(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 January 2008 (17.01.2008)

PCT

(10) International Publication Number
WO 2008/007390 A2

(51) International Patent Classification:
C07D 413/06 (2006.01)

(21) International Application Number:
PCT/IN2007/000267

(22) International Filing Date: 29 June 2007 (29.06.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1203/CHE/2006 10 July 2006 (10.07.2006) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

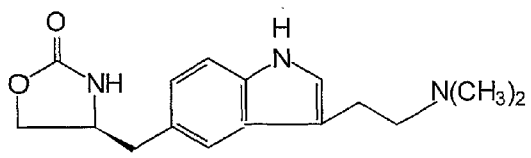
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2008/007390 A2

(54) **Title:** AN IMPROVED PROCESS FOR PURIFICATION OF ZOLMITRIPTAN



(I)

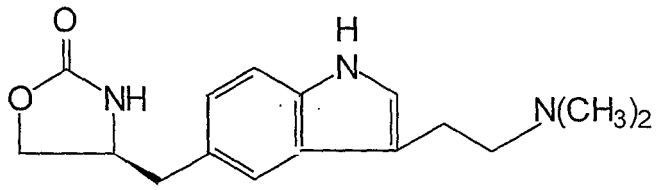
(57) **Abstract:** The present invention relates to an improved and novel process for the purification of the Zolmitriptan (I) to get highly pure drug substance of greater than 99.8% purity. Zolmitriptan is a $5HT_1$-like receptor agonist useful in the treatment and prophylaxis of migraine and is chemically known as (S)-4-[(3-[2-(Dimethylamino) ethyl]-1H-indol-5-yl] methyl]-2-oxazolidinone (I). A novel method of purification of the drug substance Zolmitriptan (I) is developed and is described.

AN IMPROVED PROCESS FOR PURIFICATION OF ZOLMITRIPTAN

Introduction

The present invention relates to an improved and novel process for the purification of the Zolmitriptan (I) to get highly pure drug substance of greater than 99.8% purity.

Zolmitriptan is a $5HT_1$-like receptor agonist useful in the treatment and prophylaxis of migraine and is chemically known as (S)-4-[(3-[2-(Dimethylamino) ethyl]-1H-indol-5-yl] methyl]-2-oxazolidinone (I)



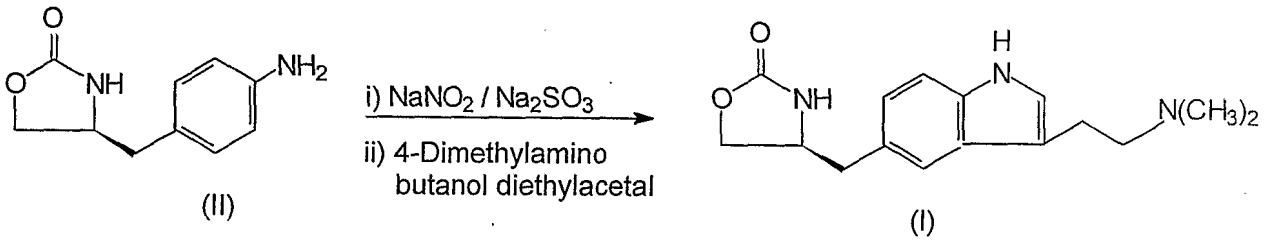
(I)

Zolmitriptan (I) is generally prepared according to the methods described in the patents like WO 91/18897, WO 97/06162, and EP 1227095. The product prepared by any of these methods is initially obtained in the crude form and needs extensive purification to meet the pharmacological standards.

A novel method of purification of the drug substance Zolmitriptan (I) is developed and is described here.

Background of the invention

Zolmitriptan (I) is generally prepared according to the following scheme by indolization of the intermediate, (S)-4-(4-Aminobenzyl)-1,3-oxazolidin-2-one (II) by known processes described in WO 91/18897



(II) (I)

Crude Zolmitriptan (I) obtained as above is usually contaminated with impurities and a method of purification is disclosed in the patents WO 97/06162 and EP 1227095. In this procedure, Zolmitriptan obtained from the reaction mixture is extracted with ethyl acetate at 50°C and the solvent is distilled off after charcoal treatment. The concentrated mass is chilled to 5°C and the crude product is centrifuged and dried. The crude dry product thus obtained is dissolved in a mixture of 10% ethanol in ethyl acetate, treated with decolorizing charcoal and filtered hot. On cooling and filtering, Zolmitriptan is obtained as a 'solvated product'. To remove the solvated ethyl acetate from the semi-purified product, the dry product as 'ethyl acetate solvate' is treated with a mixture of 20% acetone in water, cooled and filtered. The filtered product is again washed with ethyl acetate and finally dried to get purified Zolmitriptan

Objective and summary of the present invention

The process of purification described in the prior art procedure described above is complex and cumbersome and involves preparation and isolation of the drug substance

Zolmitripan as 'ethylacetate solvate'. Further purification of this isolated solvate is essential to 'desolvate' this intermediate product rendering the process further complicated. Therefore, a need is felt to develop a simplified method of purification of crude Zolmitriptan free of intermediate formation of solvates.

Taking into consideration the above mentioned shortcomings of the hitherto known prior art processes for the preparation of zolmitriptan of the formula I, our aim was directed towards developing an improved environmentally safe and industrially applicable process, which is devoid of the above-mentioned insufficiencies.

Therefore the main objective of the present invention is to provide an improved process for the preparation of highly pure (> 99.8%) zolmitriptan overcoming the drawbacks of the hitherto known prior art processes.

Still another objective of the present invention is to provide an improved process for the preparation of highly pure (> 99.8%) zolmitriptan of the formula (I) avoiding the solvate formation thereby making the process simple.

Yet another objective of the present process is to provide an improved process for the preparation of highly pure (> 99.8%) zolmitriptan by isolating crude zolmitriptan by extracting with chloroform at room temperature thereby avoiding extractions at 50°C.

Yet another objective of the present process is to provide an improved process for the preparation of highly pure (> 99.8%) zolmitriptan by crystallization with aqueous acetonitrile, which is hitherto not known.

Still another objective of the present invention is to provide an improved process for the preparation of highly pure (> 99.8%) zolmitriptan of the formula (I) by using Isopropanol (IPA) as a second crystallization solvent.

Yet another objective of the present invention is to provide a process for the preparation of highly pure zolmitriptan (>99.8%) of the formula (I) is to distill off IPA to the desired residual volume and add water to precipitate zolmitriptan

Another objective of the present invention is to provide an improved process for the purification of highly pure (> 99.8%) zolmitriptan by separating it from the unwanted by products and other impurities formed during the course of indolization

Still another objective of the present invention is to provide an improved process for the preparation of highly pure (>99.8%) zolmitriptan of the formula (I) avoiding additional purification steps and reducing operational time thereby making the process economical.

Accordingly, the present invention provides an improved process for the preparation of highly pure (>99.8%) zolmitriptan of the formula (I) and therefore obviates the 'desolvation step' of purification.

The process of this invention consists of the following steps:

a) After indolization, extracting the impurity from the reaction mixture with Chloroform by adjusting reaction mass pH to 7.0 at room temperature.

b) Extracting the Product with Chloroform by adjusting the reaction mass pH to 10.0 at room temperature.

c) Decolourizing the chloroform layer using activated charcoal in hot condition.

d) Isolating the zolmitriptan crude by distilling off the Chloroform layer, filtering and drying e) Dissolving the crude Zolmitriptan in refluxing mixture of aqueous acetonitrile

f) Slowly cooling the solution to a temperature of about 0 °C.

g) Filtering the product and washing with DM water.

h) Dissolving the product in refluxing Isopropanol.

i) Decolourizing suitably the Isopropanol layer using activated charcoal in hot condition

j) Concentrating, filtering Isopropanol to the desired volume and adding DM water to it.

k) Filtering the product from step (j)

l) Washing with DM water and then drying

The decolourization of step (c) is carried out at temperature 45-55 °C, which is more preferably at 50 °C. The drying stage of step (d) is preferably carried out under vacuum. Suitably the product is dried at temperature 40-60 °C, which is more preferably at 50 °C. The preferable refluxing mixture of step e) is 40% acetonitrile in water. The cooled solution of step (f) is suitably stirred over a prolonged period, which is preferably approximately 8 hours.

The decolourization of step (i) is carried out at temperature 50-70°C, which is preferably approximately 60 °C.

The desired IPA volume of step (j) is preferably approximately 3 volumes with respect to the weight of the crude product of step d).

The drying stage of step (l) is preferably carried out under vacuum. Suitably the product is dried at temperature 40-60 °C, which is more preferably at 50 °C.

The details of the invention are given in the Example, which is provided for illustration only and therefore the Example should not be construed to limit the scope of the invention.

Example

The starting material (S)-4-(4-Aminobenzyl)-2-oxazolidinone is made in accordance with Example-as per Natco's granted patent IN 198915 titled 'Novel Process for the preparation of (S)-4-(4-Aminobenzyl)-2-oxazolidinone' granted on 17-02-2006. The corresponding PCT application has been published with publication no. WO/2004/063175.

Example - 1

The preparation of (S)-4-[(3-[2-(Dimethylamino)ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone (I):

Charge to the flask 300 ml of conc. hydrochloric acid, 3L of demineralised water and 250 gms of (S)-4-(4-aminobenzyl)-2-oxazolidinone. Cool the reactor contents to between 0-5 DEG C and add aqueous sodium nitrite solution (99 gms in 900ml water), maintaining the temperature below 5 DEG C. After stirring for about 30 minutes add the diazonium salt solution to a chilled aqueous solution of sodium sulphite (492 gms in 800 ml water) maintaining the temperature below 10 DEG C. After stirring for 15 minutes slowly heat the resulting mixture to about 55-60 DEG C, and then slowly add 50 ml of conc. hydrochloric acid. The solution is maintained at about 60 DEG C for about 18 hours. Dilute the reaction mixture with 5L of water and heat to about 90 DEG C. Under a nitrogen atmosphere slowly add 246 gms of 4,4-diethoxy-N, N-dimethylbutylamine and heat at reflux for about 3 hours. Cool, and adjust the mixture to about pH7 using sodium hydroxide solution. Extract with chloroform and then adjust the aqueous layer to about pH10, again using sodium hydroxide solution. Extract the product using chloroform. Treat the combined chloroform extracts (containing the product) with decolorizing charcoal, and filter through filter aid. Distil off most of the solvent and chill the suspension to about 0 DEG C. Centrifuge the crude product, wash with chloroform and vacuum dry at 50 DEG C. (150 gms, pale yellow powder, 99.4% HPLC purity)

Example – 2

Purification of (S)-4-{3-[2-(dimethylamino)ethyl]-1H-indol-5-yl]methyl}-2-oxazolidinone :

The crude product of example- 1 is dissolved in a refluxing mixture of 1.5L of 40% acetonitrile in water, treated with decolourising charcoal and filtered hot through filter aid. The solution is slowly cooled to above 0 DEG C and stirred for 8 hours. The purified product is then filtered, washed with water and vacuum dried at 50 DEG C, the wet solid

is dissolved in 3L of refluxing IPA, treated with decolourising charcoal and filtered hot through filter aid. The filtrate is concentrated to approximately 0.5L cooled to about 25 DEG C treated with 750 ml water and stirred for 2 hrs before filtering the product, washing with water and drying in vacuum at about 50 DEG C. (60 gms, white powder, 99.87% HPLC purity)

Advantages of the process of the present invention:

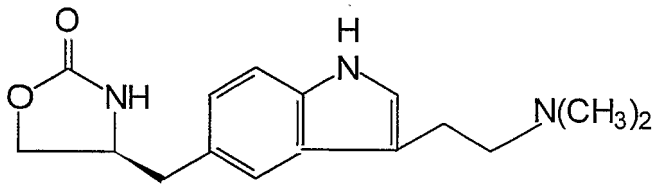
1. The isolation and purification process of zolmitriptan described here does not involve any 'solvated form' of zolmitriptan.

2. The process does not necessitate any 'desolvation step' and free of any rigorous monitoring control needed to ensure that 'desolvation' is complete.

3. Pure pharmaceutical grade of zolmitriptan with HPLC purity of more than 99.8% is obtained.

We Claim:

1. An improved process for the purification of zolmitriptan (I) which process comprises the steps of



(I)

a) Extracting the impurity with Chloroform by adjusting reaction mass pH to 7.0 at room temperature

b) Extracting the Product with Chloroform by adjusting the reaction mass pH to 10.0 at room temperature

c) Decolorizing suitably the chloroform layer using activated charcoal in hot condition.

d) Isolating the zolmitriptan crude by distilling off the Chloroform layer, filtering and drying

e) Dissolving the crude Zolmitriptan in refluxing mixture of aqueous acetonitrile

f) Slowly cooling the solution to a temperature of about 0 °C.

g) Filtering the product and washing with DM water

h) Dissolving the product in refluxing Isopropanol

i) Decolourizing the Isopropanol layer using decolourising charcoal in hot condition

j) Concentrating, filtering Isopropanol to the desired volume and adding DM water to it.

k) Filtering the product

l) Washing with DM water then drying

2. An improved process as claimed in claim1 wherein the preferable refluxing mixture of step (e) is 40% acetonitrile in water.
3. Non-solvated highly pure (> 99.8%) zolmitriptan

4. A novel method of preparing Non-solvated highly pure (> 99.8%) zolmitriptan essentially as herein described with reference to examples 1 & 2.