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

(19) **World Intellectual Property Organization**
International Bureau

(43) **International Publication Date**
13 January 2011 (13.01.2011)

PCT

(10) **International Publication Number**
WO 2011/004391 A2

(51) **International Patent Classification**: ***C07D 403/06*** (2006.01)

(21) **International Application Number**: PCT/IN2010/000432

(22) **International Filing Date**: 24 June 2010 (24.06.2010)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
1487/CHE/2009 25 June 2009 (25.06.2009) IN

(71) **Applicant** *(for all designated States except US)*: **MATRIX LABORATORIES LTD** [IN/NA]; 1-1-151/1/, IV Floor, Sairam Towers, Alexander Road, Secunderabad 500 003 (IN).

(72) **Inventors; and**
(75) **Inventors/Applicants** *(for US only)*: **KARUSALA, Nageswara Rao**; Plot No 34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak Dist, Hyderabad 500 055, Andhra Pradesh (IN). **CHAVHAN, Bhausaheb**; Plot No 34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak Dist, Hyderabad 500 055, Andhra Pradesh (IN). **SIGAMSETTY, Radha Krishna**; Plot No 34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak Dist, Hyderabad 500 055, Andhra Pradesh (IN). **KOTHAKONDA, Sudarshan Rao**; Plot No 34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak Dist, Hyderabad 500 055, Andhra Pradesh (IN). **CHANDUPATLA, Siva Kumar**; Plot No 34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak Dist, Hyderabad 500 055, Andhra Pradesh (IN). **DATTA, Debashish**; Plot No 34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak Dist, Hyderabad 500 055, Andhra Pradesh (IN).

(74) **Agent**: **NARAHARI, Babu Ambati**; Plot No 34A, Anrich Industrial Estate, Bollaram, Jinnaram Mandal, Medak Dist, Hyderabad 500 055, Andhra Pradesh (IN).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, 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, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2011/004391 A2

(54) **Title**: AN IMPROVED PROCESS FOR THE PREPARATION OF ELETRIPTAN AND ITS SALT THEREOF

(57) **Abstract**: The present invention relates to an improved process for the preparation of Eletriptan hydrobromide by hydrolyzing (R)-1-acetyl-5-(2-phenylsulphonylethenyl)-3-(N- methylpyrrolidin-2-ylmethyl)-1 H-indole, followed by reduction in the presence of a metal catalyst, methanesulphonicacid in a solvent, to get the Eletriptan methanesulphonate. Setting free of the methanesulphonate salt with a base and the compound is extracted into an organic solvent, optionally passed the organic layer through silica gel column, the solvent is evaporated to get residue. The residue is dissolved in another solvent followed by addition of aqueous hydrobromic acid to get Eletriptan hydrobromide.

AN IMPROVED PROCESS FOR THE PREPARATION OF ELETRIPTAN AND ITS SALT THEREOF

This patent application claims priorities from Indian patent applications 1487/CHE/2009 dated Jun 25, 2009; the contents of which are incorporated by reference in their entirety.

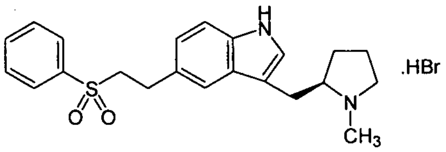
FIELD OF THE INVENTION:

The present invention relates to an improved process for the preparation of Eletriptan or its pharmaceutically acceptable salt thereof.

The present invention also relates to novel Eletriptan methanesulphonate monohydrate and further converted to Eletriptan hydrobromide polymorphic forms such as α and β.

BACK GROUND OF THE INVENTION:

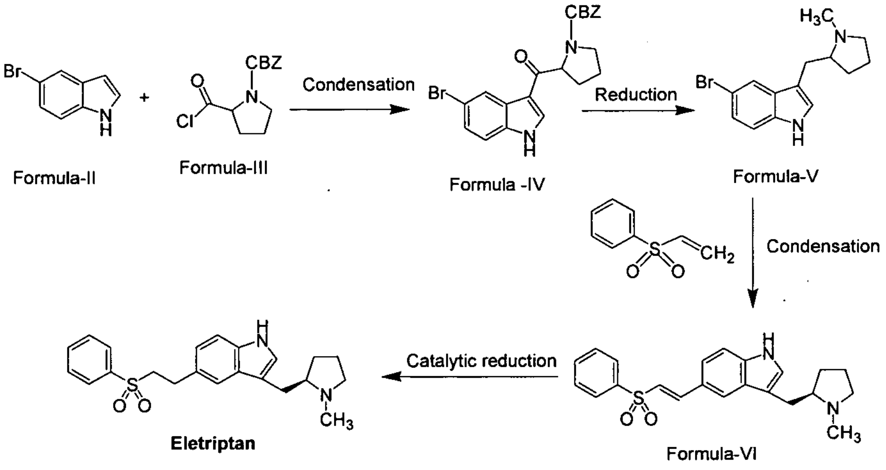
Eletriptan is used for the acute treatment of migraine with or without aura in adults. Eletriptan is a selective 5-hydroxytryptamine 1B/1D receptor agonist. Eletriptan hydrobromide having structure of formula-I is chemically known as 3-[[(2*R*)-1-Methyl-2-pyrrolidinyl] methyl]-5-[2-(phenylsulfonyl)ethyl]-1*H*-indole hydrobromide and is being sold under the trade name RELPAX®.



Formula-I

European Patent No. 0592438 describes the preparation of Eletriptan by the catalytic reduction of (R)-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1*H*-indole of formula-VI, which is prepared by reaction of N-benzyloxycarbonyl-D-proline acid chloride of formula-III with 5-bromoindole of formula-II to get the compound of formula-IV, upon reduction of compound of formula-IV to produce (R)-5-bromo-3-(N-methylpyrrolidin-2-ylmethyl)-1*H*-indole of formula-V followed by reaction with phenylvinyl sulphone in the presence of a palladium catalyst, a triarylphosphine to produce the compound of formula-VI.

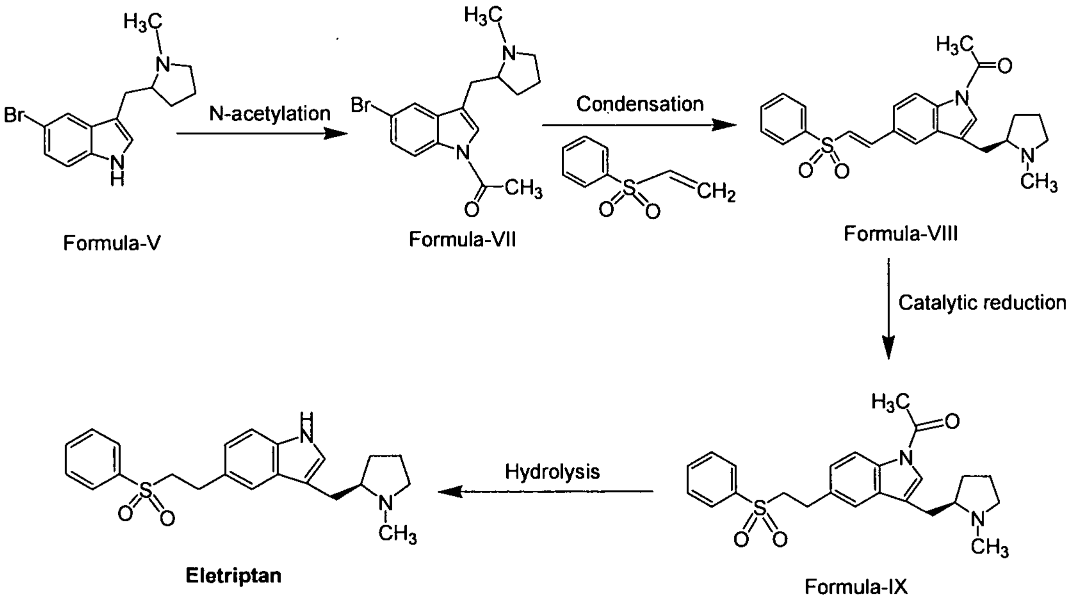
Scheme-I



US patent no 7288662 describes the preparation of Eletriptan by hydrolysis of (R)-1-acetyl-5-(2-phenylsulphonylethyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1*H*-indole of formula-IX, which is prepared by N-acetylation of (R)-5-bromo-3-(N-methylpyrrolidin-2-ylmethyl)-1*H*-indole of formula-V, upon reacting the resulting N-acetyl derivative of formula-VII with phenyl vinyl sulphone to give (R)-1-acetyl-5-(2-phenyllsulphonylethenyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1*H*-indole of formula-VIII followed by reducing the compound of formula-VIII in the presence of a palladium catalyst to give compound of formula-IX.

The schematic description is as shown in the scheme-II given below.

Scheme-II



Main drawbacks associated with the prior art processes are that the compound of formula-VI is prone to dimerise which is difficult to remove. Additional crystallization steps are required to remove the dimer impurity and structurally similar impurities that are formed in the reaction to achieve the desired purity, which leads yield.

PCT publication WO2009142771 describes p-toluene sulfonic acid, benzene sulphonic acid, trifluoroacetic acid, methane sulphonic acid, formic acid or succinic acid salts of (R)-5-(2-phenylsulphonylethenyl)-3(N-methylpyrrolidine-2-ylmethyl)-1*H*-indole, process for its preparation of Eletriptan and further conversion to hydrobromide salt.

US patent 6110940 discloses the process of α-polymorphic form of Eletriptan hydrobromide by reacting 62% w/w Hydrobromic acid with Eletriptan in acetone under reflux condition. The US '940 patent also disclosed process of β-polymorphic form by reacting 49% w/w Hydrobromic acid with Eletriptan in 1,2-dimethoxyethane at about 5°C. After completion of the reaction the cooling bath was removed and the resulting slurry was allowed to granulate by stirring at room temperature for a further 18 hours.

The above process involves the high concentration of hydrobromic acid under extreme conditions. Keeping in view of the difficulties in commercialization of the above mentioned processes for the preparation of Eletriptan, still there is a need for the alternate, more convenient, improved process for producing Eletriptan or its pharmaceutically acceptable salts. The present invention does not involve the isolation of compound of formula-VI, thereby overcomes the problems associated with dimer impurity.

SUMMARY AND OBJECT OF THE INVENTION:

The present invention relates to an improved and efficient process for the preparation of Eletriptan or its pharmaceutically acceptable salts thereof.

One aspect of the present invention provides a process for the preparation of Eletriptan hydrobromide of formula-I which comprises: a) hydrolyzing (R)-1-acetyl-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidin-2-ylmethyl-)-1H-indole of formula-VIII in the presence of a base in a solvent to get (R)-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidine-2-yl-methyl)-1H-indole of formula-VI, b) reducing the compound of formula-VI in the presence of a metal catalyst, methane sulphonic acid in a solvent to get the compound of formula-X, c) setting free of the compound in step b), d) extracting the compound into an organic solvent, e) optionally passing the organic layer through silica gel column, f) removing the solvent, adding another solvent, g) treating with hydrobromic acid, and h) isolating Eletriptan hydrobromide of formula-I.

Another aspect of the present invention provides a process for purification of Eletriptan methanesulphonate of formula-X which comprises: a) setting free of Eletriptan acid addition salt, b) extracting the compound into an organic solvent, c) optionally passing the organic layer through silica gel column, d) removing the solvent, adding another solvent, e) treating with methanesulphonic acid, and f) isolating pure Eletriptan methanesulphonate of compound of formula-X.

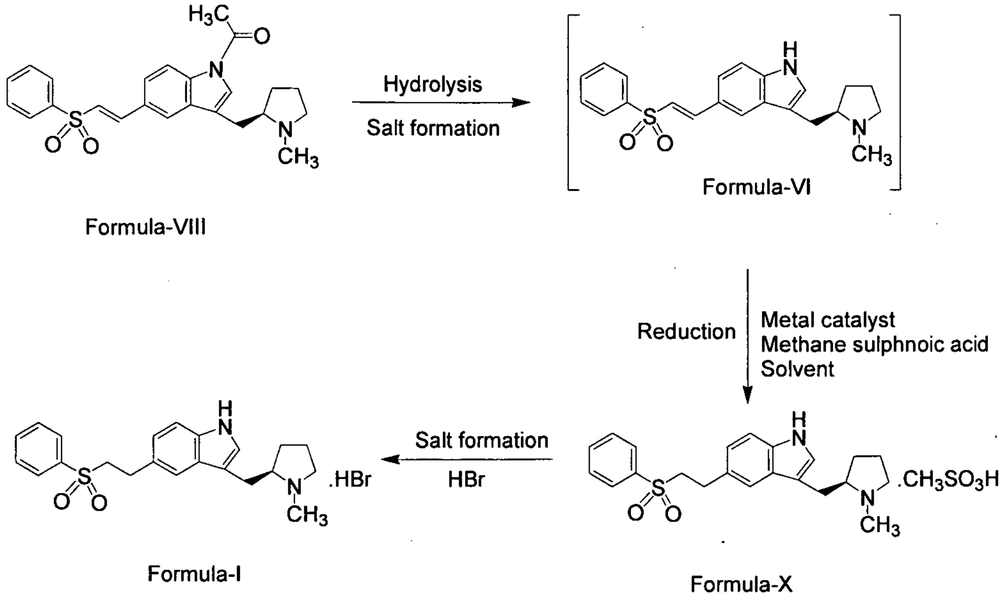
Yet another aspect of the present invention provides an improved process for the preparation of α-polymorphic form of Eletriptan hydrobromide which comprises: a) dissolving Eletriptan in a solvent, b) treating with hydrobromic acid, c) adding step b) solution to an antisolvent containing the seed of Eletriptan hydrobromide α-polymorphic form, d) adding an antisolvent to step c), and e) isolating Eletriptan hydrobromide α-polymorphic form.

Yet another aspect of the present invention provides a novel process for the preparation of β polymorphic form of Eletriptan hydrobromide which comprises: a) dissolving Eletriptan in a solvent, b) treating with hydrobromic acid, c) adding step b) solution to an antisolvent containing the seed of Eletriptan hydrobromide β-polymorphic form, d) adding an antisolvent to step c), and d) isolating Eletriptan hydrobromide β-polymorphic form.

Yet another aspect of the present invention is to provide novel Eletriptan methanesulphonate monohydrate.

The schematic representation of the present invention is as shown in Scheme-III.

Scheme-III



BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a representative X-ray diffraction pattern of Eletriptan methanesulphonate monohydrate.

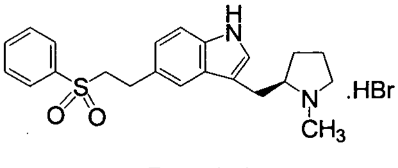
FIG. 2 is a representative of Differential scanning calorimetric (DSC) curve of Eletriptan methanesulphonate monohydrate.

FIG. 3 is a representative of Thermal Gravimetric Analysis (TGA) of Eletriptan methanesulphonate monohydrate.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an improved process for the preparation of Eletriptan hydrobromide by hydrolyzing (R)-1-acetyl-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidin-2-ylmethyl)-1H-indole, followed by reduction in the presence of a metal catalyst, methane sulphonic acid in a solvent, to get the Eletriptan methane sulphonate. Setting free of the methanesulphonate salt with a base and the compound is extracted into an organic solvent, optionally passed the organic layer through silica gel column, the solvent is evaporated to get residue. The residue is dissolved in another solvent followed by addition of aqueous hydrobromic acid to get Eletriptan hydrobromide.

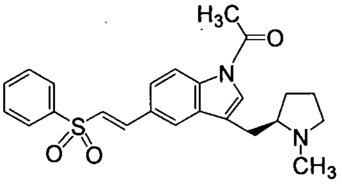
One embodiment of the present invention provides an improved process for the preparation of Eletriptan hydrobromide of formula-I



Formula-I

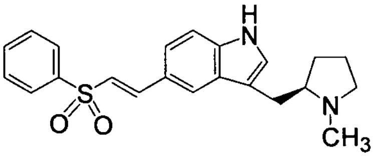
which comprises:

a) hydrolyzing (R)-1-acetyl-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidin-2-ylmethyl-)-1H-indole of formula-VIII



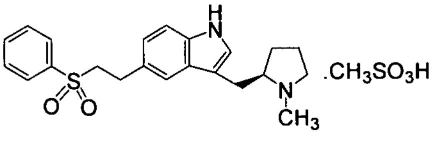
Formula-VIII

in the presence of a base in a solvent to get (R)-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidine-2-yl-methyl)-1H-indole of formula-VI,



Formula-VI

b) reducing the compound of formula-VI in the presence of a metal catalyst, methane sulphonic acid in a solvent to get the compound of formula-X,



Formula-X

c) setting free of the compound of formula-X with a base,

d) extracting the compound into an organic solvent,

e) optionally passing the organic layer through silica gel column,

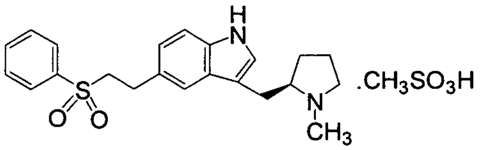
f) removing the solvent, adding another solvent,

g) treating with hydrobromic acid, and
h) isolating Eletriptan hydrobromide of formula-I.

According to the present invention (R)-1-acetyl-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidin-2-ylmethyl-)-1H-indole of formula-VIII is dissolved in a solvent, inorganic base is added in a single lot and reaction mass is stirred for about 1-3 hours at 25-35°C. After completion of hydrolysis, treated with carbon, followed by distillation to get residue solvent is removed by distillation. The residue thus obtained is dissolved in another solvent and reduction is carried out in the presence of metal catalyst and methane sulphonicacid under hydrogen gas pressure 2-6 kg for about 6-12 hrs at 25-35°C. The catalyst is filtered, solvent is removed by distillation and water is added. The resulting solution pH is adjusted to 7-10 with a base and compound is extracted in solvent. The organic layer is optionally passed through silica gel column and distilled off the solvent. The residue thus obtained is dissolved in a solvent and hydrobromic acid is slowly added to the solution for about 20-60 min at room temperature and stirred the reaction mass for about 1-2 hours to get Eletriptan hydrobromide of formula-I.

According to the present invention the solvent used for dissolution of compound of formula-VIII is selected from methanol, ethanol, propanol, butanol or isopropanol and the base is selected from potassium carbonate or sodium carbonate. The metal catalyst used for reduction is selected from palladium on carbon, palladium hydroxide, palladium on alumina, platinum dioxide, platinum on carbon or Raney nickel, preferably palladium on carbon and the solvent is selected from acetone, methylethylketone, methylisobutyl ketone, water or mixtures thereof. Base used for the pH adjustment is selected from sodium hydroxide, potassium hydroxide preferably aqueous sodium hydroxide. The extraction solvent is selected from ethylacetate, methylacetate, dichloromethane, chloroform, toluene or ether. Solvent used in the hydrobromide preparation is selected from acetone, methylethyl ketone, methyl butyl ketone, acetonitrile, methanol, ethanol, isopropanol or n-butanol.

Yet another embodiment of the present invention provides a process for the purification of Eletriptan methanesulphonate of compound of formula-X



Formula-X

which comprises:

a) setting free of Eletriptan acid addition salt with a base,
b) extracting the compound into an organic solvent,
c) optionally passing organic layer through silica gel column,
d) removing the solvent, adding another solvent,
e) treating with methanesulphonic acid, and
f) isolating pure Eletriptan methanesulphonate of compound of formula-X.

According to the present invention Eletriptan methane sulphonate is dissolved in water and clear solution pH is adjusted to about 7-10 with a base. The compound is extracted in to a solvent and removed the solvent by distillation. Optionally the organic layer is passed through silica gel column and removed the solvent by distillation to get residue. The residue thus obtained is dissolved in another solvent, methane sulphonic acid is slowly added, cooled to 0-10°C for about 1-3 hrs and filtered to get pure compound of formula-X.

According to the present invention base used for the pH adjustment is selected from sodium hydroxide, potassium hydroxide preferably aqueous sodium hydroxide. The extraction solvent is selected from ethylacetate, methylacetate, dichloromethane, chloroform, toluene or ether. Solvent used in step e) in the preparation of methanesulphonate salt formation is selected from acetone, methylethyl ketone, methyl butyl ketone, acetonitrile, methanol, ethanol, isopropanol or n-butanol.

According to the present invention the solution is adjusted to 7-10 and extracted the compound into organic solvent. Here, only pure product is extracted, dimeric impurities and other structurally related impurities are washed in water.

Yet another embodiment of the present invention provides an improved process for the preparation of Eletriptan hydrobromide α-polymorphic form which comprises:

a) dissolving Eletriptan in a solvent,
b) treating with hydrobromic acid,
c) adding step b) solution to an antisolvent containing the seed of Eletriptan hydrobromide α-polymorphic form,
d) adding an antisolvent to step c), and
e) isolating Eletriptan hydrobromide α-polymorphic form.

According to the present invention Eletriptan is dissolved in a solvent, aqueous hydrobromic acid is slowly added to the solution for about 20-60 min at 20-35°C and stirred the solution for about 1-2 hours. This solution is added to an antisolvent which is seeded with Eletriptan hydrobromide α-polymorphic form at 5-20°C. This solution is further diluted by slow addition of an antisolvent for a period of 30-60min at 5-20°C and the obtained solid is filtered to get Eletriptan hydrobromide α-polymorphic form.

According to the present invention solvent used for dissolution of Eletriptan is selected from acetone, methylethyl ketone, methyl butyl ketone, acetonitrile, methanol, ethanol, isopropanol or n-butanol. And the anti-solvent is selected from methyl tertiary butyl ether, diisopropyl ether or diethyl ether.

Yet another embodiment of the present invention provides an improved process for the preparation of Eletriptan hydrobromide β-polymorphic form which comprises:

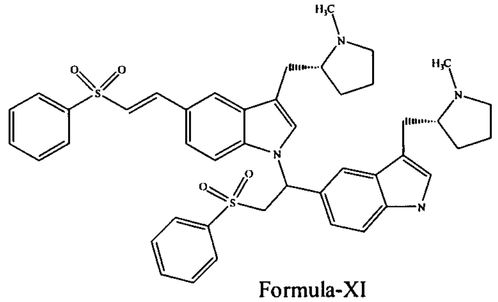
a) dissolving Eletriptan in a solvent,
b) treating with hydrobromic acid,
c) adding step b) solution to an antisolvent containing the seed of Eletriptan hydrobromide β-polymorphic form,
d) adding antisolvent to step c), and
e) isolating Eletriptan hydrobromide β-polymorphic form.

According to the present invention Eletriptan is dissolved in a solvent, aqueous hydrobromic acid is slowly added to the solution for about 20-60 min at 20-35°C and stirred the solution for about 1-2 hours. This solution is added to an antisolvent which is seeded with Eletriptan hydrobromide β-polymorphic form at 5-20°C. This solution is further diluted by slow addition of an antisolvent for a period of 30-60min at 5-20°C and the obtained solid is filtered to get Eletriptan hydrobromide β-polymorphic form.

According to the present invention solvent used for dissolution of Eletriptan is selected from acetone, methylethyl ketone, methyl butyl ketone, acetonitrile, methanol, ethanol, isopropanol or n-butanol: And the anti-solvent is selected from methyl tertiary butyl ether, diisopropyl ether or diethyl ether.

According to the present invention said Eletriptan acid addition salt is selected from methanesulphonic acid, p-toluenesulphonic acid, formic acid, acetic acid, hydrochloric acid or sulfuric acid.

Yet another embodiment of the present invention provides Eletriptan free of dimeric impurity formula-XI,



Formula-XI

Yet another embodiment of the present invention provides a crystalline Eletriptan methanesulphonate monohydrate.

Yet another embodiment of the present invention provides a crystalline Eletriptan methanesulphonate monohydrate is characterized by an X-ray diffraction pattern with peaks at 14.07, 14.92, 15.31, 17.56, 18.39, 18.54, 19.02, 20.87, 21.17, 22.35, 22.60, 22.83, 23.49, 23.86 ± 0.2 degrees 2θ as shown in Fig.1.

Yet another embodiment of the present invention provides a crystalline Eletriptan methanesulphonate monohydrate, is characterized by Thermal Gravimetric Analysis (TGA) with water loss of about 3.5 -3.8% as shown in Fig.2.

Yet another embodiment of the present invention provides a crystalline Eletriptan methanesulphonate monohydrate, is characterized by a Differential Scanning Calorimetry (DSC) with two endothermic peaks at 101.95°C and 131.58°C. The typical DSC thermogram is shown in figure Fig.3.

Yet another embodiment of the present invention provides a pharmaceutical composition comprising therapeutically effective amount of Eletriptan or pharmaceutically acceptable salt and at least one pharmaceutically acceptable carrier

Advantages of the present invention:

1. High yield of Eletriptan hydrobromide is achieved by the process of the present invention with purity more than 99%,
2. By extracting the product in a solvent at pH 7.4 to 7.6, only pure product is extracted in to the organic layer leaving almost all the impurities in aqueous layer,
3. By passing organic layer through silica gel column all dimeric impurities are holding in silica gel and thus helping to get pure product with maximum yield.

The invention is illustrated with the following examples, which are provided by way of illustration only and should not be construed to limit the scope of the invention.

EXPERIMENTAL SECTION

Powder X-ray Diffraction (PXRD)

The PXRD measurements were carried out using *PANalytical*, *X'Pert PRO* powder diffractometer equipped with goniometer of θ/θ configuration and X'Celerator detector. The Cu-anode X-ray tube was operated at 40kV and 30mA. The experiments were conducted over the 2θ range of 2.0°-50.0°, 0.030° step size and 50 seconds step time.

Differential Scanning Calorimetry (DSC)

The DSC measurements were carried out on Mettler Toledo 822 Stare and TA Q1000 of TA instruments. The experiments were performed at a heating rate of 10.0°C/minute over a temperature range of 30°C-300°C purging with nitrogen at a flow rate of 50ml/minute. Standard aluminum crucibles covered by lids with three pin holes were used.

Thermal Gravimetric Analysis (TGA)

TGA is carried out using instrument TGA/SDTA 851. The experiments were performed at a heating rate of 10.0°C/minute over a temperature range of 30-250°C purging with nitrogen at a flow rate of 25ml/minute.

Example-1: Preparation of (R)-1-Acetyl-5-(2-phenylsulphonylethenyl)-3(N-methyl pyrrolidine-2-ylmethyl)-1-H-indole:

Part-A:

To a mixture of acetonitrile (180ml) and 5-bromo-N-methyl-pyrrolidine-1*H*-indole (100g) was added acetic anhydride (52.2g) and triethylamine (51.7g) at 25-35°C. The reaction mass was heated to 78-83°C and stirred the reaction mass at the same temperature for about 6-7 hours. The reaction mass was cooled to 25-35°C to yield N-acetyl derivative of 5-bromo-N-methyl-pyrrolidine-1*H*-indole.

Part-B:

Mixture of acetonitrile (185ml), tri-O-tolyl phosphine (23.4g) and palladium acetate (4.84g) were stirred for about 1 hour at 25-35°C. Phenyl vinyl sulphone (62.75g) and triethyl amine (37.9g) were added to the reaction mass at 25-35°C and stirred for about 15-20 minutes. Reaction mass obtained in part-A was added to the reaction mixture for about 20-30 minutes at 25-35°C. The temperature of the reaction mass was raised to 78-83°C and stirred at the same temperature for about 6-8 hrs. The reaction mass was cooled to 25-35°C and dilute HCl solution (HCl-76ml and water 468ml) was slowly added over a period of two hours. The reaction mass was stirred at 25-35°C for about two hours, filtered through hyflo bed to remove unwanted salts and washed with acetonitrile (30ml). The filtrate is washed with toluene (200ml X 3) to remove the impurities. The product was recovered back from toluene layer with water and HCl and combined to the main aqueous layer. Further water (968ml) was added to aqueous layer before precipitation with 50% sodium hydroxide solution at pH 10.5 to 11 at 25-30°C. The slurry was stirred at 25-30°C for one hour filtered and washed with water to obtain 200-225g of crude product.

The crude wet material was leached in a mixture of methanol (300ml) and water (200ml) at 25-35°C for about 2-3 hrs. The obtained solid was filtered, washed with water and dried at 45°C for about 6-10 hrs to get 110-130g of the title compound.

Example-2: Preparation of (R)-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidine-2-yl-methyl)-1*H*-indole methanesulphonate:

To a mixture of methanol (600ml) and (R)-1-acetyl-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidine-2-ylmethyl)-1*H*-indole (100g) was added potassium carbonate (11.45g) in one lot at 25-30°C and stirred the reaction mass for about 90-120 min. Carbon (5g) was added to the reaction mass and stirred for about 30 minutes at 25-35°C. The reaction mass was filtered through hyflo bed and washed with methanol (100ml). Methanol was distilled out completely u/v at 40-45°C. Acetone (700ml) was added to the residue thus obtained and stirred for about 20-30 minutes at 25-35°C to get clear solution. Molecular sieves (~25g) was added to the reaction mass and stirred for about 20 min to remove water traces if any. The reaction mass was filtered to remove molecular sieves and washed with acetone (100ml). Methanesulphonic acid (22.75g) was slowly added to the filtrate at 25-35°C, stirred the slurry for about 6-8 hours at 25-35°C. The product was collected by filtration, washed with acetone (100ml) and dried at 40-45°C for about 4-6 hours to obtain 80-90g of title compound with HPLC purity of 99 %.

Example-3: Preparation of (R)-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidine-2-yl methyl)-1-H-indole methanesulphonate:

To a mixture of methanol (600ml) and (R)-1-acetyl-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidine-2-ylmethyl)-1-H-indole (100g) was added potassium carbonate (11.45g) in one lot at 25-30°C and stirred the reaction mass at the same temperature for about 90-120 min. Carbon (5g) was added to the reaction mass and stirred for about 30 minutes at 25-35°C. The reaction mass was filtered through hyflo and washed with methanol (100ml). Methanol was distilled out completely u/v at 40-45°C. Ethyl acetate (1000ml) was added to the residue and stirred for about 20-30 minutes at 25-35°C to get clear solution. Molecular sieves (~25g) was added to the clear solution and stirred for about 20 minutes to remove water traces if any. Thre reaction mass was filtered, washed with ethyl acetate (100ml). Methanesulphonic acid (22.75g) was slowly added to the filtrate for about 20 to 30 minutes at 25-35°C, stirred the slurry for about 6-8 hours at 25-35°C. The product was collected by filtration and washed with ethyl acetate (100ml) and dried at 40-45°C for 4-6 hours to obtain 80-90g of the title compound with HPLC purity of 99%.

Example-4: Preparation of (R)-5-(2-phenylsulphonylethenyl)-3(N-methylpyrrolidine-2-ylmethyl)-1-H-indole methane sulphonate:

To a mixture of methanol (600 ml) and (R)-1-Acetyl-5-(2-phenylsulphonylethenyl)-3(N-methylpyrrolidine-2-ylmethyl)-1H-indole (100g) was added potassium carbonate (11.45g) in one lot at 25-35°C and stirred for about 90-120 min. Carbon (5g) was added and stirred for about 30 minutes at 25-35°C. Filtered through hyflo and washed with methanol (100 ml). Methanol was distilled out completely u/v at 40-45°C. Traces of methanol were removed by distilling out acetone (100 ml). Acetone 400 ml was added to the residue and stirred for 20-30 minutes at 25-35°C to get clear solution. Molecular sieves (~12.5 g) were added to the clear solution and stirred for 20 minutes to remove water traces if any. Filtered and washed with acetone (200 ml). This acetone layer is used and proceeds to next step preparation.

Example-5: Preparation of (R)-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidine-2-yl methyl)-1-H-indole formate:

To a mixture of methanol (300ml) and (R)-1-acetyl-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidine-2-ylmethyl)-1*H*-indole (50g) was added potassium carbonate (5.73g) in one lot and stirred the reaction mass for about 90-120 min. Carbon (2.5g) was added to the reaction mass and stirred for about 30 minutes at 25-35°C. Filtered the reaction mass through hyflo and washed with methanol (50ml). Methanol was distilled out completely u/v at 40-45°C. Acetone (400ml) was added to the residue and stirred for 20-30 minutes at 25-35°C to get clear solution. Molecular sieves (~25g) were added to the clear solution and stirred for 20 minutes to remove water traces if any. Filtered and washed with 50 ml ethyl acetate. Formic acid (5.45g) was slowly added to the filtrate for about 20 to 30 minutes at 25-35°C, stirred the reaction mass for about 1 hour and distilled out acetone completely. Hexane was added to the residue and stirred for about 1 hour at 25-35°C. The product was collected by filtration, washed with hexane (50ml) and dried at 40-45°C for about 4-6 hours to get 40-45 g of title compound with HPLC purity of 99%.

Example-6: Preparation of (R)-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidine-2-yl methyl)-1-H-indole acetate:

To a mixture of methanol (300ml) and (R)-1-acetyl-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidine-2-ylmethyl)-1*H*-indole (50g) was added potassium carbonate (5.73g) in one lot and stirred for about 90-120 min. Carbon (2.5g) was added and stirred for about 30 min at 25-35°C. Filtered through hyflo and washed with methanol (50ml). Methanol was distilled out completely u/v at 40-45°C. Traces of methanol were removed by distilling out acetone (50ml). Acetone (400) ml was added to the residue and stirred for about 20-30 minutes at 25-35°C to get clear solution. Molecular sieves (~25g) were added to the clear solution and stirred for 20 minutes to remove water traces if any. Filtered and washed with 50 ml ethyl acetate. Acetic acid (7.1g) was slowly added to the filtrate for about 20 to 30 minutes at 25-35°C, stirred for about 1 hour and distilled out acetone completely. Hexane was added to the residue and stirred for about 1 hour at 25-35°C. The product was collected by filtration, washed with hexane (50ml) and dried at 40-45°C for about 4-6 hours to get 40-45 g of title compound with HPLC purity of 99%.

Example-7: Preparation of (R)-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidine-2-yl methyl)-1-H-indole hydrobromide:

To a mixture of methanol (300ml) and (R)-1-acetyl-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidine-2-ylmethyl)-1*H*-indole (50g) was added potassium carbonate (5.73g) in one lot and stirred for about 90-120 min. Carbon (2.5g) was added and stirred for about 30 min at 25-35°C. Filtered through hyflo and washed with methanol (50ml). Methanol was distilled out completely u/v at 40-45°C. Traces of methanol were removed by distilling out acetone (50ml). Acetone (400) ml was added to the residue and stirred for about 20-30 minutes at 25-35°C to get clear solution. Molecular sieves (~25g) were added to the clear solution and stirred for 20 minutes to remove water traces if any. Filtered and washed with 50 ml ethyl acetate. 48% hydrobromic acid solution (19.74g) was slowly added to the filtrate for about 20 to 30 minutes at 25-35°C, stirred for about 1 hour and distilled out acetone completely. Hexane was added to the residue and stirred for about 1 hour at 25-35°C. The product was collected by filtration, washed with hexane (50ml) and dried at 40-45°C for about 4-6 hours to get 40-45 g of title compound with HPLC purity of 99%.

Example-8: Preparation of (R)-5-(2-phenylsulphonylethyl)-3(N-methylpyrrolidine-2-ylmethyl)-1-H-indole methane sulphonate:

To a mixture of the compound (acetone layer) obtained in Example-4 and acetone (200 ml) was added DM water (100 ml) and methane sulphonic acid (34.1g). Purged nitrogen gas for 5-10 minutes and palladium on carbon (20 g, 5% Pd/C 50% wet) was added. Maintained the reaction mass under hydrogen atmosphere for 7-10 hours at 25-35°C. Filtered the catalyst, fresh palladium on carbon (10g) was added and maintained the reaction mass under hydrogen atmosphere for 7-10 hours. The reaction mass was again filtered and washed with acetone-water mixture (40+10ml). Distilled out acetone completely u/v at 40-45°C. Ethyl acetate (200 ml) was added and adjusted pH 7.4 to 7.6 with 10% sodium hydroxide solution.

Stirred the reaction mass for about 20 minutes and separated the ethyl acetate layer. Again aqueous layer was extracted twice with ethyl acetate at pH 7.4 to 7.6 for maximum recovery of product. Combined all ethyl acetate layers and washed with 25% brine solution. Ethyl acetate was distilled out from organic layer. Acetone (200 ml) was added to the residue and distilled out acetone completely. Again acetone (200 ml) was added and stirred at 25-30°C to get clear solution. Methane sulphonic acid (18g) was slowly added to the clear solution for about 15-20 minutes. Optionally seeded with Eletriptan methanesulphonate and stirred at 25-30°C for about 5-8 hours. Cooled the reaction mass to 0-5°C and stirred for about 2 hours. Filtered the reaction mass and washed with acetone (50 ml) and dried under vacuum at 40°C for about 5 hrs to get 45-60 g of the title compound.

Example-9: Preparation of (R)-5-(2-phenylsulphonylethyl)-3(N-methylpyrrolidine-2-ylmethyl)-1-H-indole methane sulphonate.

To a mixture of the compound (acetone layer) obtained in Example-4 and acetone (200 ml) was added DM water (100 ml) and methane sulphonic acid (34.1g). Purged nitrogen gas for 5-10 minutes and palladium on carbon (20 g, 5% Pd/C 50% wet) was added. Maintained the reaction mass under hydrogen atmosphere for 7-10 hours at 25-35°C. Filtered the catalyst, fresh palladium on carbon (10g) was added and maintained the reaction mass under hydrogen atmosphere for 7-10 hours. The reaction mass was again filtered and washed with acetone-water mixture (40+10ml). Distilled out acetone completely u/v at 40-45°C. Ethyl acetate (200 ml) was added at 25-35°C and stirred for 15-20 minutes. Separated the layers ethyl acetate (500 ml) was added to the aqueous layer and adjusted the pH 9-9.5 with 30% sodium hydroxide solution. Stirred the reaction mass for about 20 minutes and again separated the layers. Aqueous layer was extracted with ethyl acetate (500 ml). Combined both ethyl acetate layers and washed with DM water (300ml). The aqueous layer was separated. Ethyl acetate layer was passed through silica gel column (80 g silica gel, 100-200 mesh size) and washed the column with ethyl acetate till ethyl acetate layer is colourless. Combined all ethyl acetate elutes and distilled out ethyl acetate completely under vacuum at 45°C. Acetone (100ml) was added to the residue and distilled out acetone completely. Again acetone (200 ml) was added and maintained at 25-30°C to get clear solution. Methane sulphonic acid (18g) was slowly added to the reaction mass for about 15-20 minutes. Optionally seeded with Eletriptan methane sulphonate and stirred at 25-30°C for 5-8 hours. Cooled the reaction mass to 0-5°C and maintained for about 2 hours. Filtered the solid obtained and washed with acetone (50 ml) and dried the solid under vacuum at 40°C for 5 hrs to get 55-70g of the title compound.

Example-10: Preparation of (R)-5-(2-phenylsulphonylethyl)-3-(N-methylpyrrolidine-2-yl methyl)-1-H-indole methanesulphonate:

To a mixture of acetone (400ml) and (R)-5-(2-phenylsulphonylethenyl)-3(N-methylpyrrolidine-2-ylmethyl)-1-H-indole methanesulphonate (50g) was added DM water (100ml) and stirred for about 10-15 minutes to get clear solution. Purged nitrogen gas for 5-10 minutes and palladium on carbon (10 g, 5% Pd/C 50% wet) was added. The reaction mass was maintained under hydrogen atmosphere for about 7-10 hours at 25-35°C. Filtered the catalyst, fresh palladium on carbon (10g) was added and maintained the reaction mass under hydrogen atmosphere for about 7-10 hours. Again filtered the catalyst and fresh palladium was added. Maintained the reaction mass under hydrogen gas till HPLC shows absence of starting material. Filtered the reaction mass, washed with acetone (25ml) and distilled out acetone completely u/v at 40-45°C. Further distilled out water completely u/v at 50-55°C. Isopropyl alcohol was added to the residue and distilled out IPA completely u/v at 45-50°C to remove traces of water. Finally acetone (200ml) was added and maintained the reaction mass at 50°C for 30 minutes to get clear solution. The reaction mass was slowly cooled to 25-30°C, optionally seeded with Eletriptan methanesulphonic acid salt and stirred for about 5-6 hours at 25-30°C. Cooled the reaction mass to 0-5°C and stirred for about 2 hours at 0-5°C. Filtered the reaction mass, washed with acetone (50ml) and dried at 35-40°C for about 4-5 hours to get 30-40g title compound.

Example-11: Preparation of (R)-5-(2-phenylsulphonylethyl)-3(N-methylpyrrolidine-2-yl methyl)-1-H-indole methanesulphonate.

To a mixture of acetone (400ml) and (R)-5-(2-phenylsulphonylethenyl)-3(N-methylpyrrolidine-2-ylmethyl)-1-H-indole methanesulphonate (50g) was added DM water (100ml) and stirred for about 10-15 minutes to get clear solution. Nitrogen gas was purged for 5-10 minutes and palladium on carbon (10 g, 5% Pd/C 50% wet) was added. The reaction mass was maintained under hydrogen atmosphere for about 7-10 hours at 25-35°C. The catalyst was filtered, fresh palladium on carbon (10g) was added and maintained the reaction mass under hydrogen atmosphere for about 7-10 hours. Again the catalyst was filtered and fresh palladium was added. Maintained the reaction mass under hydrogen gas till HPLC shows absence of starting material. The reaction mass was filtered, washed with acetone (25ml) and distilled out acetone completely u/v at 40-45°C. Ethyl acetate (200 ml) was added and adjusted pH of the residue to 7.1-7.4 with 40% sodium hydroxide solution. The reaction mass was stirred for about 20 minutes and separated the ethyl acetate layer. Again aqueous layer was extracted ethyl acetate at pH 7.1 to 7.4 for maximum recovery of product. All ethyl acetate layers were combined and washed with 25% brine solution. Ethyl acetate was distilled out from organic layer. Acetone (50ml) was added to the residue and distilled out acetone completely. Acetone (200ml) was added to the residue and stirred at 25-30°C to get clear solution. Methanesulphonic acid (11g) was slowly added to the clear solution for about 15-20 minutes, optionally seeded with Eletriptan methanesulphonate and stirred at 25-30°C for about 5-6 hours. The reaction mass was cooled to 0-5°C and stirred for about 2 hours. Filtered the reaction mass, washed with acetone (50ml) and dried u/v at 40°C for 5 hrs to get 30-40 g title compound.

Example-12: Purification of Eletriptan methanesulphonate salt:

Mixture of methanol (60ml) and (R)-5-(2-phenylsulphonylethyl)-3(N-methylpyrrolidine-2-ylmethyl)-1-H-indole methanesulphonate (40g) was stirred for about 10-15 minutes to get clear solution. Methanol was distilled off completely u/v at 40-45°C. Acetone (160ml) was added to the residue at 45-50°C and stirred for about 15-20 minutes to get clear solution. The reaction mass was cooled to 25-30°C, seeded with Eletriptan methanesulphonate and maintained at the same temperature for about 5 hours. The reaction mass was cooled to 0-5°C and maintained for about 2 hrs. The obtained solid was filtered and washed with acetone to obtain 30-34g of pure Eletriptan methanesulphonate salt characterized by melting point in the range of 112-119°C.

Example-13: Purification of Eletriptan methane sulphonate salt:

Mixture of IPA (200ml) and (R) -5-(2-phenylsulphonylethyl)-3(N-methylpyrrolidine-2-ylmethyl)-1H-indole methanesulphonate (40g) were heated to 55-65°C to get clear solution. The reaction mass was cooled to 45-50°C and distilled out IPA completely under vacuum. Acetone (40 ml) was added to the residue at 45-50°C and distilled out acetone completely under vacuum. Acetone (200ml) was added and maintained the reaction mass at 55-60°C for about 3 hours. The reaction mass was cooled to 15-20°C and maintained for about 3 hours at 15-20°CThe solid thus obtained was filtered, washed with acetone (40ml) and dried the solid under vacuum for about 6-8 hours to obtain 30-34g of pure Eletriptan methane sulphonate.

Example-14: Purification of Eletriptan methane sulphonate salt:

Mixture of acetone (200ml) and (R)-5-(2-phenylsulphonylethyl)-3(N-methylpyrrolidine-2-ylmethyl)-1H-indole methane sulphonate (40g) were heated 55-60°C. Water (~10-20ml) was added slowly to the reaction mass to get clear solution. Carbon was added to the reaction mass at 55-60°C, stirred for about 20-30 minutes, filtered the obtained solid and washed with acetone. The filtrate was cooled to 20-25°C and stirred for about 3 hours at 20-25°C. Acetone (200ml) was added to the reaction mass, further cooled to 0-5°C and stirred the reaction mass at 0-5°C for about 90-120 minutes. The obtained solid was filtered, washed the reaction mass with acetone (40ml) and dried the solid under vacuum for about 6-8 hours to obtain 30-34g of pure Eletriptan methane sulphonate.

Example-15: Preparation of Eletriptan hydrobromide form Eletriptan methanesulphonate:

To a mixture of DM water (90ml) and ethyl acetate (120ml) was added Eletriptan methanesulphonate (30g) from example-8 at 25-30ºC. The pH of the reaction mass was slowly adjusted to 7-10 with 40% sodium hydroxide solution. The reaction mass was stirred for about 20 minutes and separated the organic layerAll the ethyl acetate layers were combined and washed with 25% brine solution (100ml). The layers were separated and ethyl acetate was distilled completely u/v at 40-45ºC. Acetone (50ml) was added and distilled out acetone completely u/v. Acetone (150ml) was added and stirred at 20-25º to get clear solution. 48% hydrobromic acid (10.41g) was slowly added to the clear solution thus obtained and stirred for about 30 minutes at 20-25ºC. The reaction mass was stirred at 20-25ºC for about 10 hours. The obtained solid was filtered, washed with acetone and dried u/v at 45ºC for about 6-8 hours to get 20-26g of the title compound.

Example-16: Preparation of Eletriptan hydrobromide β-form:

To a mixture of water (90 ml) and ethyl acetate (120 ml) was added Eletriptan methanesulphonate (30 g) at 25-30ºC and stirred for about 10 minutes to get clear solution. The pH of the reaction mass was adjusted to 9-9.5 with 10% sodium hydroxide solution, stirred for about 20 minutes and separated the layers. The aqueous layer was extracted with ethyl acetate (120 ml), combined all ethyl acetate layers and washed with water (120 ml). Ethyl acetate layer was added to the washings and distilled out ethyl acetate completely u/v at 40-45ºC to get viscous residue. Methanol (100 ml) was added to the residue and stirred for about 20 minutes to get clear solution. 48% aqueous hydrobromide solution (10.4g) was slowly added to the reaction mass for about 30-45 minutes at 0-40°C and the stirred the reaction mass for about one hour. Methanol was distilled off completely u/v at 40-45°C and IPA (100 ml) was added. IPA was distilled off completely u/v at 40-45°C, methanol (50 ml) was added and stirred the reaction mass to get clear solution. The methanolic solution was slowly added to a mixture of diisopropyl ether (250 ml) and seed of Eletriptan β-form for about 30-45 minutes at 20-30°C and stirred the slurry for about 1-3 hours. Filtered the solid, washed with diisopropyl ether (50 ml) and dried u/v at 40-50°C for 8-10 hours to obtain 25 g Eletriptan hydrobromide β-form.

Particle size distribution of Eletriptan hydrobromide β-form d90 is less than 100μm.

Example-17: Preparation of Eletriptan hydrobromide α-form:

To a mixture of water (90ml) and ethyl acetate (120ml) was added Eletriptan methanesulphonate (30 g) at 25-30°C and stirred for about 10 minutes to get clear solution. The pH of the reaction mass was adjusted to 9-9.5 with 10% sodium hydroxide solution, stirred for about 20 minutes and separated the layers. The aqueous layers were extracted with ethyl acetate (120 ml), combined all ethyl acetate layers and washed with water (120ml). Ethyl acetate layer was added to the washings and distilled out ethyl acetate completely u/v at 40-45°C to get viscous residue. Methanol (100 ml) was added to the residue and stirred for about 20 minutes to get clear solution. 48% aqueous hydrobromide solution (10.4g) was slowly added to the reaction mass for about 30-45 minutes at 20-25°C and the stirred the reaction mass for about one hour. Distilled out methanol completely u/v at 40-45°C and IPA (100 ml) was added. Distilled out IPA completely u/v at 40-45°C, methanol (50ml) was added and stirred the reaction mass to get clear solution. Slowly added the methanolic solution to a mixture of diisopropyl ether (250 ml) and seed of Eletriptan α-form for about 30-45 minutes at 20-30°C, raised the temperature to 40-50°C and maintained the reaction mass for about 2 hours at the same temperature. Cooled to 20-30°C and maintained for about 2 hours at the same temperature. Filtered the solid, washed with diisopropyl ether (50 ml) and dried u/v at 40-50°C for 8-10 hours to obtain 25 g Eletriptan hydrobromide α-form.

Example-18: Preparation of Eletriptan hydrobromide α-form:

To a mixture of water (90 ml) and ethyl acetate (120 ml) was added Eletriptan methanesulphonate (30 g) at 25-30°C and stirred for about 10 minutes to get clear solution. The pH of the reaction mass was adjusted to 9-9.5 with 10% sodium hydroxide solution, stirred for about 20 minutes and separated the layers. The aqueous layer was extracted with ethyl acetate (120 ml), combined all ethyl acetate layers and washed with water (120 ml). Ethyl acetate layer was added to the washings and distilled out ethyl acetate completely u/v at 40-45°C to get viscous residue. Methanol (100 ml) was added to the residue and stirred for about 20 minutes to get clear solution. 48% aqueous hydrobromide solution (10.4 g) was slowly added to the reaction mass for about 30-45 minutes at 20-25°C and the stirred the reaction mass for about one hour. Methanol was distilled out completely u/v at 40-45°C and IPA (100 ml) was added. IPA was completely distilled off u/v at 40-45°C, methanol (50 ml) was added and stirred the reaction mass to get clear solution. Methanol was distilled off completely u/v at 40-45°C, IPA (200 ml) was added and heated the reaction mass to reflux temperature of 80-85°C. The reaction mass was stirred at reflux temperature for about 3 hours. The reaction mass was cooled to 30-40°C and maintained for about one hour and optionally seeded with α-form. The obtained solid was filtered, washed with IPA (50 ml) and dried u/v at 40-50°C for about 8-10 hours to obtain 25 g Eletriptan hydrobromide α-form. Particle size distribution of Eletriptan hydrobromide α-form d90 is less than 100μm.

Example-19: Preparation of Eletriptan hydrobromide β-form:

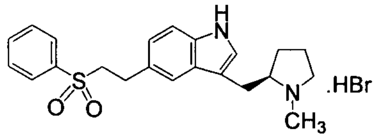
To a mixture of water (90ml) and ethyl acetate (150ml) was added Eletriptan methane sulphonate (30g) at 25-30°C and stirred for about 10 minutes to get clear solution. The pH of the reaction mass was adjusted to 9-9.5 with 10-30 % sodium hydroxide solution at 25-30°C, stirred for about 20 minutes and separated the layers. The aqueous layer was extracted with ethyl acetate (90ml). Ethyl acetate layers were combined and washed with water (100ml). The ethyl acetate layer was passed though silica column, collected the ethyl acetate elutes and Butylated hydroxyl toluene (0.15 g) was added. Ethyl acetate was distilled out completely u/v at 40-45°C to get viscous residue. Methanol (100 ml) was added and stirred for about 20 minutes to get clear solution. 48% aqueous hydrobromide solution (10.4 g) was slowly added for about 30-45 minutes at 20-25°C. The reaction mixture was stirred at 20-25°C for about an hour and distill out methanol completely u/v at 40-45°C. IPA (90 ml) was added and distill out IPA completely u/v at 45-50°C. Again IPA (60 ml) was added and distill out IPA completely u/v at 45-50°C. Methanol (60 ml) was added and distilled out completely u/v. Methanol (72 ml) was added and stirred at about 40-45°C to get clear solution. The reaction mass was filtered through micron filer.

In a separate flask mixture of MTBE (90 ml) and Eletriptan β-form seed (0.3 g) was added. The above methanolic reaction mass was added to the mixture and cooled to 10-15°C.

Again MTBE (270 ml) was slowly added to the reaction mass over a period of 45-60 minutes at 10-15°C. The reaction mass stirred for about 60 minutes at 10-15°C, filtered and washed with MTBE (30 ml). The obtained solid was dried u/v at 40-50°C for about 12 hours 21-26 g of Elertiptan Hydrobromide **β** -form; HPLC purity 99.58%.

We Claim:

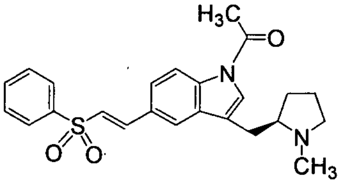
1. Improved process for the preparation of Eletriptan hydrobromide of formula-I



Formula-I

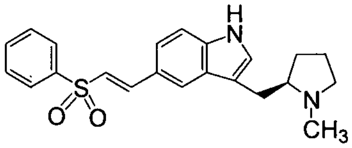
which comprises:

a) hydrolyzing (R)-1-acetyl-5-(2-phenylsulphonylethenyl)-3-(N-methylpyrrolidin-2-ylmethyl-)-1H-indole of formula-VIII



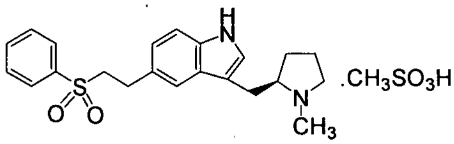
Formula-VIII

in the presence of a base in a solvent to get (R)-5-(2-phenylsulphonylethenyl)-3-(N- methylpyrrolidine-2-yl-methyl)-1H-indole of formula-VI,



Formula-VI

b) reducing the compound of formula-VI in the presence of a metal catalyst, methane sulphonic acid in a solvent to get the compound of formula-X,



Formula-X

c) setting free of the compound of formula-X with a base,

d) extracting the compound into an organic solvent,

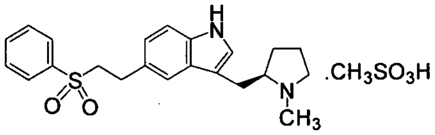
e) optionally passing the organic layer through silica gel column,

f) removing the solvent, adding another solvent,
g) treating with hydrobromic acid, and
h) isolating Eletriptan hydrobromide of formula-I.

2. The process according to claim 1, wherein said base used for hydrolysis in step a) is selected from potassium carbonate or sodium carbonate and the solvent is selected from methanol, ethanol, propanol, butanol or isopropanol.

3. The process according to claim 1, wherein the said metal catalyst used for reduction in step b) is selected from the group consisting of palladium on carbon, palladium hydroxide, palladium on alumina, platinum dioxide, platinum on carbon or Raney nickel and the solvent is selected from acetone, methylethylketone, methylisobutyl ketone, water or mixtures thereof.

4. A process for purification of Eletriptan methanesulphonate of compound of formula-X



Formula-X

which comprises:

a) setting free of Eletriptan acid addition salt with a base,
b) extracting the compound into an organic solvent,
c) optionally passing organic layer through silica gel column,
d) removing the solvent, adding another solvent,
e) treating with methanesulphonic acid, and
f) isolating pure Eletriptan methanesulphonate of compound of formula-X.

5. The process according to claim 4, Eletriptan acid addition salt is selected from methanesulphonic acid, p-toluenesulphonic acid, formic acid, acetic acid, hydrochloric acid or sulfuric acid

6. The process according to claims 1 and 4, wherein the another solvent is selected from acetone, methylethyl ketone, methyl butyl ketone, acetonitrile, methanol, ethanol, isopropanol or n-butanol.

7. The process according to claims 1 and 4, wherein said base used for setting free of acid is selected from sodium hydroxide or potassium hydroxide.

8. The process according to claims 1 and 4, wherein said solvent used for extraction is selected from ethylacetate, methylacetate, dichloromethane, chloroform, toluene or ether

9. Improved process for the preparation of Eletriptan hydrobromide α-polymorphic form which comprises:
   a) dissolving Eletriptan in a solvent,
   b) treating with hydrobromic acid,
   c) adding step b) solution to an antisolvent containing the seed of Eletriptan hydrobromide α-polymorphic form, and
   d) adding antisolvent to step c), and
   e) isolating Eletriptan hydrobromide α-polymorphic form.

10. An improved process for the preparation of Eletriptan hydrobromide β-polymorphic form which comprises:
    a) dissolving Eletriptan in a solvent,
    b) treating with hydrobromic acid,
    c) adding step b) solution to an antisolvent containing the seed of Eletriptan hydrobromide β-polymorphic form, and
    d) adding antisolvent to step c), and
    e) isolating Eletriptan hydrobromide β-polymorphic form.

11. The process according to claims 9 and 10, wherein said solvent used in step a) is selected from methanol, ethanol, isopropanol or n-butanol.

12. The process according to claim 9 and 10, wherein said anti-solvent used in step c) is selected from methyl tertiary butyl ether, diisopropyl ether or diethylether.

13. Crystalline Eletriptan methanesulphonate monohydrate.

14. Crystalline Eletriptan methanesulphonate monohydrate according to claim 16, having at least three peaks at 14.07, 14.92, 15.31, 17.56, 18.39, 18.54, 19.02, 20.87, 21.17, 22.35, 22.60, 22.83, 23.49, 23.86 ± 0.2 degrees 2θ.

15. A pharmaceutical composition comprising therapeutically effective amount of Eletriptan or pharmaceutically acceptable salt and at least one pharmaceutically acceptable carrier.

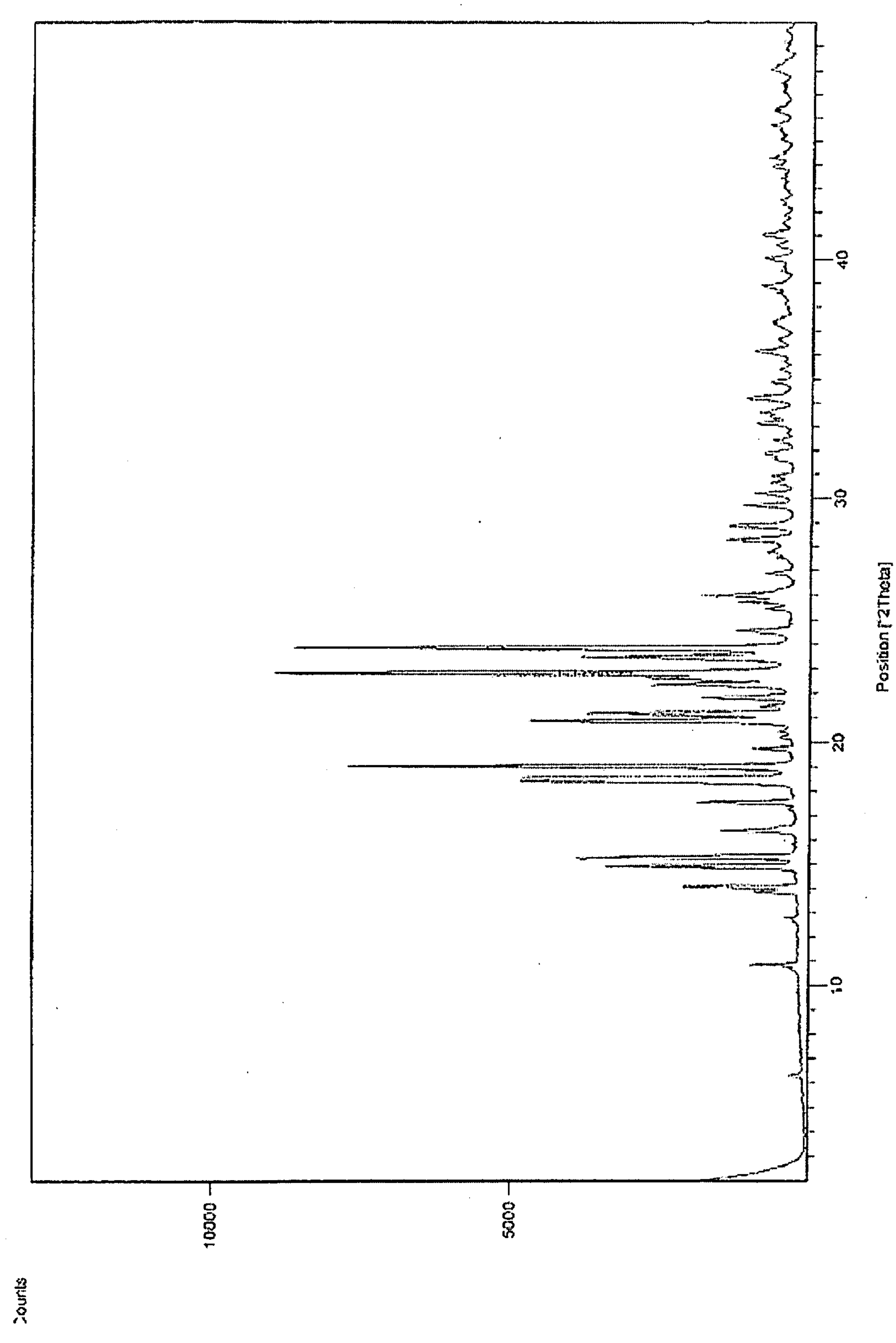


Figure 1

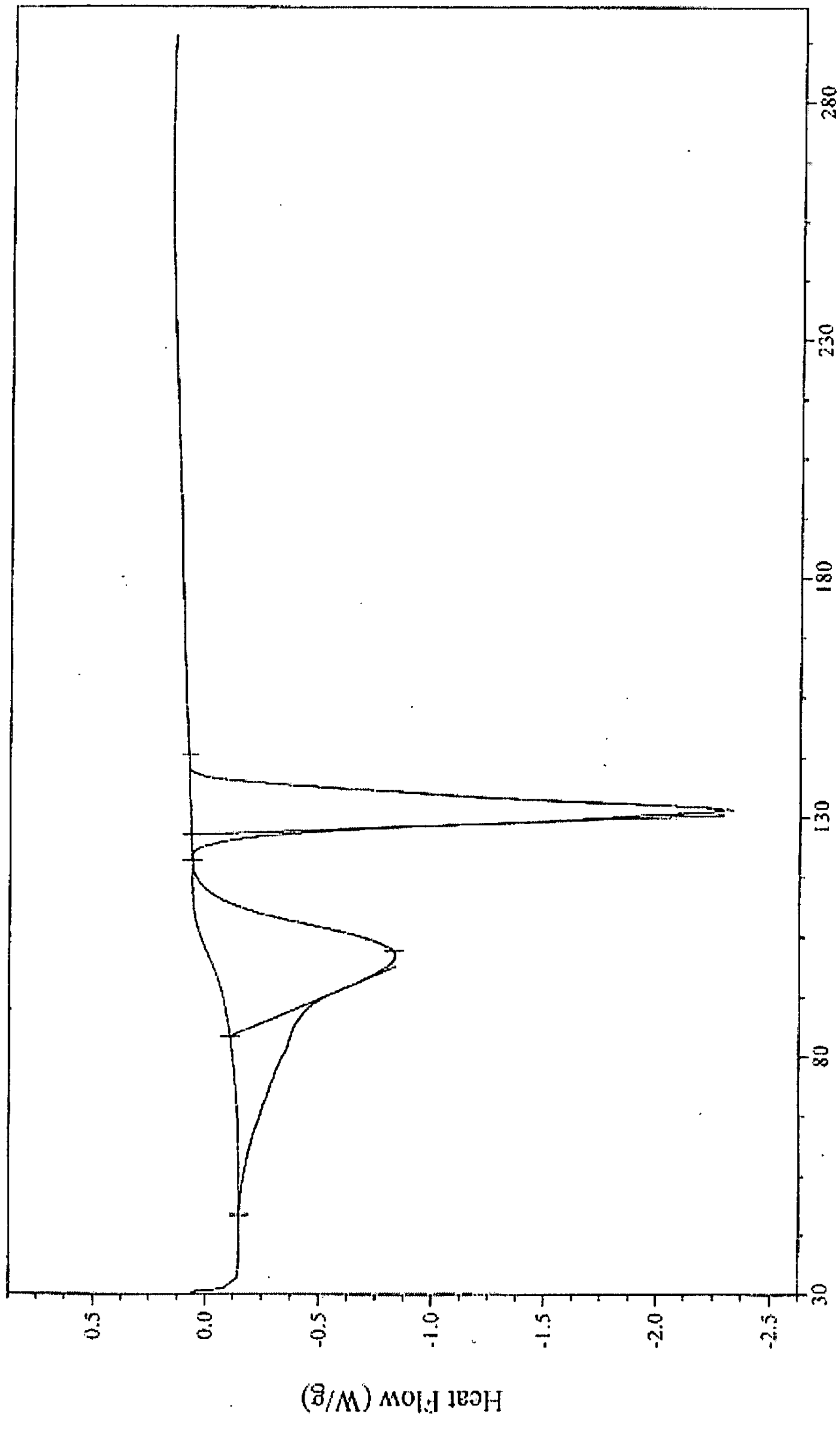


Figure 2

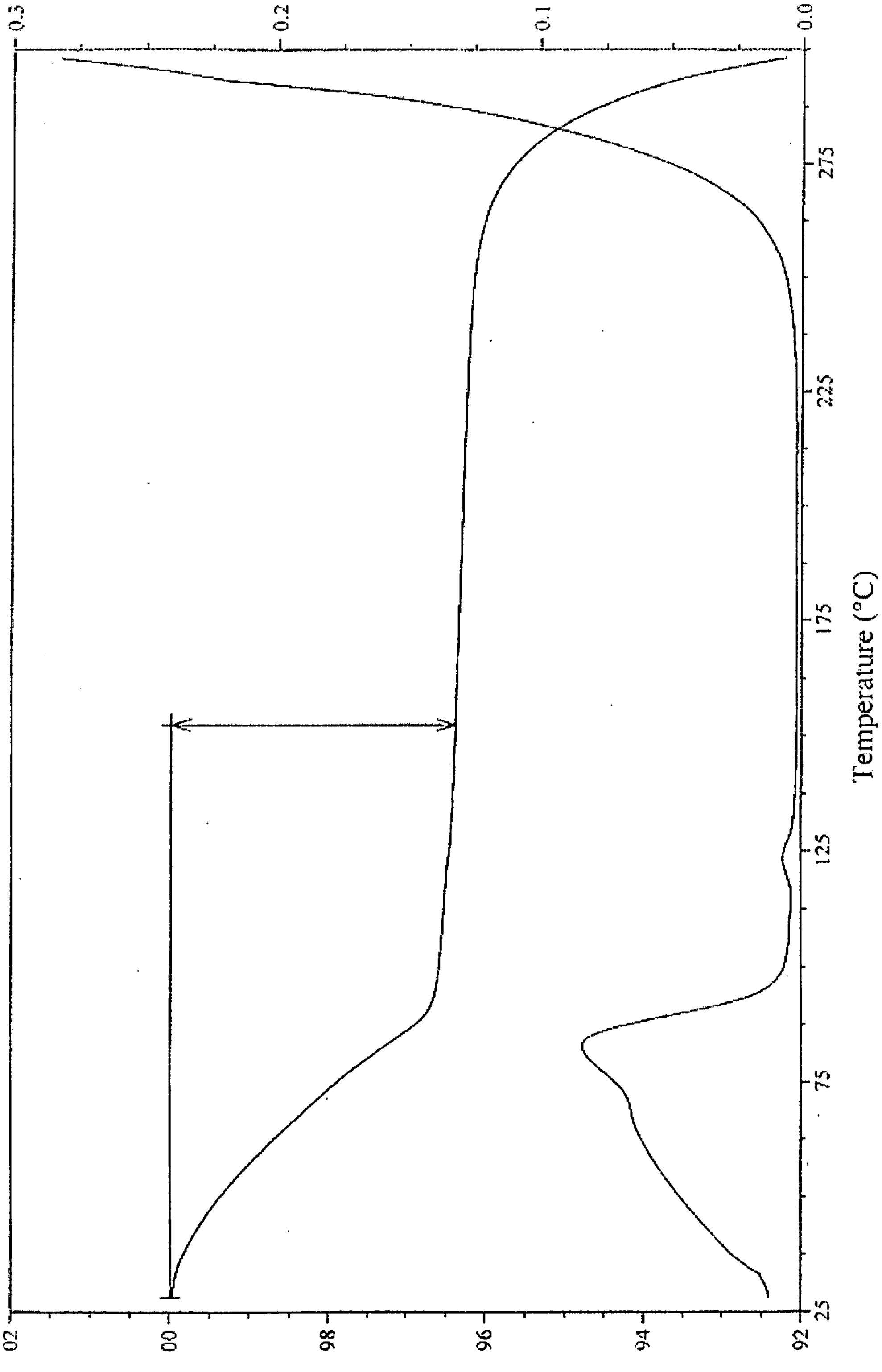


Figure 3