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[Continued on next page]

(54) Title: ORAL PHARMACEUTICAL COMPOSITION OF LURASIDONE

(57) Abstract: Provided is an oral pharmaceutical composition comprising lurasidone or pharmaceutically acceptable salts thereof; one or more water-soluble pharmaceutical excipients, a disintegrating agent consisting essentially of a single disintegrating agent. The composition is free of starch. The present oral pharmaceutical composition of lurasidone or pharmaceutically acceptable salts of the invention exhibits an invariant level of dissolution even when the content of lurasidone or pharmaceutically acceptable salts thereof is varied.

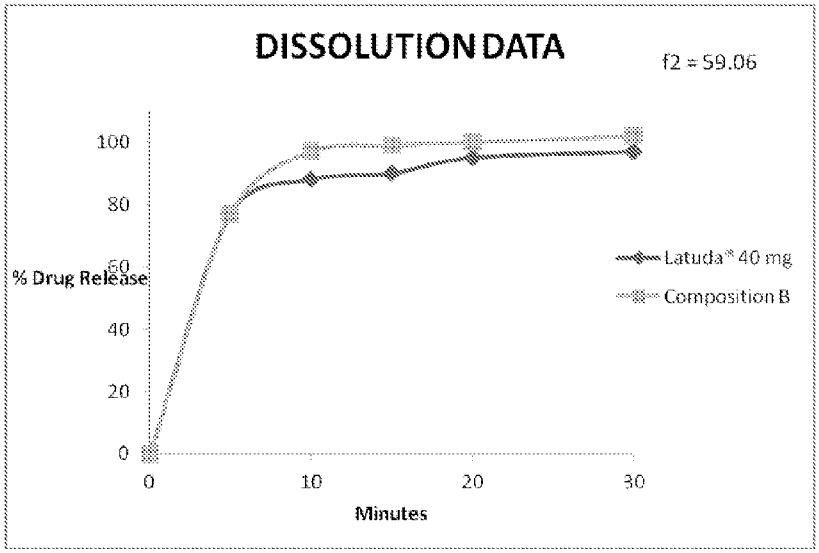

Fig: 1

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

ORAL PHARMACEUTICAL COMPOSITION OF LURASIDONE

FIELD OF THE INVENTION

The present invention relates to an oral pharmaceutical composition of lurasidone or pharmaceutically acceptable salts thereof. The invention relates to an oral pharmaceutical composition of lurasidone or pharmaceutically acceptable salts thereof; one or more water-soluble pharmaceutical excipients and a single disintegrating agent wherein the composition is free of starch. The oral pharmaceutical composition of lurasidone or pharmaceutically acceptable salts of the invention exhibits an invariant level of dissolution even when the content of lurasidone or pharmaceutically acceptable salts thereof is varied.

BACKGROUND OF THE INVENTION

Lurasidone is an atypical antipsychotic which belongs to the chemical class of benzisothiazol derivatives and its chemical name is (3a*R*,4*S*,7*R*,7a*S*)-2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl)piperazin-1ylmethyl]cyclohexylmethyl}hexahydro-4,7-methano-2*H*-isoindole-1,3-dione.

US patent No. 5,532,372 claims lurasidone or acid addition salt thereof.

Lurasidone hydrochloride is developed by Dainippon Sumitomo Pharma under the trade name Latuda®. Latuda® tablet contains 20 mg, 40 mg, 60 mg, 80 mg, or 120 mg of lurasidone hydrochloride. Latuda® tablet contains inactive ingredients which include mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry® and carnauba wax, yellow ferric oxide and FD&C Blue No. 2 Aluminum Lake.

US patent No. 7,727,553 discloses a pharmaceutical preparation for oral administration particularly granules, comprising combination of first and second disintegrating agents, a water-soluble excipient and a polymer binder. It also mentions that such granules can rapidly release the active ingredient and can show equivalent dissolution profile even though content of active ingredient are varied in the range of 5 mg to 20 mg or in the range of 5 mg to 40

mg. It further discloses that in order to secure the bioequivalence when a pharmaceutical preparation having different amounts is administered at the same dose, there was issued "Guideline for Bioequivalence testing of Oral Solid Dosage Forms with Different Content" (Notification No. 64 of the Evaluation and Licensing Division, PMSD dated Feb. 14, 2000), by which it has been required that a pharmaceutical preparation having different amounts should be equivalent in dissolution profile in test medias such as buffers of pH 1.2, 3.0 to 5.0 and 6.8 (which correspond to the pH values of the stomach, the intestine and the oral cavity, respectively), water, and saline solution etc.

US patent No. 8,729,085 discloses a composition comprising lurasidone, pregelatinized starch, a water-soluble excipient and water-soluble polymer binder which shows a rapid dissolution and has an equivalent dissolution profile even though contents of the active ingredient therein are varied in the wide range. It further discloses that the preparation which comprises pregelatinized starch can provide an equivalent dissolution profile with higher contents of lurasidone.

WO 2012/156981 discloses a pharmaceutical composition comprising lurasidone or salts thereof and one or more water-insoluble pharmaceutical excipients, wherein the composition is free of water-soluble excipients. It further discloses that none of the prior art discloses or teaches or suggests how to develop stable formulations of lurasidone without using water-soluble excipients which can also exhibit rapid or modified disintegration as well as equivalent dissolution profile over wide dose range.

It is easy to prepare pharmaceutical compositions of active ingredient which shows good solubility in water, having an equivalent in-vitro dissolution profile even if content of active ingredient varies in such pharmaceutical compositions. On the contrary, it is difficult to prepare a pharmaceutical composition having slightly water-soluble active ingredient with an equivalent in-vitro dissolution profile over a wide range of content of active ingredient in pharmaceutical composition. Lurasidone has solubility of less than several pg/ml in water

and thus can impose a challenge to make a pharmaceutical composition having an equivalent in-vitro dissolution profile over a wide range of lurasidone content.

Thus one of the prior arts discloses pharmaceutical compositions of lurasidone using water-soluble excipients with combination of first and second disintegrating agents. Another prior art teaches the use of only water-insoluble excipients in pharmaceutical compositions of lurasidone. Another prior art essentially involves the use of pregelatinised starch for the pharmaceutical compositions of lurasidone. There is no disclosure or teaching or suggestion in the art about how to develop an oral pharmaceutical composition of lurasidone employing water-soluble excipients and a single disintegrating agent, wherein the composition is free of starch which can also exhibit an equivalent in vitro dissolution profile over wide range of lurasidone content.

Hence, there still remains a need for the development of an alternative pharmaceutical composition of lurasidone or pharmaceutically acceptable salt which comprises one or more water-soluble pharmaceutical excipients, and a single disintegrating agent, wherein the composition is free of starch and the composition exhibits an equivalent dissolution even when the content of lurasidone is varied.

SUMMARY OF THE INVENTION

In accordance, the present invention provides an oral pharmaceutical composition(s) comprising lurasidone or pharmaceutically acceptable salts thereof; one or more water-soluble pharmaceutical excipients, and a single disintegrating agent, wherein the composition is free of starch.

Yet another aspect of invention provides an oral pharmaceutical composition(s) comprising lurasidone or pharmaceutically acceptable salts thereof; one or more water-soluble pharmaceutical excipients and a disintegrating agent consisting essentially of a single disintegrating agent, wherein the composition is free of starch.

Yet another aspect of the invention provides an oral pharmaceutical composition(s) comprising lurasidone or pharmaceutically acceptable salts thereof; one or more water-soluble pharmaceutical excipients and a disintegrating agent consisting essentially of a single disintegrating agent, wherein the composition is free of starch and the said composition exhibits an equivalent dissolution even when the content of lurasidone is varied.

Yet another aspect of the invention provides an oral pharmaceutical composition(s) comprising lurasidone or pharmaceutically acceptable salts thereof; one or more water-soluble pharmaceutical excipients and a disintegrating agent consisting essentially of a single disintegrating agent, wherein the composition is free of starch and the said composition releases at least 90% within 30 minutes in diluted Mcilvaine buffer of pH 3.8.

Yet another aspect of the invention provides an oral pharmaceutical composition(s) comprising lurasidone or pharmaceutically acceptable salts thereof; one or more water-soluble pharmaceutical excipients and a disintegrating agent consisting essentially of a single disintegrating agent, wherein the composition is free of starch and the said composition releases at least 50% within 5 minutes in diluted Mcilvaine buffer of pH 3.8.

Yet another aspect of the invention provides an oral pharmaceutical composition(s) is prepared by mixing lurasidone, one or more water-soluble pharmaceutical excipients and a disintegrating agent consisting essentially of a single disintegrating agent, optionally granulating said mixture using a water-soluble binder and further mixing with other pharmaceutically acceptable additives.

BRIEF DESCRIPTION OF THE DRAWINGS:

Fig. 1: shows a comparative dissolution profile of Example 2 (Composition B) with Latuda® 40 mg tablet which contains pregelatinized starch.

Fig. 2: shows a comparative dissolution profile of Example 2 (Composition C) with Latuda® 80 mg tablet which contains pregelatinized starch.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an oral pharmaceutical composition(s) comprising lurasidone or pharmaceutically acceptable salts thereof; one or more water-soluble pharmaceutical excipients and a single disintegrating agent, wherein the composition is free of starch.

Yet another aspect of invention provides an oral pharmaceutical composition(s) comprising lurasidone or pharmaceutically acceptable salts thereof; one or more water-soluble pharmaceutical excipients and a disintegrating agent consisting essentially of a single disintegrating agent, wherein the composition is free of starch.

Yet another embodiment of the invention provides an oral pharmaceutical composition(s) comprising lurasidone or pharmaceutically acceptable salts thereof; one or more water-soluble pharmaceutical excipient and a disintegrating agent consisting essentially of a single disintegrating agent, wherein the composition is free of starch and the said composition exhibits an equivalent dissolution even when the content of lurasidone is varied.

Yet another embodiment of the invention provides an oral pharmaceutical composition(s) comprising lurasidone or pharmaceutically acceptable salts thereof; one or more water-soluble pharmaceutical excipients and a disintegrating agent consisting essentially of a single disintegrating agent, wherein the composition is free of starch and the said composition releases at least 90% within 30 minutes in diluted Mcilvaine buffer of pH 3.8.

Yet another embodiment of the invention provides an oral pharmaceutical composition(s) comprising lurasidone or pharmaceutically acceptable salts thereof; one or more water-soluble pharmaceutical excipients, and a disintegrating agent consisting essentially of a

single disintegrating agent, wherein the composition is free of starch, and the said composition releases at least 50% within 5 minutes in diluted Mcilvaine buffer of pH 3.8.

Yet another embodiment of the invention provides an oral pharmaceutical composition(s) prepared by mixing lurasidone, one or more water-soluble pharmaceutical excipients and a single disintegrating agent optionally granulating said mixture using a water-soluble binder and further mixing with other pharmaceutically acceptable additives.

The term 'lurasidone' as used herein, includes lurasidone base or it's pharmaceutically acceptable acid addition salts with an organic or inorganic acid. Non-limiting examples of inorganic acid are hydrochloric acid, hydrobromic acid, hydroiodic acid and sulfuric acid. Non-limiting examples of organic acid are acetic acid, oxalic acid, citric acid, malic acid, tartaric acid, maleic acid and fumaric acid. The preferred salt is hydrochloric acid. The term 'lurasidone' may further encompass its pharmaceutically acceptable solvates, hydrates, enantiomers, derivatives, polymorphs and pharmaceutically acceptable pro-drugs thereof.

The pharmaceutical composition of present invention comprises about 10 to about 160 mg of lurasidone, preferably about 20 to about 120 mg of lurasidone and more preferably about 40 to about 120 mg of lurasidone. The pharmaceutical composition comprises lurasidone in the range of about 10% to about 50% by weight, preferably in the range of about 20% to about 45% by weight, particularly in the range of about 20% to about 45% by weight on the basis of the total weight of the composition. Additionally, lurasidone or pharmaceutically acceptable salts may be unmicronised or micronized. Lurasidone used herein may have 90% by volume particles having about 27 µm or less of particle size and preferably 90% by volume particles having about 20 µm or less of particle size. Particle size may be determined by a suitable technique known in the art.

One or more water-soluble pharmaceutical excipient is selected from lactose, sucrose, fructo-oligosaccharide, paratinose, glucose, maltose, hydrogenated maltose, maltotetraose, fructose,

lactulose, lactitol, honey sugar, sorbitol, mannitol, maltitol, erythritol, xylitol or mixtures thereof. Preferably, the water-soluble pharmaceutical excipient is mannitol. The water-soluble pharmaceutical excipient is incorporated in the composition in an amount of about 30% to about 65% by weight, preferably about 40% to about 60% by weight on the basis of the total weight of the composition.

The term “starch” includes but not limited to corn starch, pregelatinized starch or other starch derivatives thereof. The term “free of starch” refers to complete absence of starch in the composition.

Water-soluble binder includes but not limited to hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol or mixtures thereof. More preferable one includes hydroxypropyl cellulose, hydroxypropyl methylcellulose. The water-soluble binder is incorporated in composition an amount of about 1% to about 10% by weight, preferably about 2% to about 8% by weight on the basis of the total weight of the composition.

The term "disintegrant" includes but not limited to carmellose, carmellose calcium, carmellose sodium, croscarmellose sodium, cross-linked polyvinylpyrrolidone, sodium starch glycolate, microfine cellulose, low substituted hydroxypropylcellulose, calcium carboxymethyl cellulose, sodium alginate. The disintegrant is used in the composition in an amount of about 2% to about 3 % by weight, preferably about 5% to about 12% by weight on the basis of the total weight of the composition. The term “single disintegrating agent” refers to the use of only one disintegrant.

As used herein, "about" means plus or minus approximately twenty percent of the indicated value, such that "about 20 percent" indicates approximately 16 to 24 percent.

The oral pharmaceutical composition can optionally include one or more additives known in the art. These additives include but not limited to fillers, glidants, lubricants and/or wetting agents known in the art.

The oral pharmaceutical composition of the present invention can be formulated into granules, tablet, capsule, caplets or mini-tablets.

The oral pharmaceutical composition(s) of lurasidone or pharmaceutically acceptable salts thereof may be further coated with a suitable film coating known in the art.

The film-coating composition comprises a base material or mixture of base material selected from hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol. The film-coating composition may further comprise a plasticizer such as polyethylene glycol, propylene glycol, triacetin, triethyl citrate, glycerin, glycerin fatty acid ester, polyethylene glycol or mixtures thereof. If necessary, an additive such as titanium oxide may also be added therein.

The oral pharmaceutical composition(s) of lurasidone or pharmaceutically acceptable salts thereof can be prepared by any suitable method known in the art but not limited to direct compression, dry granulation, wet granulation, fluidized bed granulation, spray drying and solution evaporation.

The oral pharmaceutical composition(s) of the invention can be prepared by granulating the mixture of lurasidone hydrochloride, one or more water-soluble pharmaceutical excipients, a single disintegrating agent and optionally other pharmaceutical additives by using water soluble binder. Granules thus formed can be compressed in to a tablet dosage form or alternatively can be filled in to capsule dosage form.

The oral pharmaceutical composition of lurasidone or pharmaceutically acceptable salts of the invention exhibits an invariant level of dissolution even when the content of lurasidone or pharmaceutically acceptable salts thereof is varied. This invariant dissolution of the composition of the invention is described with the help of similarity factor of dissolution profile.

A similarity factor *f*2 shown in Scale-Up and Past-Approval Changes for Intermediate Release Products (SUPAC-IR) is used as an indicative for evaluating a similarity of dissolution profiles. The *f*2 value is calculated by the following equation. It was determined that each manufactured preparation had a similar dissolution profile in case that the *f*2 value calculated from dissolution ratio of each preparation by SUPAC-IR was in the range of $50 \leq f2 \leq 100$. Dissolution ratios at five time points such as 5 min, 10 min, 15 min, 20 min and 30 min after starting the test were used for the calculation of *f*2 value.

$$f2 = 50 \cdot \mathrm{LOG}\left\{\frac{100}{\sqrt{1 + \frac{\sum_{i=1}^{n}(Ti - Ri)^2}{n}}}\right\}$$

Ti and Ri are the percent dissolved of active at each point.

n is the number of points to be compared.

Dissolution Test

Lurasidone hydrochloride tablets were prepared according to Examples 1 and 2 (Composition A, B & C). The tablets were subjected to a dissolution test according to the Pharmacopoeia of Japan, Method 2, under the following conditions:

Test Media: Diluted Mcilvaine buffer, pH 3.8.

Paddle Rotation: 50 rpm

Volume of test media: 900 ml

The following examples are further illustrative but by no means limitative of the present invention.

Example 1:

Ingredients	**Quantity/Tablet (mg)**
Lurasidone Hydrochloride	40.00
Mannitol	68.40
Lactose Monohydrate	38.00
Crosscarmelose sodium	8.00
Hydroxypropyl methylcellulose	4.00
Water	q.s.
Lubrication	
Magnesium stearate	1.60
Total Weight of Uncoated Tablet	160.00
Film Coating	4.80
Total Weight of Coated Tablet	164.80

Brief Manufacturing Procedure:

1) Mix Lurasidone Hydrochloride, Mannitol, Lactose monohydrate and Crosscarmelose sodium.
2) Prepare solution of Hydroxypropyl methylcellulose in water.
3) Granulate step 1 material with solution of step 2.
4) Dry the granules of step 3 using fluid bed drier so the loss on dry is within 3% by weight.
5) Lubricate the dried granules of step 4 with Magnesium stearate.
6) Compress the lubricated granules of step 5 into tablet using compression machine & film coat the compressed tablet.

Example 2

Ingredients	**Composition A Quantity/Tablet (mg)**	**Composition B Quantity/Tablet (mg)**	**Composition C Quantity/Tablet (mg)**
Lurasidone Hydrochloride	20.00	40.00	80.00
Mannitol	37.75	75.50	151.00
Crosscarmelose sodium	6.00	12.00	24.00
Hydroxypropyl methylcellulose	3.50	7.00	14.00
Water	q.s	q.s	q.s
Lubrication			
Magnesium Stearate	0.75	1.50	3.00
Total Weight of Uncoated Tablet	68.00	136.00	272.00
Film Coating	1.70	3.40	6.80
Total Weight of Coated Tablet	69.70	139.40	278.80

Brief Manufacturing Procedure:

1) Mix Lurasidone Hydrochloride, Mannitol and Crosscarmelose sodium.
2) Prepare solution of Hydroxypropyl methylcellulose in water.
3) Granulate step 1 material with solution of step 2.
4) Dry the granules of step 3 using fluid bed drier so the loss on dry is within 3% by weight.
5) Lubricate the dried granules of step 4 with Magnesium stearate.

6) Compress the lubricated granules of step 5 into tablet using compression machine & film coat the compressed tablet.

The results of the dissolution test are shown below:

Table 1 shows percent release of lurasidone hydrochloride of compositions prepared according to Example 1 and Example 2 (Composition A, B & C)

Table 1

Time (min)	% Drug Release of Example 1	% Drug Release of Example 2		
		Composition A	Composition B	Composition C
0	0	0	0	0
5	73	73	77	53
10	81	92	97	88
15	85	98	99	89
20	88	99	100	92
30	89	96	102	95

Table 2 shows percent release and *f*2 value of lurasidone hydrochloride of compositions prepared according to Example 2 (B) and Latuda® (40 mg tablets)

Table 2

Time (min)	% Drug Release Composition B	% Drug Release of Latuda® (40 mg tablets)
0	0	0
5	77	77
10	97	88

15	99	90
20	100	95
30	102	97
f2	**59.06**	

Table 3 shows percent release and *f*2 value of lurasidone hydrochloride of composition prepared according to Example 2 (C) and Latuda® (80 mg tablets)

Table 3

Time (min)	**% Drug Release Composition C**	**% Drug Release of Latuda® (80 mg tablets)**
0	0	0
5	53	46
10	88	83
15	89	89
20	92	90
30	95	93
f2	**68.99**	

Each film coated tablets (Composition B and Composition C) comprising 40 and 80 mg lurasidone hydrochloride of Example 2 and Latuda® 80 mg tablets were subjected to above mentioned dissolution test and a similarity of each dissolution profile was evaluated by determining *f*2 value as shown in table 2 and 3.

The pharmaceutical composition has similar dissolution profile in comparison to Latuda® tablets. The pharmaceutical compositions of current invention do not contain starch and exhibit invariant dissolution profile across the wide content of lurasidone hydrochloride which is evident by *f*2 value as mentioned in table 2 and 3.

As evident by Table 2 and 3, *f*2 value obtained for Example 2 (Composition B and Composition C) showed similar dissolution profile to the Latuda® 40 and 80 mg tablet containing pregelatinized starch. In other words, as evident by figure 1 and figure 2, which reflect similarity of the dissolution profile of composition of the current invention without relying upon lurasidone hydrochloride content in tablets and such compositions are also free of starch. The pharmaceutical compositions of current invention have similar dissolution profile in comparison to Latuda® tablets. The compositions of current invention do not contain starch and exhibit invariant dissolution profile across the wide content of lurasidone.

CLAIMS

1. An oral pharmaceutical composition comprising lurasidone or pharmaceutically acceptable salts thereof; one or more water-soluble pharmaceutical excipients, a disintegrating agent consisting essentially of a single disintegrating agent, wherein the composition is free of starch.

2. The oral pharmaceutical composition of claim 1, wherein the one or more water-soluble pharmaceutical excipient is selected from lactose, sucrose, fructo-oligosaccharide, paratinose, glucose, maltose, hydrogenated maltose, maltotetraose, fructose, lactulose, lactitol, honey sugar, sorbitol, mannitol, maltitol, erythritol, xylitol or mixtures thereof.

3. The oral pharmaceutical composition of claim 1, wherein the single disintegrating agent is selected from carmellose, carmellose sodium, carmellose calcium, croscarmellose sodium, crosslinked polyvinylpyrrolidone, sodium starch glycolate, microfine cellulose, low substituted hydroxypropylcellulose, calcium carboxymethyl cellulose, sodium alginate.

4. The oral pharmaceutical composition of claim 1, wherein the composition comprises about 10 mg to about 160 mg of lurasidone hydrochloride.

5. The oral pharmaceutical composition of claim 1, wherein the composition releases at least about 90% of lurasidone hydrochloride within 30 minutes in diluted Mcilvaine buffer of pH 3.8.

6. The oral pharmaceutical composition of claim 1, wherein the composition releases at least about 50% of lurasidone hydrochloride within 5 minutes in diluted Mcilvaine buffer of pH 3.8.

7. The oral pharmaceutical composition of claim 1, wherein the composition is in form of granules, tablets, capsules, caplets, and minitablets.

8. The oral pharmaceutical composition of claim 1, wherein the composition is prepared by mixing lurasidone, one or more water-soluble pharmaceutical excipients and a disintegrating agent consisting essentially of a single disintegrating agent, optionally granulating said mixture using a water-soluble binder and further mixing with other pharmaceutically acceptable additives.

9. The oral pharmaceutical composition of claim 8, wherein the water-soluble binder is selected from hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrollidone, polyvinylalcohol or mixtures thereof.

10. The oral pharmaceutical composition of claim 8, wherein the pharmaceutically acceptable additives are selected from glidants, lubricants, wetting agents or mixtures thereof.

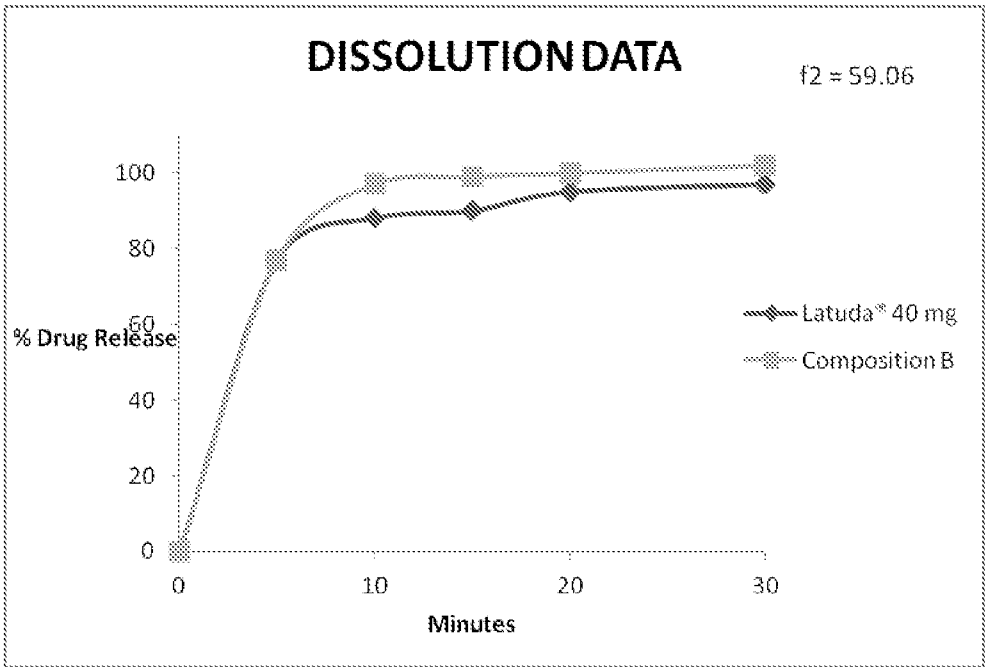
DISSOLUTION DATA
f2 = 59.06
% Drug Release
100
80
60
40
20
0
0
10
20
30
Minutes
Latuda® 40 mg
Composition B

Fig: 1

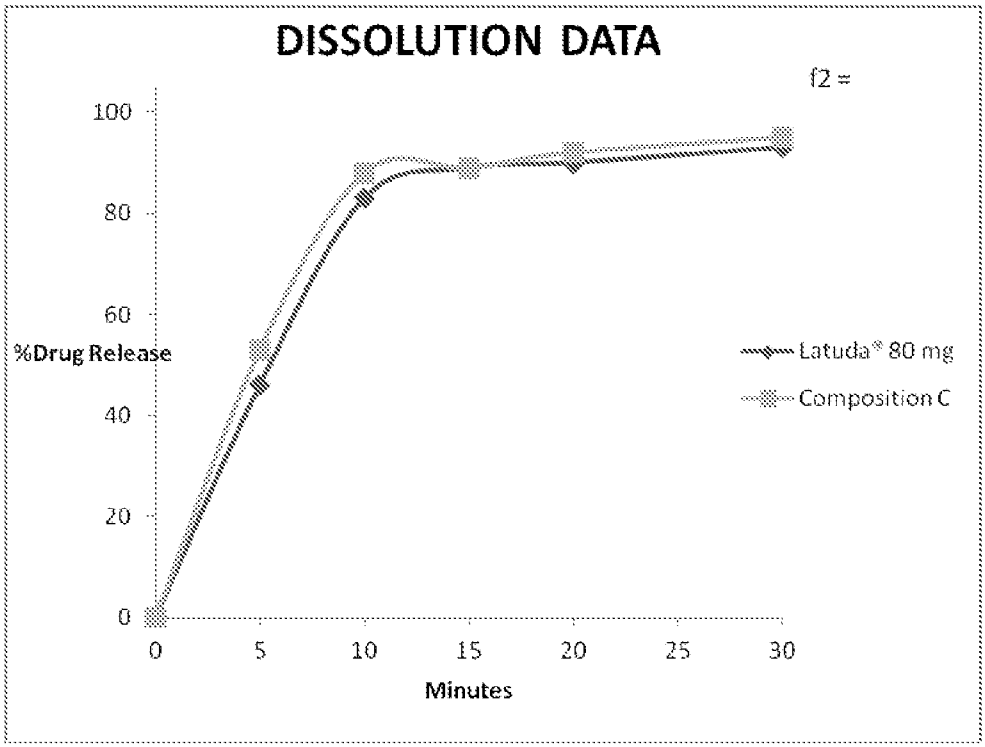
DISSOLUTION DATA
f2 =
100
80
60
40
20
0
%Drug Release
0
5
10
15
20
25
30
Minutes
Latuda® 80 mg
Composition C

Fig: 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/055249

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20 A61K31/496
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, 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	EP 1 884 242 A1 (DAINIPPON SUMITOMO PHARMA CO [JP]) 6 February 2008 (2008-02-06) paragraphs [0001], [0004], [0007], [0100], [0116], [0123]; table 35	1-10
A	WO 2014/076712 A2 (HETERO RESEARCH FOUNDATION [IN]; PARTHASARADHI REDDY BANDI [IN]; RATHN) 22 May 2014 (2014-05-22) claims 1,2,9; example 2	1-10
X	WO 2012/156981 A1 (CADILA HEALTHCARE LTD [IN]; KHERA BRIJ [US]; TREHAN AMAN [IN]; PATEL P) 22 November 2012 (2012-11-22) tables 4,5	1,3,4, 7-10

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 October 2015	20/10/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kardas-Llorens, Eyüp

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	CN 104 248 769 A (CSPC ZHONGQI PHARMACEUTICAL TECHNOLOGY SHIJIAZHUAN) 31 December 2014 (2014-12-31) see embodiment 1, comparative example 5	1-3,7-10
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