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(54) Title: IMPROVED MANUFACTURING METHOD FOR THE FORMULATIONS COMPRISING VORTIOXETINE HBR BUTANOL SOLVATE FORM H

(57) Abstract: The present invention relates to an immediate release pharmaceutical formulation comprising Vortioxetine HBr butanol solvate and at least one pharmaceutically acceptable excipient manufactured by using direct compression method.

IMPROVED MANUFACTURING METHOD FOR THE FORMULATIONS COMPRISING VORTIOXETINE HBR BUTANOL SOLVATE FORM H

FIELD OF INVENTION

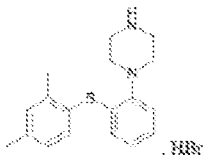
The present invention relates to an immediate release pharmaceutical formulation comprising Vortioxetine HBr butanol solvate and at least one pharmaceutically acceptable excipient manufactured by using direct compression method.

BACKGROUND OF THE INVENTION

Vortioxetine, the chemical name of which is 1-[2-(2, 4-dimethyl-phenylsulfanyl)-phenyl]-piperazine, is an antagonist on the 5-HT3, 5-HT7 and 5-HT1D receptors, an agonist on the 5-HT1A receptor and a partial agonist on the 5-HT1B receptor and an inhibitor of the serotonin transporter. In addition to that, Vortioxetine is reported to raise the levels of the neurotransmitters serotonin, noradrenalin, dopamine, acetylcholine and histamine in specific areas of the brain

According to the results of the clinical trials, Vortioxetine is declared to be a safe and efficacious treatment for depression. Thus, it is known to be a novel antidepressant for the treatment of major depressive disorder (MDD).

The empirical formula of Vortioxetine is $C_{18}H_{22}N_2S.HBr$ and its relative molecular mass is 298.45 mg/mol as a free base and 379.36 mg/mol as the hydrobromide salt. The chemical structure of Vortioxetine is shown in the Formula I.



Formula I

Vortioxetine hydrobromide appears as a white to very slightly beige powder, non-hygroscopic, soluble in methanol and ethanol and slightly soluble in water and aqueous solutions at pH 2.0 to 8.3. Its pKa is 9.1 as the free base and 3.0 as the salt.

Vortioxetine base and its pharmaceutically acceptable acid addition salts first have been described in EP1436271 by H. Lundbeck A/S.

Vortioxetine hydrobromide presents polymorphism and exhibits in four polymorphs, and also it has a non-chiral molecular structure.

Vortioxetine HBr was firstly commercially authorized in FDA by the U.S. Food &Drug Administration in September 2013. The medicinal product of it available on the market at film-coated tablet comprising Vortioxetine as the HBr salt and as an oral drop solution comprising Vortioxetine as the DL lactate salt under the name of the BRINTELLIX® which are used for the treatment of major depressive disorder (MDD) in adults.

BRINTELLIX® film-coated tablet is presented as immediate-release dosage form in strengths of 5, 10, 15 or 20 mg of Vortioxetine as the active substance wherein each tablet contains 6.355 mg, 12.71 mg, 19.065 mg, or 25.42 mg of Vortioxetine HBr equivalent to 5 mg, 10 mg, 15 mg, or 20 mg of Vortioxetine, respectively. Other ingredients in the film-coated tablets are mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate and magnesium stearate which are present in the tablet core and hypromellose, macrogol 400, titanium dioxide and iron oxide red and/or iron oxide yellow present in the tablet coating.

The recommended starting dose is 10 mg administered orally once daily without regard to meals and the dose should then be increased to 20 mg/day, as tolerated.

Vortioxetine is slowly absorbed after oral administration of immediate release tablets or solution. Following single and multiple oral doses of 5, 10, or 20 mg for immediate release, median t_{max} values of 7 to 11 hours were observed. The reported absolute bioavailability (BA) was approximately 75%. The administration of 20 mg Vortioxetine did not have a statistically significant effect on gastric emptying, but did have a statistically significant pro-kinetic effect on small intestinal transit and subsequent colon arrival.

In the state of art there are many patents/patent applications which are summarized below.

EP2470166 relates to a pharmaceutical composition comprising Vortioxetine or pharmaceutically acceptable acid addition salt thereof, wherein said composition is adapted so that said compound is not released in the stomach.

EP2044043 relates to a pharmaceutical composition comprising Vortioxetine or pharmaceutically acceptable acid addition salt thereof wherein the beta form of crystal Vortioxetine hydrobromide salt having XRPD reflections at approximately 6.89, 9.73, 13.78

and 14.64 (2Θ), and wherein a process for the manufacturing of crystalline hydrobromic acid addition salt is disclosed.

EP2421534 relates to a liquid pharmaceutical composition comprising Vortioxetine or pharmaceutically acceptable acid addition salt thereof wherein the salt is selected from the DL-lactic acid addition salt, L-lactic acid addition salt and the D-lactic acid addition salt.

EP2142193 relates to a pharmaceutical composition comprising Vortioxetine or pharmaceutically acceptable acid addition salt thereof and at least one pharmaceutical excipient manufactured by using wet granulation method wherein the composition is used for the treatment of pain.

EP3294719 relates to a pharmaceutical composition comprising Vortioxetine pyroglutamate and its use in pharmaceutical compositions manufactured by using direct compression method.

EP3184104 relates to a pharmaceutical composition comprising Vortioxetine hydrobromide in a matrix formed from at least one polyethylene oxide and optionally one or more further matrix forming polymers wherein the at least one polyethylene oxide is present in the matrix in an amount of 75-98 % (w/w) based on the total weight of the matrix, and wherein the composition is prepared by using direct compression method.

WO2018065348 relates to an enteric-coated tablet comprising Vortioxetine having a particle size distribution of D90 of 100 μm or less and at least one pharmaceutically acceptable excipient wherein the tablet core being coated with a pH sensitive coating.

WO2017041680 relates to a pharmaceutical composition of an amorphous Vortioxetine or a salt thereof and two or more pharmaceutically acceptable excipients.

EP3184102 relates to a solid oral pharmaceutical composition comprising an inert core comprising, preferably consisting of, at least one acidic reacting compound, and a coating comprising Vortioxetine hydrobromide and at least one pharmaceutically acceptable polymer.

WO2018042168 relates to novel premixes of Vortioxetine and at least one pharmaceutically acceptable polymer.

WO2017125504 relates to the preparation of novel polymorphic forms of Vortioxetine hydrobromide wherein the preparation of Vortioxetine hydrobromide 2-butanol solvate Form R3 and Form R4 are disclosed.

EP3582759 relates to a pharmaceutical composition comprising Vortioxetine hydrobromide having particle size distribution corresponding to D98 100-200μ, D50 35-90μ and D5 7-30μ wherein the composition is manufactured by using wet granulation method.

Based on the prior art, there are many studies about the various salts, solvates, polymorphic forms and matrix forms of the Vortioxetine hydrobromide to overcome its solubility problem in high pH buffer solutions. In addition, these salts present various physicochemical characteristics such as low solubility and high hygroscopicity. Moreover, the physicochemical properties have challenging effect on the processes of formulation design and manufacturing method of the pharmaceutical composition comprising it.

It has now been found that the pharmaceutical compositions comprising Vortioxetine HBr 2-butanol solvate form H as active ingredient and at least one pharmaceutically acceptable excipient manufactured by using direct compression method can overcome all the problems stated above and pharmaceutical compositions with improved solubility and hygroscopicity can be obtained.

SUMMARY OF THE INVENTION

The object of this invention is to develop an immediate release solid oral pharmaceutical composition comprising a therapeutically effective amount of Vortioxetine HBr 2-butanol solvate, which is an antagonist on the 5-HT3, 5-HT7 and 5-HT1D receptors, an agonist on the 5-HT1A receptor and a partial agonist on the 5-HT1B receptor and an inhibitor of the serotonin transporter.

Another object of the present invention is related to an immediate release dosage form composition for the treatment of major depressive disorder (MDD).

Another object of the present invention is to provide an immediate release pharmaceutical formulation comprising Vortioxetine hydrobromide is in crystalline form. Preferably, the crystalline form exists in the 2-butanol solvate form H.

Another object of the present invention is to provide a preparation method of a pharmaceutical composition of Vortioxetine hydrobromide 2-butanol solvate form H wherein the pharmaceutical compositions herein disclosed can be manufactured into solid dosage forms, such as tablets having desired dissolution profiles.

Another object of the present invention is to provide a solid oral pharmaceutical composition comprising Vortioxetine hydrobromide 2-butanol solvate and at least one pharmaceutically acceptable excipients manufactured by using direct compression method.

Another object of the present invention is to provide a solid oral pharmaceutical composition comprising Vortioxetine hydrobromide 2-butanol solvate form H manufactured by using direct compression method wherein provided for the manufacture of tablets containing the active ingredient, diluent, disintegrant, binder and lubricant selected as to be the most suitable ones with respect to the intended form of administration.

Also present invention particularly related to provide an immediate release pharmaceutical formulation manufactured by using direct compression method, including the steps of:

1. Vortioxetine hydrobromide 2-butanol solvate Form H, Mannitol, Microcrystalline cellulose, Hydroxypropyl methylcellulose and Sodium starch glycolate are screened through a proper sieve and stirred,
2. Magnesium stearate is screened through a proper sieve and added to the powder blend prepared in Step 1 and are stirred to obtain a uniform a final blend,
3. Tablet compression is performed with the final blend in Step 2.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an immediate release pharmaceutical formulation comprising Vortioxetine hydrobromide 2-butanol solvate form H and at least one pharmaceutically acceptable excipient is developed in the immediate release dosage form wherein the prepared composition is manufactured by using direct compression method to get desired dissolution properties.

In a preferred embodiment of the present invention is to provide a pharmaceutical compositions comprising Vortioxetine hydrobromide 2-butanol solvate form H is crystalline and presents characteristic peaks at particularly 6.7°, 13,3°, 16.0° and 19.2° 2-theta angles.

Solvates are known to exhibit faster dissolution rate, higher solubility and better bioavailability than the crystal form of active ingredient. However, it is also known that solvate forms are very hygroscopic which may have an impact on processibility of active substance.

One of the technical properties of processibility is powder characteristics, because the powder characteristics of active substance are considered while deciding how to handle it during manufacturing process and selecting the excipients used for the formulation design. Thus, flowability is controlled by performing dedicated analysis stated international guidelines.

According to the literature knowledge, there is a limited information about Vortioxetine hydrobromide 2-butanol solvate. Thus, to learn the physicochemical characterization of the Vortioxetine hydrobromide 2-butanol solvate Form H, it was determined by performing analytical method in accordance with USP <1174>.

The compressibility index and Hausner ratio were calculated as 35 and 1.54, respectively based on the results of densities 0.426 g/ml (tapped) and 0.277 g/ml (bulk).

Table 1 given below shows scale of flowability depending on the value of the Compressibility index and Hausner ratio.

Table 1: Scale of Flowability

Compressibility Index (%)	Flow character	Hausner Ratio
≤10	Excellent	1.00 - 1.11
11 - 15	Good	1.12 - 1.18
16 - 20	Fair	1.19 - 1.25
21 - 25	Passable	1.26 - 1.34
26 - 31	Poor	1.35 – 1.45
32 - 37	Very poor	1.46 – 1.59
>38	Very, very poor	>1.60

Based on the results of scale of flowability, the final blend was found "very poor.

In addition, the physical appearances of Vortioxetine hydrobromide used in reference drug product and Vortioxetine hydrobromide 2-butanol solvate Form H is very different. Vortioxetine hydrobromide presents mean crystal particles, however Vortioxetine hydrobromide 2-butanol solvate form H exhibits damp, fine and bright particles. The damp, fine particles have a tendency to exhibit poor flowability due to the cohesion force arising around the particles.

In a preferred embodiment of the present invention is to provide pharmaceutical compositions comprising 2-butanol solvate form H of Vortioxetine hydrobromide and at least one pharmaceutically acceptable excipient wherein the composition is manufactured by using the proper manufacturing method. It is known that there is common three manufacturing method

like direct compression, dry granulation or wet-granulation. The choice of the proper manufacture process highly depends on the properties of the active ingredient and the excipients preferred.

Direct compression, refers to the powdered materials are compressed directly without changing the physical and chemical properties of the drug, thus; it is a relatively quick process having less processing steps than other granulation techniques. The manufacturer can blend the active ingredient(s) with other pharmaceutical excipients in a blender or similar apparatus before being compressed into tablets. However, when the drug has poor flow characteristics and low dose in the composition, direct compression makes it difficult to obtain a homogenously acceptable solid dosage form due to the potency of segregation.

Moreover, there is a strong possibility of Vortioxetine hydrobromide 2-butanol solvate form H to be able to exhibit unstable polymorphic characteristics while using wet granulation due to the wetting and drying processes and polymorphic change while using dry granulation due to double tablet compression process.

Thus, in the present invention, the physicochemical properties of pharmaceutical composition comprising Vortioxetine hydrobromide 2-butanol solvate form H predominantly are affected by the mixing, formulation ingredients, and selection of the proper manufacturing step. In the present invention, the manufacturing step is selected as direct compression method and based on that also convenient pharmaceutically acceptable excipients are preferred.

Even if, there is a knowledge about a limitation of using direct compression when the drug is present as low dose drug and exhibits poor flowability characteristics with the solvate forms of the Vortioxetine hydrobromide which increase the water content in the granule causes poor flow, the inventors of the present invention have surprisingly succeeded in formulating a pharmaceutical composition comprising Vortioxetine hydrobromide 2-butanol solvate form H and at least one pharmaceutically acceptable excipient manufactured by using direct compression method. Moreover, pharmaceutically acceptable excipients are selected based on the functional effect of being diluent, disintegrant, binder and lubricant for the immediate release solid dosage form.

In a preferred embodiment, the pharmaceutical composition comprising at least two diluents which can be selected from dibasic calcium phosphate dehydrate, polysaccharides, primarily microcrystalline cellulose, lactose, mannitol, sugars, sorbitol, sucrose, inorganic salts, primarily

calcium salts and the like and mixtures thereof. Preferably, diluents are mannitol and microcrystalline cellulose.

In a preferred embodiment, the pharmaceutical composition comprises at least a binder which can be selected from hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, cellulose or cellulose derivatives, povidone, starch, sucrose, polyethylene glycol, or mixtures thereof. Preferably, the binder is hydroxypropyl methylcellulose.

In a preferred embodiment, the pharmaceutical composition comprising at least one disintegrant which can be selected from croscarmellose sodium, sodium starch glycolate, crospovidone, corn starch, pregelatinized starch, low-substituted hydroxypropyl cellulose and microcrystalline cellulose. Preferably, the disintegrant is sodium starch glycolate.

In a preferred embodiment, the pharmaceutical composition comprising at least one lubricant which can be selected from sodium stearyl fumarate, magnesium stearate, calcium stearate talc, stearic acid and mixtures thereof. Preferably, the lubricant is magnesium stearate.

The inventors surprisingly have found that an immediate release composition comprising Vortioxetine Hydrobromide 2-butanol solvate form H and pharmaceutically acceptable excipients manufactured by using direct compression method can exhibit proper dissolution profiles both in low pH and high pH aqueous solutions as simulation of gastrointestinal fluids.

The embodiment in accordance with the present invention was designed with adjusted quantitative composition composed of pharmaceutically acceptable ingredients mentioned above by using direct compression method.

The embodiment, Example 1 was based on the invention provides an immediate release oral solid pharmaceutical composition wherein the amounts in w/w% by weight of the total composition are as stated below:

Table 2: Unit Formula of Example 1

Ingredients	**w/w, %**
Vortioxetine hydrobromide 2-butanol solvate Form H	5.0 – 7.0
Mannitol	55.0 – 65.0
Microcrystalline cellulose	25.0 – 30.0
Hydroxypropyl methylcellulose	2.0 – 4.0
Sodium starch glycolate	2.0 – 4.0
Magnesium stearate	0.0 – 2.0
Core tablet	**100.0**

The detailed manufacturing steps are presented below:

a. Vortioxetine hydrobromide 2-butanol solvate Form H, Mannitol, Microcrystalline cellulose, Hydroxypropyl methylcellulose and Sodium starch glycolate were screened through a proper sieve and stirred,

b. Magnesium stearate was screened through a proper sieve and added to the powder blend prepared in Step a and were stirred to obtain a uniform final blend,

c. Tablet compression was performed with the final blend in Step b.

Firstly, flowability of the final blend is controlled by measuring bulk and tapped densities in accordance with USP <1174>.

The compressibility index and Hausner ratio were calculated as 21 and 1.27, respectively based on the results of bulk and tapped densities which were 0.439 g/ml and 0.556 g/ml. Based on the results of scale of flowability, the final blend had "passable" flow characteristic.

It was observed that the flowability of the final blend was improved to obtain immediate release pharmaceutical formulation manufactured by direct compression method.

Tablets were subjected into in vitro dissolution study. The conditions of dissolution study are set by US FDA, based on the information dissolution medium is 0.1N HCl. Also, pH 6.8 phosphate buffer solution is the other dissolution medium to observe the behavior of drug product in high pH aqueous solutions. The conditions for the dissolution analysis are defined as;

Volume of dissolution media : 900 ml

Temperature : 37°C±0.5°C

Rotation speed : 50 rpm

Apparatus : Paddle

Time : 60 minutes

Table 4: The results of dissolution study for Example 1 in 0.1N HCl

Time, min	Results, %	
	Example 1	Reference drug product (BRINTELLIX®)
10	86.8	93.8
15	92.1	96.9
20	94.5	97.1
30	95.5	97.9

45	95.9	96.7
60	95.8	96.8

Table 5: The results of dissolution study of Example 1 in pH 6.8 phosphate buffer

Time, min	Results, %	
	Example 1	Reference drug product (BRINTELLIX®)
10	26.1	39.3
15	34.9	41.5
20	43.3	56.8
30	53.9	65.6
45	65.8	72.4
60	73.3	75.8

The similarity factor f_2 is the most common comparison index that is used to indicate the similarity of dissolution profiles between examples and reference drug product.

According to the Guideline on the Investigation of Bioequivalence, the similarity index f_2 parameter should be higher than 50 to be similar with reference drug product.

In accordance with FDA regulations, similarity of two drug products can be compared based on the results of in vitro dissolution profile studies of these drug products by using a similarity factor f_2. The similarity factor f_2 is the most common comparison index and if the estimated value is in the range from 50 to 100, the dissolution profiles of two drug products in comparison are concluded as similar. In the present invention, the similarity factor f_2 of Example 1 was calculated as 55.8 for 0.1N HCI and f_2 was calculated as 50.2 for 6.8 phosphate buffer, which means the developed formulation was suitable.

In the present invention, the developed pharmaceutical composition comprising Vortioxetine hydrobromide 2-butanol solvate Form H and at least one pharmaceutically acceptable excipient exhibits similar dissolution profiles both in 0.1N HCl and pH 6.8 phosphate buffer with the reference drug product, wherein the prepared composition is manufactured by using direct compression method.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

CLAIMS

1. An immediate release pharmaceutical composition manufactured by direct compression method comprising Vortioxetine hydrobromide 2-butanol solvate crystalline form H and at least one pharmceutically acceptable excipient.

2. The immediate release pharmaceutical composition according to Claim 1, wherein at least one pharmaceutically acceptable excipient is selected from diluent, disintegrant, binder and lubricant.

3. The immediate release pharmaceutical composition according to Claim 2, wherein at least one pharmaceutically acceptable excipient is a diluent selected from dibasic calcium phosphate dehydrate, polysaccharides, primarily microcrystalline cellulose, lactose, mannitol, sugars, sorbitol, sucrose, inorganic salts, primarily calcium salts and the like and mixtures thereof.

4. The immediate release pharmaceutical composition according to Claim 2, wherein at least one pharmaceutically acceptable excipient is a binder selected from hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, cellulose or cellulose derivatives, povidone, starch, sucrose, polyethylene glycol and mixtures thereof.

5. The immediate release pharmaceutical composition according to Claim 2, wherein at least one pharmaceutically acceptable excipient is a disintegrant selected from croscarmellose sodium, sodium starch glycolate, crospovidone, corn starch, pregelatinized starch, low-substituted hydroxypropyl cellulose, microcrystalline cellulose and mixtures thereof.

6. The immediate release pharmaceutical composition according to Claim 2, wherein at least one pharmaceutically acceptable excipient is a lubricant selected from sodium stearyl fumarate, magnesium stearate, calcium stearate talc, stearic acid and mixtures thereof.

7. The immediate release pharmaceutical composition according to any one of the preceding claims; wherein the composition is:

Ingredients	**w/w, %**
Vortioxetine hydrobromide 2-butanol solvate Form H	5.0 – 7.0
Mannitol	55.0 – 65.0
Microcrystalline cellulose	25.0 – 30.0
Hydroxypropyl methylcellulose	2.0 – 4.0

Ingredients	**w/w, %**
Sodium starch glycolate	2.0 – 4.0
Magnesium stearate	0.0 – 2.0
Core tablet	**100.0**

8. The immediate release pharmaceutical composition according to any one of the preceding claims, wherein the direct compression method comprises the steps of;

a. Vortioxetine hydrobromide 2-butanol solvate, Mannitol, Microcrystalline cellulose, Hydroxypropyl methylcellulose and Sodium starch glycolate are screened through a proper sieve and stirred,

b. Magnesium stearate is screened through a proper sieve and added to the powder blend prepared in Step b and are stirred to obtain a uniform final blend,

c. Tablet compression is performed with the final blend in Step c.

9. The immediate release pharmaceutical composition according to any one of the preceding claims for use in the treatment of major depressive disorder (MDD).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/TR2020/051190

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/495 (2006.01)i; A61K 9/28 (2006.01)i; A61P 25/24 (2006.01)i

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; A61P

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)

EPODOC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	CN 105193763 A (KAMP PHARMACEUTICALS CO LTD) 30 December 2015 (2015-12-30) Abstract; paragraphs 1, 5, 24-28, 34 (EPO translation)	1-9
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A	US 2018273499 A1 (TEVA PHARMACEUTICALS INT GMBH) 27 September 2018 (2018-09-27) Abstract; paragraphs 2, 6	1-9

☐ 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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Date of the actual completion of the international search	Date of mailing of the international search report
30 June 2021	**30 June 2021**

Name and mailing address of the ISA/TR	Authorized officer
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INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
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