising escitalopram at least at 0.1% by weight is that said formulations comprise at least one excipient selected from a group comprising binders, filling agents, lubricants, effervescent acids, effervescent bases, flavoring agents, sweeteners, coloring agents, solvents or combinations thereof.

The binders that can be used in the effervescent formulations of the invention comprising escitalopram at least at 0.1% by weight can be selected from a group comprising carboxymethyl cellulose sodium, ethyl cellulose, gelatin, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hypromellose, magnesium aluminum silicate, maltodextrin, methyl cellulose, povidone, starch, sorbitol or combinations thereof.

The filling agents that can be used in the effervescent formulations of the invention comprising escitalopram at least at 0.1% by weight can be selected from a group comprising lactose, sugar, starch modified starch, mannitol, sorbitol, maltodextrin, inorganic salts, microcrystalline cellulose, cellulose, calcium sulphate, xylitol and lactitol or combinations thereof.

The lubricants that can be used in the effervescent formulations of the invention comprising escitalopram at least at 0.1% by weight can be selected from a group comprising calcium stearate, magnesium stearate, polyethylene glycol, sodium benzoate, potassium benzoate, sodium lauryl sulphate, talc, stearic acid, zinc stearate or combinations thereof.

The effervescent acids that can be used in the effervescent formulations of the invention comprising escitalopram at least at 0.1% by weight can be selected from a group comprising organic acids such as malic acid, citric acid, tartaric acid, fumaric acid, maleic acid; hydrates, anhydrates or combinations thereof.

The effervescent formulations of the invention comprise at least one pharmaceutically acceptable effervescent acid in the range of 50 to 80%, preferably in the range of 55 to 80% by weight.

The effervescent acid comprised in the effervescent formulations of the invention is preferred to be in "anhydrate" form.

The effervescent bases that can be used in the effervescent formulations of the invention comprising escitalopram at least at 0.1% by weight can be selected from a group comprising sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate or combinations thereof.

The effervescent formulations of the invention comprise at least one pharmaceutically acceptable effervescent base in the range of 15 to 40%, preferably in the range of 20 to 40% by weight.

The sweeteners that can be used in the effervescent formulations of the invention comprising escitalopram by at least at 0.1% by weight can be selected from a group comprising acesulfame, aspartame, dextrose, fructose, maltitol, maltose, mannitol, saccharine, saccharine sodium, sodium cyclamate, sorbitol, sucralose, sucrose, xylitol, sodium chloride or combinations thereof.

The flavoring agents that can be used in the effervescent formulations of the invention comprising escitalopram at least at 0.1% by weight can be selected from a group comprising menthol, lemon, orange, vanilla, strawberry, raspberry, caramel or combinations thereof.

The solvents that can be used in the effervescent formulations of the invention comprising escitalopram at least at 0.1% by weight can be various alcohols or alcohol mixtures or deionized water.

Another characteristic of the effervescent formulations of the invention is that said formulations comprise escitalopram oxalate as active agent in the range of 0.1 to 5% by weight.

The effervescent formulations of the invention comprising escitalopram at least at 0.1% by weight can be produced by any production method in the prior art.

These production methods can be exemplified by wet granulation, dry granulation, dry mixing, direct compression methods etc.

However, the preferred production method for the effervescent formulations of the invention comprising escitalopram at least at 0.1% by weight is wet granulation method.

The preferred production method for the effervescent formulations of the invention comprising escitalopram at least at 0.1% by weight comprises the following steps;

a) Obtaining the granulation solution by mixing at least one pharmaceutically acceptable binder, at least one filling agent and/or optionally at least one pharmaceutically acceptable solvent,

b) Dry-mixing at least one pharmaceutically acceptable excipient and the active agent,

c) Wet-granulating the obtained dry mixture with the granulation solution obtained in the first step,

d) Drying the obtained granules, sieving them and optionally mixing them with at least another excipient,

e) Compressing the granules into tablets or filing them into sachets in order to obtain the desired dosage form.

The effervescent formulations of the invention comprising escitalopram as active agent at 0.1% by weight can be used in the treatment and/or prevention of depression (major depressive disorder), geriatrics, obesity, alcoholism, neurotic disorders, anxiety disorder [Agoraphobia (aeroacrophobia) or non-agoraphobia panic disorder, social anxiety disorder, generalized anxiety disorder and obsessive compulsive disorder] , post-traumatic stress disorder, panic attack.

The following examples were presented to explain the pharmaceutical formulations of the invention; the scope of the invention is not limited to these examples.

EXAMPLE: Effervescent Granule Formulation

Content	**Amount in Unit Dose (%)**
Escitalopram Oxalate	0.50
Effervescent couple	87.00
Lubricant	1.50
Filling agent	6.00
Binder	2.00
Sweetener	1.00
Flavoring agent	2.00
Total	**100**

To obtain the given effervescent granule composition, escitalopram and the effervescent couple is wet-granulated with the granulation solution comprising the filling agent and the binder. The obtained granules are dried and the sweetener, flavoring agent and then the lubricant are added into the granules. The granules are optionally compressed into tablets.

EXAMPLE: Effervescent Tablet Formulation

Content	**Amount in Unit Dose (%)**
Escitalopram Oxalate	0.80
Effervescent couple	86.70
Lubricant	1.50
Filling agent	6.00
Binder	2.00
Sweetener	1.00
Flavoring agent	2.00
Toplam	**100**

Active agent and pharmaceutically acceptable excipients are mixed; the composition is wet granulated with granulation solution comprising a pharmaceutically acceptable binder and filling agent. The obtained granules are dried and optionally a pharmaceutically acceptable sweetener and other excipients are added into granules. The obtained escitalopram oxalate granules are sent to tablet compressing machine.

CLAIMS

1. A pharmaceutically formulation comprising escitalopram as active agent at least at 0.1% by weight characterized in that said formulation is in effervescent form
2. The effervescent formulation according to claim 1, characterized in that escitalopram used in said formulations is in the form of its pharmaceutically acceptable salts, enantiomers, racemates, solvates, hydrates, various polymorphic forms, amorphous and crystalline forms or combinations thereof.
3. The effervescent formulation according to claim 2, characterized in that escitalopram used in said formulations is in the form of escitalopram oxalate salt.
4. The effervescent formulation according to any one of the preceding claims, characterized in that said formulations is in the form of effervescent tablet or effervescent sachet.
5. The effervescent formulation according to any one of the preceding claims, characterized in that said formulations comprise at least one pharmaceutically acceptable excipient in addition to the active agent.
6. The effervescent formulation according to claim 5, characterized in that the excipients used in said formulations are selected from a group comprising binders, filling agents, lubricants, effervescent acids, effervescent bases, flavoring agents, sweeteners, coloring agents, solvents or combinations thereof.
7. The effervescent formulation according to claim 6, characterized in that the effervescent acid used in said formulations is selected from a group comprising organic acids such as malic acid, citric acid, tartaric acid, fumaric acid, maleic acid; hydrates, anhydrates or combinations thereof.
8. The effervescent formulation according to claim 7, characterized in that said formulations comprise at least one effervescent acid in the range of 50 to 80% by weight.
9. The effervescent formulation according to claims 7 and 8, characterized in that said formulations comprise at least one effervescent acid in the range of 55 to 80% by weight.
10. The effervescent formulation according to claim 6, characterized in that the effervescent base used in said formulations is selected from a group comprising sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate or combinations thereof.

11. The effervescent formulation according to claim 10, characterized in that said formulations comprise at least one effervescent base in the range of 15 to 40% by weight.

12. The effervescent formulation according to claims 10 and 11, characterized in that said formulations comprise at least one effervescent base in the range of 20 to 40% by weight.

13. The effervescent formulation according to any one of the preceding claims, characterized in that said formulations comprise escitalopram oxalate as active agent in the range of 0.1 to 5% by weight.

14. According to any one of the preceding claims a method for production of the effervescent formulations comprising escitalopram as active agent at least at 0.1% by weight, characterized in that said method is one of wet granulation, dry granulation, dry mixing or direct compression methods.

15. The production method according to claim 14 characterized in that said method is wet granulation method.

16. The production method according to claim 15 characterized in that said method comprises the following steps;

a) Obtaining the granulation solution by mixing at least one pharmaceutically acceptable binder and at least one filling agent and/or optionally at least one pharmaceutically acceptable solvent,

b) Dry-mixing at least one pharmaceutically acceptable excipient and the active agent,

c) Wet-granulating the obtained dry mixture with the granulation solution obtained in the first step,

d) Drying the obtained granules, sieving them, and optionally mixing them with at least another excipient,

e) Compressing the granules into tablets or filing them into sachets in order to obtain the desired dosage form

17. The effervescent formulation according to any one of the preceding claims, characterized in that said formulation is used in the treatment and/or prevention of depression (major depressive disorder), geriatrics, obesity, alcoholism, neurotic disorders, anxiety disorder [Agoraphobia (aeroacrophobia) or non-agoraphobia panic

disorder, social anxiety disorder, generalized anxiety disorder and obsessive compulsive disorder] , post-traumatic stress disorder, panic attack.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2012/000206

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/46 A61K31/343
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/149196 Al (GENEPHARM A E [GR] ; MURPANI DEEPAK [GR] ; PANDORA ALEXAKI [GR]) 29 December 2010 (2010-12-29) page 3, lines 13-17 ; claims 1-40 page 2, lines 1-20	1-17
X	W0 2007/050697 A2 (ALAMO PHARMACEUTICALS LLC [US] ; CUTLER NEAL R [US]) 3 May 2007 (2007-05-03) claims 1-19	1-17
X	US 4 614 648 A (BRU JEAN [FR]) 30 September 1986 (1986-09-30) the whole document	1-17

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
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European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Konter, Jbrg

1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/TR2012/000206

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