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(54) Title: POLYMORPHIC FORMS OF DOLASETRON MESYLATE AND PROCESSES THEREOF

(57) **Abstract:** The present disclosure relates to novel crystalline polymorphs, Form II, III, IV, V, VI, VII, VIII and IX of Dolasetron mesylate and industrial processes for producing them. Further, it discloses processes for producing Form I of Dolasetron mesylate. Furthermore, it relates to the novel amorphous form of Dolasetron mesylate and industrial processes for producing it.

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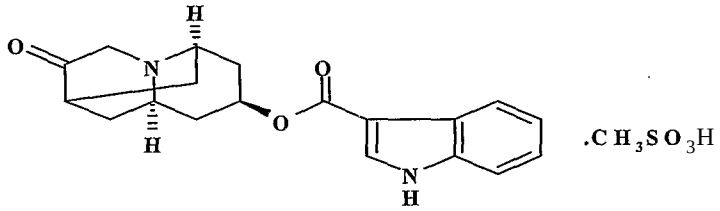
POLYMORPHIC FORMS OF DOLASETRON MESYLATE AND PROCESSES THEREOF

This specification claims priority from 1635/MUM/2005 dt 29/12/2005 and 1610/MUM/2005 dt 23/12/2005

TECHNICAL FIELD

The present disclosure relates to novel crystalline polymorphs of Dolasetron mesylate having formula (1) and industrial processes for producing the same. Further, it discloses processes for producing Form I of Dolasetron mesylate. Furthermore, the present disclosure teaches novel amorphous form and industrial processes for producing amorphous form.



Formula (1)

BACKGROUND AND PRIOR ART

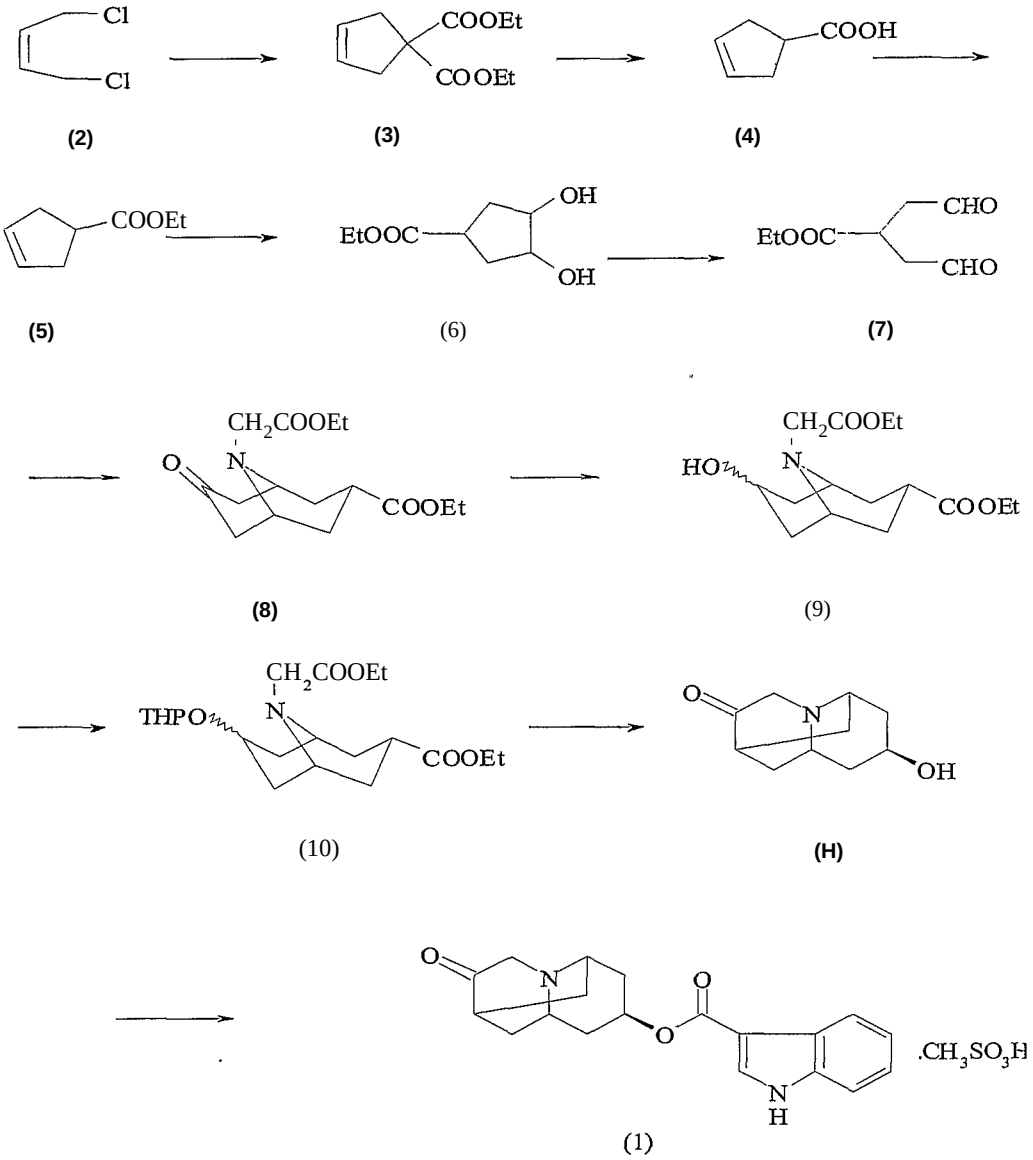
Dolasetron mesylate is an antinauseant and antiemetic agent. It is a selective serotonin 5-HT_3 receptor antagonist and is indicated for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy.

Synthesis of Dolasetron mesylate is not very widely reported in literature. EP0266730/US4906755 describes process for the preparation endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-qumolizin-3(4H)-one methanesulfonate or Dolasetron mesylate (1) by the condensation of diethyl malonate with cis-l,4-dichloro-2-butene (2) in presence of lithium hydride in dimethylformamide to give diethyl-3-cyclopentene-l,l-dicarboxylate (3), which on hydrolysis and decarboxylation gave 3-cyclopentene-1-carboxylic acid (4). The compound (4) was further treated with thionyl chloride and pyridine in ethanol to obtain ethyl 3-cyclopentene-l-carboxylate (5). Compound (5) was oxidized to 4-ethoxycarbonyl-l, 2-cyclopentanediol (6) by using N-methylmorpholine N-oxide in the presence of osmium tetroxide catalyst. The diol (6) was cleaved to the /3-ethoxycarbonylglutaraldehyde (7) using sodium periodate and used directly in the next reaction. Robinson-Schopf cyclisation of the compound (7) with potassium hydrogen phthalate, acetonedicarboxylic acid and glycine ethyl ester

hydrochloride resulted in the pseudopelletierine derivative i.e. 7-ethoxycarbonyl-9-(ethoxycarbonylmethyl)-9-azabicyclo-[3.3.1]nonan-3-one (8). The ketone group of compound (8) was reduced with sodiumborohydride in ethanol to give 7-ethoxycarbonyl-9-(ethoxycarbonylmethyl)-9-azabicyclo-[3.3.1]nonan-3-ol (9). The reduced alcohol (9) was treated with dihydropyran to protect the hydroxyl group as a tetrahydropyranyl ether (10). Dieckmann cyclisation of the compound (10) using strong base (potassium t-butoxide) followed by aqueous acid hydrolysis and decarboxylation gave the desired alcohol. The resulting alcohols can exist in two conformations - axial and equatorial. The main product obtained by above procedure was the axial alcohol or endo-hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3-(4H)-one (11) and it can be separated from the equatorial isomer by crystallization of the camphorsulfonate or tetrafluoroborate salt. The tetrafluoroborate salt of endo-hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3-(4H)-one (11) was further reacted with 3-indolecarboxylic acid chloride in presence of silver tetrafluoroborate in anhydrous nitroethane at -78^{0}C to endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)-one or Dolasetron base, which was further converted into Dolasetron mesylate monohydrate **(Scheme I)** with a yield of 66%. No further purification is described.

The above process uses column chromatography for purification of compounds (9) and (10), which is expensive, time consuming and impractical on an industrial scale. The above patent does not disclose the yield and purity of Dolasetron mesylate obtained and so also for the intermediates. In addition, Osmium tetroxide used for preparation of compound (6) is toxic, has a corrosive action on eyes and hence difficult to use at industrial scale. Also, this process uses high volume of water during preparation of the compound (8); preparation of compound (11) from compound (10) is tedious, because the workup involves several extractions with ethyl acetate and preparation of compound (1) in presence of silver tetrafluoroborate involves the use of expensive silver compound.

SCHEME I



Another method described in EP0339669 provides a process for the preparation of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)-one methanesulfonate or Dolasetron mesylate (1) by the condensation of dimethyl malonate with cis-l,4-dichloro-2-butene (2) in presence of lithium hydride in dimethyl formamide to give dimethyl-3-cyclopentene-l,l-dicarboxylate (12), which was decarboxymethylated to obtain methyl-3-cyclopentene-l-carboxylate (13). This compound (13) was treated with m-chloroperbenzoic acid in dichloromethane to obtain l-methoxycarbonyl-3-cyclopenteneoxide (14). The compound (13) on ozonolysis gave β-

methoxycarbonylglutaraldehyde (15) or the epoxide (14) was reacted with periodic acid to obtain the β-methoxycarbonylglutaraldehyde (15), which was used directly in the next reaction. Robinson-Schopf cyclisation of the compound (15) with potassium hydrogen phthalate, acetonedicarboxylic acid and glycine ethyl ester hydrochloride gave the pseudopelletierine derivative i.e. 7-methoxycarbonyl-9-(methoxycarbonylmethyl)-9-azabicyclo [3.3.1] nonan-3-one (16). The ketone group of compound (16) was reduced with sodiumborohydride in methanol to give 7-methoxycarbonyl-9-(methoxycarbonylmethyrj-P-azabicyclo-p.S.lJnonan-S-ol (17). The reduced alcohol (17) was treated with dihydropyran to protect the hydroxyl group as a tetrahydropyranyl ether **(18a)** or treated with methylal to protect the hydroxyl group to obtain 3-methoxymethoxy-7-methoxycarbonyl-9-(methoxycarbonylmethyl)-9-azabicyclo[3.3.1]nonan-3-ol **(18b).**

Dieckmann cyclisation of the compound (18) using strong base (potassium t-butoxide) followed by aqueous acid hydrolysis and decarboxylation gave the endo-hexahydro-8-hydroxy-2, 6-methano-2H-quinolizin-3-(4H)-one (11). The alcohol (11) was further reacted with 3-indolecarboxylic acid in presence of trifluoroacetic anhydride in dichloromethane to endo-hexahydro-8-(3-indolylcarbonyloxy)-2, 6-methano-2H-quinolizin-3(4H)-one or Dolasetron base, which was then converted into Dolasetron mesylate **(1) (Scheme II)** by treating with methanesulphonicacid in acetone. Further, crude Dolasetron mesylate (1) was dissolved in aqueous isopropanol and regenerated by adding ether to obtain Dolasetron mesylate (1) with a yield of 85.90 %.

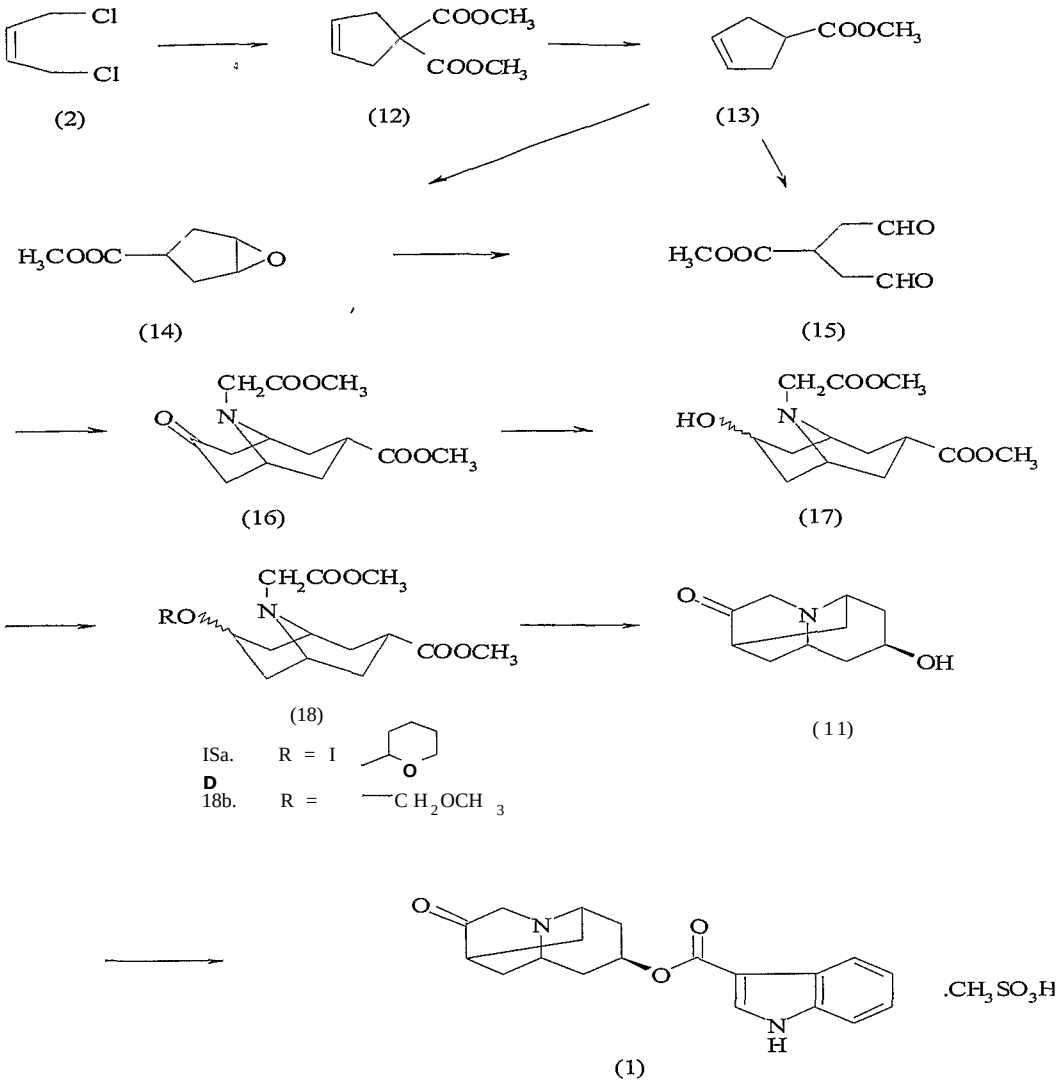
Disadvantages of this process are:

(i) use of high volume of water for preparation of compound (16) and

(ii) preparation of compound (11) from compound (18) which is tedious because at the time of workup, ethyl acetate extractions take up longer period (20 hr);

The process is not only time consuming but also expensive on an industrial scale. The patent does not disclose purity of Dolasetron obtained nor for any of the intermediates.

SCHEME II



The process as described in EP 0266730 involves treatment of endo-hexahydro-8-(3-indolylcarbonyloxy)-2, 6-methano-2H-quinolizin-3(4H)-one with a solution of methane sulfonic acid in ethanol to provide Dolasetron mesylate monohydrate. EP 0339669 describes crystallization of crude Dolasetron mesylate by dissolution in aqueous isopropanol and regeneration by adding ether. The polymorphic form obtained by the processes described in US 4906755/EP 0266730 and EP 0339669 is designated herein as Dolasetron mesylate Form I. XRPD of Dolasetron mesylate Form **I** is disclosed in **Figure 1.**

The ability of the compound to exhibit more than one orientation or conformation of molecule within the crystal lattice is called polymorphism. Many organic compounds including active pharmaceutical ingredients (API's) exhibit polymorphism.

Drug substance existing in various polymorphic forms differs from each other in terms of stability, solubility, compressibility, flowability and spectroscopic properties, thus affecting dissolution, bioavailability and handling characteristics of the substance.

Rate of dissolution of an API's in patient's stomach fluid can have therapeutic consequences since it imposes an upper limit on the rate at which an orally administrated API can reach the patient .bloodstream. Flowability affects the ease with which the material is handled while processing a pharmaceutical product.

Investigation of crystal polymorphism is an essential step in pharmaceutical research due to the influence of solid-state properties on dosage form.

As the polymorphs are known to possess different spectroscopic properties, technique such as X-Ray powder diffraction (XRPD), Fourier transformer Infrared (FT-IR) spectroscopy, Solid State ^{13}C-NMR, and thermal method of analysis are keys to identify and characterize the new polymorphs or existing polymorphs.

The discovery of new polymorphs with same or better pharmaceutical equivalence and bioequivalence as that of the known polymorphs provides an opportunity to improve the performance characteristic of the pharmaceutical product.

Polymorphs of Dolasetron mesylate are not widely reported. CN 1629161 discloses a crystalline polymorph of Dolasetron mesylate monohydrate.

In our endeavour to develop a process for the purification of Dolasetron mesylate, we have surprisingly discovered novel polymorphic forms Dolasetron mesylate.

OBJECTS OF THE PRESENT INVENTION

It is an object of the present disclosure to provide novel polymorphic forms of Dolasetron mesylate and industrial processes for producing them.

Another object is to provide a process for preparation of Dolasetron mesylate polymorphic Form I.

It is also an object of to provide novel amorphous form of Dolasetron mesylate and industrial processes for producing it.

SUMMARY OF THE INVENTION

Accordingly, the present disclosure provides a process for the preparation of a crystalline polymorphic Form I of endo-hexahydro-8-(3-indolylcarbonyloxy)-2, 6-methano-2H-quinolizin-3 (4H)-one methanesulfonate (Dolasetron rrfesyïate).

In one aspect, the present invention provides a crystalline polymorphic Form II of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizm-3(4H)-one methanesulfonate, Dolasetron mesylate.

In another aspect, the present invention provides a process for producing polymorphic Form II of Dolasetron mesylate.

In one aspect, the present invention provides a crystalline polymorphic Form III of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3 (4H)-one methanesulfonate, Dolasetron mesylate.

In another aspect, the present invention provides a process for producing polymorphic Form III of Dolasetron mesylate.

In one aspect, the present invention provides a crystalline polymorphic Form IV of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)-one methanesulfonate, Dolasetron mesylate.

In a further aspect, the present invention relates to a process for producing polymorphic Form IV of Dolasetron mesylate.

In one aspect, the present invention provides a crystalline polymorphic Form V of endo-hexahydro~8-(3 -indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3 (4H)-one methanesulfonate, Dolasetron mesylate.

In another aspect, the present invention provides a process for producing polymorphic Form V of Dolasetron mesylate.

In yet another aspect, the present invention provides a crystalline polymorphic Form VI of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)-one methanesulfonate, Dolasetron mesylate.

In a further aspect, the present invention provides a process for producing polymorphic Form VI of Dolasetron mesylate.

In one aspect, the present invention provides a crystalline polymorphic Form VII of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methan ó-2H-quinolizin-3(4H)-one methanesulfonate, Dolasetron mesylate.

In another aspect, the present invention provides a process for producing polymorphic Form VII of Dolasetron mesylate.

In yet another aspect, the present invention provides a crystalline polymorphic Form VIII of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizm-3(4H)-one methanesulfonate, Dolasetron mesylate.

In a further aspect, the present invention provides a process for producing polymorphic Form VIII of Dolasetron mesylate.

In one aspect, the present invention provides a crystalline polymorphic Form IX of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)-one methanesulfonate, Dolasetron mesylate.

In another aspect, the present invention provides a process for producing polymorphic Form IX of Dolasetron mesylate.

In one aspect, the present invention provides an amorphous form of endo-hexahydro-8-(3-indolylcarbonyloxy)-2, 6-methano-2H-quinolizin-3 (4H)-one methanesulfonate, Dolasetron mesylate.

In another aspect, the present invention provides processes for preparation of amorphous form of Dolasetron mesylate.

BRIEF DESCRIPTION OF ACCOMPANYING **DRAWINGS**

Figure 1 shows XRPD pattern of Dolasetron mesylate Form I

Figure 2 shows XRPD pattern of Dolasetron mesylate Form II

Figure 3 shows XRPD pattern of Dolasetron mesylate Form III

Figure 4 shows XRPD pattern of Dolasetron mesylate Form IV

Figure 5 shows XRPD pattern of Dolasetron mesylate Form V

Figure 6 shows XRPD pattern of Dolasetron mesylate Form VI

Figure 7 shows XRPD pattern of Dolasetron mesylate Form VII

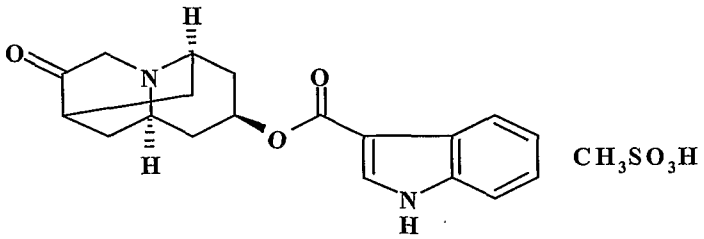
Figure 8 shows XRPD pattern of Dolasetron mesylate Form VIII

Figure 9 shows XRPD pattern of Dolasetron mesylate Form IX

Figure 10 shows XRPD pattern of amorphous form of Dolasetron mesylate

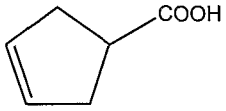
DETAILED DESCRIPTION OF THE INVENTION

The present disclosure relates to a process for preparation of Dolasetron mesylate or endo-hexahydro-8-(3-indolylcarbonyloxy)-2, 6-methano-2H-quinolizin-3 (4H)-one methanesulfonate of the formula (1) in high yield and high purity comprising:



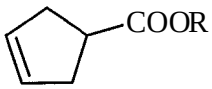
Formula (1)

a. reacting compound (4)



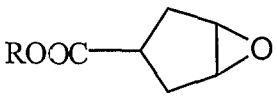
Formula (4)

with thionyl chloride in alcohol or alcoholic hydrochloric acid or anhydrous HCl gas to form compound having the structural formula (V);



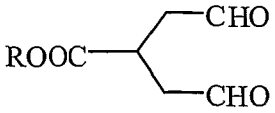
Formula (V)

b. treating the compound haying the structural formula (V) with m-chloroperbenzoic acid in dichloromethane to give an epoxide having the structural formula (XIX),



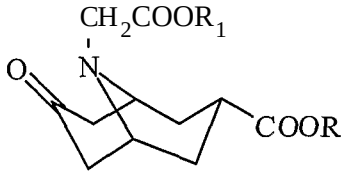
Formula (XIX)

c. treating the epoxide having the structural formula (XIX) with periodic acid to give compound having the structural formula (VII);



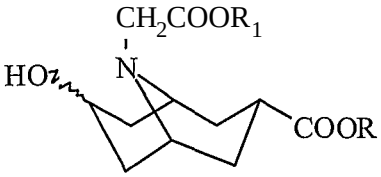
Formula (VII)

d. cyclising the compound having the structural formula (VII) with potassium hydrogen phthalate, acetonedicarboxylic acid and glycine ester hydrochloride by Robinson-Schopf cyclisation to obtain pseudopelletierine derivative having the structural formula (VIII);



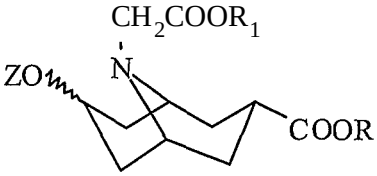
Formula (VIII)

e. reducing the compound having the structural formula (VIII) with sodiumborohydride in alcohol followed by treatment with an organic acid to obtain compound having the structural formula (IX);



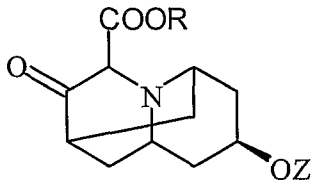
Formula (IX)

f. protecting the compound having the structural formula (IX) as a silyl derivative having the structural formula (XX) by treating it with a silyl halide in an organic solvent (wherein Z = silyl group);



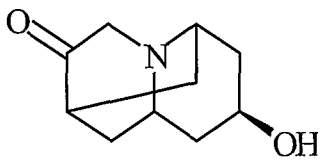
Formula (XX)

g. treating the compound having the structural formula (XX) with a strong base to form compound having the structural formula (XXI);



Formula (XXI)

h. treating the compound having the structural formula (XXI) with acid in water or an organic solvent followed by decarboxylation to yield compound (11);



Compound (11)

i. reacting the compound (11) with indole-3-carboxylic acid in presence of trifiuoroacetic acid anhydride to yield Dolasetron base; and

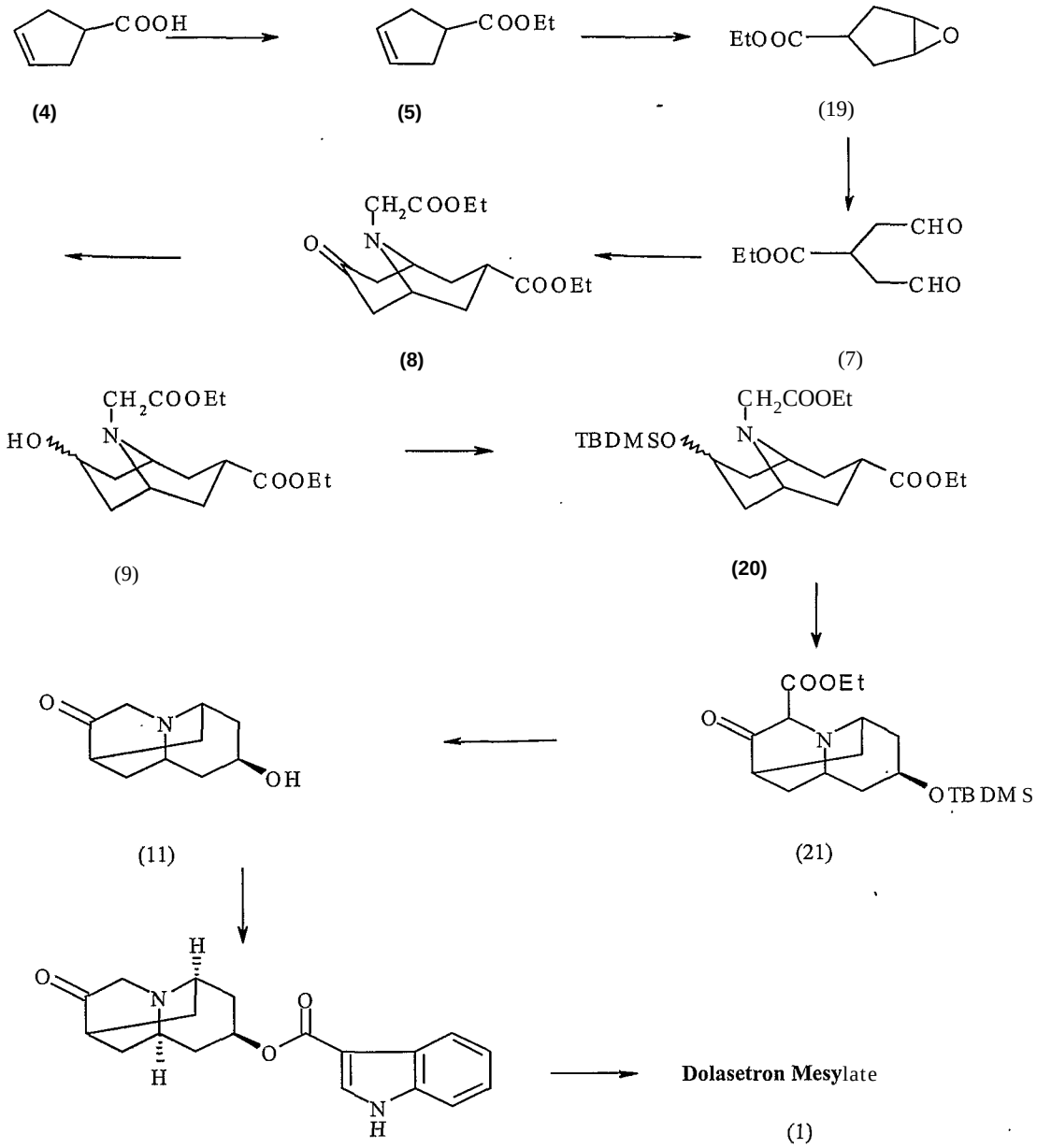
j. converting the Dolasetron base into its mesylate; and recrystallizing from a mixture of solvents to obtain highly pure compound (1);

wherein, R = Et, Me, or OCH_2Ph, Ri = Et, Me, or OCH_2Ph and Z is selected from trimethyl silyl, isopropyl dimethyl silyl, t-butyldimethyl silyl, t-butyldiphenyl silyl, tribenzyl silyl, and triisopropyl silyl.

In accordance to above, Scheme III as given below depicts a process for the preparation of 3-cyclopentene-l-carboxylic acid ester (5) is disclosed, said process comprising: reacting 3-cyclopentene-l-carboxylic acid (4) with anhydrous HCl gas or concentrated hydrochloric acid or thionyl chloride in an alcohol, wherein the alcohol is either methanol or ethanol; treating the compound (5) with m-chloroperbenzoic acid in a solvent selected from dichloromethane and ethyl acetate to obtain the corresponding epoxide (19); reacting the compound (19) with periodic acid under nitrogen atmosphere to obtain compound (7); treating the compound (7) with potassium hydrogen phthalate, acetonedicarboxylic acid and glycine ester hydrochloride in water to obtain pseudopelletierine derivative (8); reducing the compound (8) with sodiumborohydride in

an alcohol and further treating with an organic acid to obtain compound (9), wherein the organic acid is selected from formic acid, methane sulphonic acid and acetic acid; treating the compound (9) with silyl halide in presence of imidazole in an organic solvent to obtain compound (20), wherein the organic solvent is selected from ketones, esters and ethers, preferably from acetone, tetrahydrofuran, 1, 4-dioxane, dichloromethane, chloroform, N, N-dimethyl formamide, ethyl acetate and acetonitrile.

Scheme III



A major advantage of the use of silyl protecting group is that it yields greater than 95 % of compound (20) as compared to, use of dihydropyran (75%) or methylal (84%).

The compound (20) is treated with a strong base in toluene and further treated with an organic acid in an organic solvent to form compound (21). The organic solvent is selected from halogenated solvents, ethers and esters. The organic solvent is preferably selected from methylene chloride, chloroform, ethyl acetate, isopropyl acetate, diethyl

ether, diisopropyl ether or mixtures thereof. The organic acid is selected from formic acid and acetic acid.

The compound (21) is heated with hydrochloric acid in water to give compound (11). Hydrochloric acid and water are used in the ratio of 1:2 volumes. The ratio of compound (21) to water in the reaction is about 1: 8 to 1:10. The reaction mixture is concentrated and the residue obtained is treated with an organic solvent and filtered. The filtrate is concentrated to obtain compound (11). The organic solvent is selected from alcohols and halogenated solvent preferably methanol, ethanol, isopropanol, n-butanol, dichloromethane, chloroform or mixture thereof. The reaction mixture is extracted with an organic solvent selected from ethyl acetate, isopropanol or n-butanol. Alternately the reaction mixture is saturated with an inorganic salt and extracted with an organic solvent selected from ethyl acetate or n-butanol or isopropanol.

The compound (11) is reacted with indole-3-carboxylic acid in presence of trifiuoroacetic acid anhydride in dichloromethane to give Dolasetron base. The ratio of indole-3-carboxylic acid and trifluoro acetic anhydride used is in the range of 1:1.1 to 1:2. Dolasetron base thus obtained is isolated by conventional method. Dolasetron base is solubilized in acetone and converted into its mesylate salt using methane sulphonic acid. The resultant mesylate salt is dissolved in water and extracted with a halogenated solvent or ester to remove traces of impurity. The halogenated solvent is selected from dichloromethane and chloroform, and the ester is selected from methyl acetate, ethyl acetate and isopropyl acetate. The aqueous layer is basified with a base to obtain Dolasetron base. The base is selected from sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide or mixtures thereof. Dolasetron base thus obtained is treated with methane sulphonic acid in a mixture of acetone and water to provide Dolasetron Mesylate.

Polymorphic **forms of Dolasetron** mesylate

One more embodiment of the invention provides novel crystalline polymorphic forms, viz: Form II, Form III, Form IV, Form V, Form VI, Form VII, Form VIII and Form IX.

Another embodiment of the invention provides a process for manufacturing these crystalline polymorphic forms. The invention also discloses novel amorphous form of Dolasetron mesylate.

The polymorphic Form I of Dolasetron mesylate is obtained by crystallization. The process involves, dissolving Dolasetron mesylate in a solvent selected from aliphatic alcohols, aliphatic ketones, aliphatic esters, aliphatic nitriles or mixtures thereof at a temperature in the range of 30°C-80°C to yield a clear solution. The clear solution is cooled at a temperature in the range of 0°C-30°C, preferably in the range of 25°C-30°C to obtain a solid. Dolasetron mesylate form I is obtained by filtering and drying the solid at a temperature in the range of 30°C-90°C, preferably in the range of 60°C-70°C. The aliphatic alcohol selected is isopropanol; the aliphatic ester is selected from methyl acetate, ethyl acetate and butyl acetate; aliphatic ketone is selected from acetone, 2-butanone, diethylketone, and the like; and aliphatic nitrile is acetonitrile.

Dolasetron mesylate Form I is also obtained by solvent and anti-solvent process. The said process comprises: dissolving Dolasetron mesylate in a solubilizing solvent, adding an anti-solvent, stirring the suspension with or without cooling, isolating and drying the product at 50°C-70°C. The solubilizing solvents selected for dissolution are polar aprotic solvents. The polar aprotic solvent is selected from N, N-dimethyl formamide, dimethyl sulfoxide and N, N-dimethyl acetamide. The anti-solvent is selected from cyclic ethers, aromatic hydrocarbons and alcohols. The cyclic ether selected is tetrahydrofuran. The aromatic hydrocarbon is toluene and the alcohol is isopropanol.

The XRPD of Dolasetron mesylate Form I exhibit following peaks:

Position [°2Θ]	Rel. Int. [%]
7.4587	6.15
9.9618	22.96
10.5229	11.60
11.8311	13.91
12.2113	46.32
12.8014	16.93
13.0334	69.03
13.9997	5.05
14.7702	4.51
15.2057	48.73
15.4577	22.29
16.3397	6.45
16.7613	7.33
17.1871	39.45
18.0049	21.19
18.2978	10.25
19.0431	73.21
19.3804	25.15

19.8238	84.20
20.1208	70.13
20.4718	6.81
21.1534	32.28
22.1965	41.40
22.5131	100.00
22.9364	21.29
23.1046	18.63
23.5992	21.37
24.3924	29.65
24.7468	24.62
25.0691	12.40
25.6221	16.23
26.0495	18.98
26.6353	30.98
27.2251	16.77
28.0475	24.76
28.8492	15.82
29.9349	24.37
30.2157	65.62
30.5167	12.70
31.0803	9.84
31.6533	17.87
32.8171	11.68
33.3453	11.07
33.8520	15.00
34.5881	6.22
35.5587	9.61
36.6675	15.29
37.9088	6.97
38.7741	7.86
40.5258	8.59
42.5248	5.86
42.9394	10.15
43.5589	8.97
44.8652	3.63
46.3824	6.20
49.1697	6.31

The polymorphic Form II is obtained by crystallizing Dolasetron mesylate from methanol. The polymorphic Form II is obtained by dissolving Dolasetron mesylate in methanol at a temperature in the range of 30-80^{0}C, preferably in the range of 60-70^{0}C, cooling the solution at a temperature in the range of -5°C to 25^{0}C, preferably in the range of 2 to 7^{0}C, isolating and drying the product at a temperature in the range of in the range of 40-90^{0}C, preferably in the range of in the range of 60-70^{0}C. The XRPD of Dolasetron

mesylate Form II is given in Figure 2. The XRPD of Dolasetron mesylate Form II exhibits following peaks:

Position [°20]	ReI. Int. [%]
8.5677	6.09
10.0288	15.17
11.2894	4.56
12.1224	11.85
14.3549	6.44
15.3566	37.98
16.1189	100.00
17.4727	33.33
17.9848	13.61
18.2788	17.61
18.6717	7.36
19.0521	5.06
19.4583	24.09
19.9142	58.36
20.3327	62.55
20.7258	84.65
21.4927	21.14
22.8359	11.20
23.1023	10.08
24.4864	23.47
25.8654	10.96
27.1036	10.58
27.5344	32.07
27.8212	8.51
28.2995	54.08
30.0154	6.14
30.3489	6.50
30.8158	15.55
31.1764	9.57
32.1019	8.14
32.4852	8.13
32.7724	7.66
33.6263	4.20
34.9029	2.52
35.7768	7.29
36.9416	6.79
37.2354	6.99
39.4576	3.12
39.9761	7.25
42.1000	1.20
45.1580	1.23
47.4886	1.74
49.5076	4.99

The polymorphic Form III is obtained by crystallizing Dolasetron mesylate from ethanol. The polymorphic Form III is obtained by dissolving Dolasetron mesylate in ethanol at a temperature in the range of 30-80 ^{0}C, preferably in the range of 75-8O ^{0}C, cooling the solution at a temperature in the range of-5°C to 25°C, preferably in the range of 2 to 7°C, isolating and drying the product at a temperature in the range of in the range of 40-90 ^{0}C, preferably in the range of 60-70 ^{0}C.

Also, the polymorphic Form III is obtained by using solvent and anti-solvent combination process. The said process comprises: dissolving Dolasetron mesylate in a solubilizing solvent at a temperature in the range of 30-80 ^{0}C, preferably in the range of 60-80 ^{0}C, adding an anti-solvent at a temperature in the range of 30-55 ^{0}C, preferably in the range of 40-50 ^{0}C, isolating and drying the product at a temperature in the range of 40-90 ^{0}C, preferably in the range of 60-70 ^{0}C. The solubilizing solvents are selected from lower aliphatic alcohols. The lower alcohol is selected from methanol, ethanol, n-propanol and isopropanol, preferably ethanol. The anti-solvent is selected from aliphatic hydrocarbons n-pentane, n-hexane and n-heptane, preferably n-hexane. The XRPD of Dolasetron mesylate Form III is given in Figure 3. The XRPD of Dolasetron mesylate Form III exhibits following peaks:

Position [°2Θ]	Rel. Int. [%]
6.9327	2.87
9.8793	4.08
11.7303	2.68
12.6509	100.00
13.7701	15.97
16.6416	21.33
17.5613	18.64
18.1133	66.76
19.4364	37.96
19.6530	70.74
20.5969	43.14
21.2122	42.37
22.1215	27.17
22.3203	29.08
22.9997	14.64
23.2369	29.45
25.3464	22.52
25.7644	7.93
26.7943	11.14
27.9040	44.38
28.2908	11.30
29.5991	19.08
31.3094	10.72

31.5560	10.97
32.6826	7.96
34.1101	5.85
34.5722	6.62
34.9579	7.12
36.3803	5.26
37.6469	3.01
39.6600	3.13
40.8489	2.61
41.6942	4.21
44.2459	1.74
45.3305	1.76

Polymorphic Form IV is obtained by crystallizing Dolasetron mesylate from n-propanol. The polymorphic Form IV is obtained by dissolving Dolasetron mesylate in n-propanol at a temperature in the range of 30-100^{0}C, preferably in the range of 90-100^{0}C, cooling the solution at a temperature in the range of -5°C to 25^{0}C, preferably in the range of 2 to 7°C, isolating and drying the product at a temperature in the range of in the range of 40-90^{0}C, preferably in the range of in the range of 60-70^{0}C.

The XRPD of Dolasetron mesylate Form IV is given in **Figure 4.** The XRPD of Dolasetron mesylate Form IV exhibits following peaks:

Position [°2Θ]	Rel. Int. [%]
8.9231	13.20
9.8783	4.58
11.0009	9.65
12.1275	12.74
12.5348	16.42
12.7100	4.78
12.9295	13.19
13.5324	7.67
14.0712	68.91
14.4080	17.98
14.8069	33.77
15.1068	19.18
15.4202	20.16
16.6676	24.07
17.0883	13.11
17.3884	18.93
17.8087	20.51
18.1597	14.53
18.9666	19.40
19.2953	26.33

19.9217	100.00
20.3947	24.69
20.8115	42.34
21.6045	15.47
22.0471	73.52
22.4082	27.53
23.0366	20.15
23.5718	9.97
24.3224	22.76
25.0364	18.40
26.3036	14.18
27.4731	33.17
28.2271	10.21
29.2801	22.56
30.1751	24.53
32.7579	11.03
33.6510	11.10
36.5575	6.71
40.5518	2.52

Polymorphic Form V is obtained by crystallizing Dolasetron mesylate from chlorinated hydrocarbons. The polymorphic Form V is obtained by dissolving Dolasetron mesylate in a solubilizing solvent at a temperature in the range of 30-80^{0}C, cooling the solution at a temperature in the range of-5°C to 30^{0}C, preferably in the range of 25-3O^{0}C, isolating and drying the product at a temperature in the range of in the range of 40-90^{0}C, preferably in the range of in the range of 60-70^{0}C. The solubilizing solvent is chlorinated hydrocarbon and is selected from methylene dichloride or chloroform. The XRPD of Dolasetron mesylate Form V is given in **Figure 5.** The XRPD of Dolasetron mesylate Form V exhibits following peaks:

Position [°2Θ]	ReI. Int. [%]
7.0234	2.39
9.4499	10.44
10.0014	1.75
11.2346	6.13
12.3990	41.17
13.0876	5.00
13.5.899	16.75
14.2116	34.51
14.9901	23.78
16.4007	16.49
16.5997	10.27
17.2415	2.93

18.7313	61.04
19.3572	11.87
19.9122	7.47
20.3109	37.22
20.7126	63.91
21.2339	42.10
22.2956	100.00
23.8661	22.10
24.2519	26.86
24.8389	22.90
25.7209	4.60
26.7060	5.14
27.1085	15.85
27.8334	9.48
28.2062	21.05
28.8706	29.90
29.6637	32.04
30.2901	8.68
31.0608	17.14
31.3191	15.03
33.4700	8.81
34.8387	8.04
35.4257	5.99
36.2944	3.36
39.3031	3.61
40.2044	1.49
40.7189	2.00
41.9681	2.42
42.9023	5.63
44.2007	3.48
45.7069	4.46
48.3668	2.41

Polymorphic Form VI is obtained from Dolasetron mesylate by solvent and anti-solvent combination process. The said process comprises of dissolving Dolasetron mesylate in a solubilizing solvent like a polar aprotic solvent at a temperature in the range of 20-35^{0}C, preferably in the range of 25-30^{0}C, adding an anti-solvent at a temperature in the range of 20-45^{0}C, preferably in the range of 25-30^{0}C, isolating and drying the product at a temperature in the range of 40-90^{0}C, preferably in the range of 60-70^{0}C. The polar aprotic solvent selected for dissolving Dolasetron mesylate is dimethyl formamide or dimethyl sulfoxide. The anti-solvent is selected from cyclic ethers such as 1, 4-dioxane. The XRPD of Dolasetron mesylate Form VI is given in **Figure 6.** The XRPD of Dolasetron mesylate Form VI exhibits following peaks:

Position [°2Θ]	Rel. Int. [%]
7.4433	5.63
9.5049	20.13
9.9496	13.90
10.5039	6.65
11.8166	5.42
12.1944	18.96
12.6288	29.00
13.0077	30.68
13.3801	4.62
13.7613	2.83
14.7330	2.72
15.1734	34.41
15.4668	12.92
16.6316	24.00
17.1629	26.82
17.8499	53.38
19.0352	100.00
19.3432	89.80
19.8030	46.30
20.0712	36.98
20.4909	65.99
20.9356	8.65
21.3421	21.25
21.8514	7.35
22.1111	35.66
22.5010	57.85
22.7995	32.62
23.0903	11.37
23.6251	7.97
24.3860	15.83
24.7255	19.47
25.0343	14.83
25.6040	8.62
26.0387	10.14
26.6211	15.13
27.2259	59.06
28.0530	14.52
29.1029	16.69
29.9326	6.76
30.2376	29.39
31.0858	9.70
31.4142	12.45
31.6868	9.26
32.3416	4.26
32.8342	4.78
33.3082	7.59
33.8019	7.03
35.3064	11.79

36.6186	5.25
37.6928	2.32
38.5491	2.80
40.8503	3.65
42.9479	2.85
43.5321	4.78
45.8347	5.25
47.0633	3.28
49.2055	2.24

The polymorphic Form VII is obtained from Dolasetron mesylate by solvent and anti-solvent combination process. The said process comprises: dissolving Dolasetron mesylate in a polar aprotic solvent at an ambient temperature in the range of 20-35^{0}C, preferably in the range of 25-30^{0}C, adding an anti-solvent at a temperature in the range of 20-45^{0}C, preferably in the range of 25-30^{0}C, isolating and drying the product at a temperature in the range of 30-90^{0}C, preferably in the range of 60-70^{0}C. The polar aprotic solvent is selected as dissolution solvents. The polar aprotic solvent is N, N-dimethyl acetamide. The anti-solvent is selected from cyclic ethers such as 1, 4-dioxane. The XRPD of Dolasetron mesylate Form VII is given in **Figure 7.** The XRPD of Dolasetron mesylate Form VII exhibits following peaks:

Position [°2Θ]	Rel. Int. [%]
9.4384	20.32
11.6064	2.06
12.5519	72.26
13.3180	3.73
13.7754	7.33
16.5925	43.77
17.2066	32.10
17.7820	78.62
18.9901	80.48
19.2914	100.00
20.5000	95.46
20.9102	10.74
21.2835	35.90
21.7867	11.90
22.0779	36.86
22.7162	53.61
24.6939	8.55
25.0331	15.90
25.5487	10.34
26.2507	9.33

27.1538	57.00
27.7132	4.84
28.2070	7.44
29.0636	18.19
30.9147	10.15
31.3735	14.62
31.7627	9.07
32.3232	4.10
32.9013	5.62
34.0401	7.29
35.2654	13.30
39.1189	3.42
40.7887	3.73
47.0409	3.23

The polymorphic Form VIII is obtained by suspending Dolasetron mesylate in aliphatic ketones such as ethyl methyl ketone, heating at a temperature in the range of 30-85°C for one hour, preferably in the range of 75-8O^{0}C, stirring the solution with cooling at a temperature in the range of - 5 to 30^{0}C, preferably in the range of 25-30^{0}C, isolating and drying the product at a temperature in the range of in the range of 40-90^{0}C, preferably in the range of in the range of 65-7O^{0}C. The XRPD of Dolasetron mesylate Form VIII is given in **Figure 8.** The XRPD of Dolasetron mesylate Form VIII exhibits following peaks:

Position [°2Θ]	ReI. Int. [%]
7,5963	4.24
9.3846	8.81
12.3236	59.04
13.5267	3.90
14.1731	48.06
15.0400	50.64
16.2205	100.00
18.3240	92.38
18.6858	20.79
19.3579	4.00
20.7258	37.10
21.0127	82.31
22.0929	80.73
22.5425	91.43
23.7057	35.67
24.8243	13.17
25.9718	21.22
26.6736	10.77
27.9853	26.04
29.1333	33.12

29.7016	16.86
30.1635	12.14.
31.2731	12.07
32.5971	8.36
33.5183	8.64
34.7327	10.71
37.0768	10.79
45.7888	3.36

Polymorphic Form IX of Dolasetron mesylate is obtained from Dolasetron mesylate by solvent and anti-solvent combination process. The solvent used for dissolution is selected from lower aliphatic alcohols. The lower alcohol is selected from methanol, ethanol and n-propanol. The anti-solvent is selected from a group of lower aliphatic ethers. The lower aliphatic ether is selected from diethyl ether, diisopropyl ether, and methyl tert. butyl ether. The XRPD of Dolasetron mesylate Form IX is given in **Figure 9**. The XRPD of Dolasetron mesylate Form IX exhibits following peaks:

Position [°2 θ]	Rel. Int. [%]
8.9186	5.25
9.5043	13.32
9.9342	8.08
11.3309	10.50
12.2006	27.86
13.0074	25.17
13.5809	26.51
14.2218	66.49
14.7381	39.30
15.1831	41.45
16.5427	21.94
16.9310	24.23
19.0277	29.88
19.7369	88.83
20.3022	100.00
21.2529	23.15
22.5030	75.37
23.1298	18.84
24.3308	15.61
26.5618	14.00
27.3363	28.13
28.3123	62.31
30.1981	35.94
32.6226	11.17
33.8362	12.52

Amorphous form of Dolasetron mesylate is obtained by lyophilization or vacuum evaporation or by spray drying. The solution of Dolasetron mesylate in polar protic solvents is subjected to lyophilization or vacuum evaporation or spray drying to obtain the amorphous form. The polar protic solvent used for dissolution is lower alcohols or water. The lower alcohols are selected from methanol, ethanol, and n-propanol.

Another process to obtain amorphous form is melt crystallization, comprising: melting Dolasetron mesylate at a temperature range of 150-170^{0}C, preferably in the range of 160-165^{0}C and cooling the melt at a temperature range of 25-45°C, preferably in the range of 25-3O^{0}C. The XRPD of amorphous Form is given in **Figure 10.**

The crystallization process hitherto described to prepare the novel polymorphs comprises, dissolving Dolasetron mesylate in the selected solvent either with or without heating, preferably with heating at or near boiling point of the solvent. The resultant solution is cooled to –5°C to 30^{0}C for several hours to regenerate the solid. The precipitated solids are isolated and dried at about ambient to 65°C temperature.

The solvent and anti-solvent combination process described to prepare the novel polymorphs comprises dissolving Dolasetron mesylate in the selected solvent. The dissolution is carried out at room temperature or under reflux condition. Anti-solvent is added to the resulting solution under warm conditions to regenerate Dolasetron mesylate. The anti-solvent addition is generally carried out at room temperature or at 35°C-55°C. The precipitated solids are isolated and dried at about ambient to 65^{0}C temperature.

Treatment process described hitherto to prepare Form VIII comprises, suspending Dolasetron mesylate in the selected solvent, refluxing the suspension for 1 hr, and cooling the suspension to -5°C to 30° C, preferably to room temperature under stirring for 3 hr. The solids are isolated and dried at about ambient to 65^{0}C temperature to obtain crystalline Form VIII.

The melt crystallization technique described to prepare amorphous form comprises heating of Dolasetron mesylate to form a melt. The heating is generally carried out at temperature below 175^{0}C. The melt of Dolasetron mesylate is generally formed in the temperature range of 150^{0}C -175°C, preferably 16O^{0}C. The melt is allowed to solidify at -5°C to 30^{0}C to provide the novel amorphous form.

The vacuum evaporation technique described to prepare amorphous form consists of evaporation of the solvent from Dolasetron mesylate solution under vacuum.

The spray drying technique described to prepare amorphous form Dolasetron mesylate consist of aspirating the solution of Dolasetron mesylate at the inlet temperature range of 120^0C to 180^0C, preferably 155°C- 165°C and outlet temperature range of 60^0C to 110^0C, preferably 95°C -105 ^{0}C.

The lyophilisation technique described to prepare amorphous form consists of freeze drying an aqueous solution of Dolasetron mesylate.

The novel polymorphs of Dolasetron mesylate are characterized by X-ray powder diffraction. X-ray powder diffraction pattern has been obtained on Xpert'PRO, Panalytical diffractometer equipped with accelerator detector using Copper Kce (λ= 1.5406 A) radiation with scanning range between 4-50° 2Θ at a scanning speed of 2°/min.

The present invention is described herein below with examples, which are illustrative only and should not be construed to limit the scope of the present invention in any manner.

EXAMPLES

Example 1: Preparation of ethyl-S-cyclopentene-l-carboxylate **(5)**

A solution of 3-cyclopentene-l-carboxylic acid (500 g, 4.45 mole) in ethanol (500 niL) was stirred at 5-10^0C. Then thionyl chloride (257.59 g, 2.16 mole) was added in a drop wise manner for 1 hr. After complete addition was over, the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was poured into the water (1000 mL) and extracted with ethyl acetate (2 x 250 mL). The ethyl acetate layer was washed with 10% sodium carbonate solution (500 mL), with water (2 x 500 mL) and concentrated to give ethyl-3-cyclopentene-l-carboxylate (5).

Yield: 558g, 89.42%.

Example 2: Preparation of l-ethoxycarbonyl-S-cyclopenteneoxide **(19)**

A solution of ethyl-3-cyclopentene-l-carboxylate **(5)** (1 Kg, 7.13 mole) in dichloromethane (8 L) was stirred at 5-10^0C. Then 70 % meta-chloroperbenzoic acid (2.4 Kg, 9.73 mole) was added in lots for 1 hr at 5-10^0C. The reaction mixture was stirred at 5-10^0C for 3 hr. The reaction was monitored using gas chromatography. The reaction mixture was filtered and cake washed with dichloromethane (2 x 1 L). The filtrate was washed with 10 % sodium metabisulphite (5 L), 10 % sodium carbonate (10 L), dried over sodium sulphate and concentrated to give l-ethoxycarbonyl-3-cyclopenteneoxide (19). Yield: 1.1 Kg, 98.74%.

Example 3: Preparation **of** β-ethoxycarbonylglutaraldehyde **(8)**

A suspension of periodic acid (1.5 Kg, 6.58 mole) in ethyl acetate (3 L) was stirred at 0-10 ^{0}C under nitrogen atmosphere. Then was added l-ethoxycarbonyl-3-cyclopenteneoxide (19) (1 Kg, 6.40 mole) in ethyl acetate (3 L) in a drop wise manner at 0-10 ^{0}C for lhr. The reaction mixture was stirred at 0-10 ^{0}C for 4 hr. The reaction mixture was filtered through celite. The filtrate was washed with water (2 x 750 mL). The ethyl acetate layer was diluted with water (3 L). From this mixture ethyl acetate was evaporated at 30-35 ^{0}C under vacuum and aqueous layer that remained contained β-ethoxycarbonylglutaraldehyde (7). This aqueous solution was directly used in the next step.

Example 4: Preparation of 7-ethoxycarbonyl-9-(ethoxycarbonylmethyl)-9-azabicyclo- **[3.3.1]nonan-3-one (8)**

A suspension of potassium hydrogen phthalate (2.5 Kg, 12.24 mole) in water (2 L) was stirred at room temperature. Then acetonedicarboxylic acid (1.15 Kg, 8.23 mole) in water (1.4 L) and glycine ethyl ester (1.15 Kg, 8.23 mole) in water (1.6 L) were added to the reaction mixture at 15-20^{0}C. The aqueous solution containing β-ethoxycarbonyl glutaraldehy.de (7) was added in a drop wise manner for 1 hr under nitrogen atmosphere. The reaction mixture was stirred for 12 hr at room temperature and the pH was adjusted to 8-8.5 by the addition of the potassium carbonate and extracted with ethyl acetate (3 xlOOO mL). The ethyl acetate layer was separated, washed with water and concentrated to give 7-ethoxycarbonyl-9-(ethoxycarbonylmethyl)-9-azabicyclo-[3.3.1]nonan-3-one (8). Yield: 1.05 Kg, 55.14%.

Example 5: Preparation of 7-ethoxycarbonyl-9-(ethoxycarbonylmethyI)-9-azabicyclo-[3.3.1]nonan-3-ol **(9)**

To a solution of 7-ethoxycarbonyl-9-(ethoxycarbonylmethyl)-9-azabicyclo-[3.3.1]nonan-3-one **(8)** (450 g, 1.51 mole) in ethanol (4.5 L) was added, sodiumborohydride (175 g, 4.62 mole) in a portion wise manner for 30 min at 10-15^{0}C. The reaction mixture was stirred at room temperature for 2 hr and the pH was adjusted to 7 by the addition of the acetic acid. The solid was filtered and the filtrate was concentrated to yellow residue. Water (1.2 L) was added to the residue and the reaction mixture was basified using 10% potassium carbonate solution and extracted with ethyl acetate (3 x 600 mL). The ethyl acetate layer was separated and concentrated to give 7-ethoxycarbonyl-9-(ethoxycarbonylmethyl)-9-azabicyclo-[3.3.1]nonan-3-ol (9). Yield: 365 g, 80.56%.

Example 6: Preparation of 3-tertiary-butyl dimethylsilyloxy-7-ethoxycarbonyl-9-(ethoxycarbonylmethyty-P-azabicyclo- **[3**.S.llnonan-S-ol **(20)**

A solution of 7-ethoxycarbonyl-9-(ethoxycarbonylmethyl)-9-azabicyclo-[3.3.1]nonan-3-ol **(9)** (351 g, 1.17 mole), imidazole (239 g, 3.51 mole) and t-butyldimethylsilyl chloride (265 g, 1.7 mole) in N,N-dimethylformamide (700 mL) was stirred at 10^0C for 30 min. The reaction mixture was stirred at room temperature for 2 hr, after which it was poured into water (5 L) and extracted with ethyl acetate (3 χ 500 ml). The ethyl acetate layer was separated, washed with water (3 xlOOO mL) and concentrated to give 3-tertiary butyl dimethylsilyloxy 7-ethoxycarbonyl-9-(ethoxycarbonylmethyl)-9-azabicyclo-[3.3.1]nonan-3-ol (20). Yield: 480 g, 99.17%.

^{1}HNMR: 200MHz, $CDCl_3$; the chemical shifts expressed are in δ.

0.1 (s, 6H, 2 x CH_3); 0.93 (m, 15H, 5 x CH_3); 4.1 to 4.26 (m, 4H, 2 x CH_2); 1.27 to 3.47 (m, 13H, 5 x CH_2 + 3 x CH).

Example 7: Preparation of endo-hexahydro-8-(t-butyIdimethylsiIyloxy)-2-ethoxycarbonyl-2,6-methano-2H-quinoIizin-3-(4H)-one **(21)**

A mixture of 3-(t-butyldimethylsilyloxy)-7-ethoxycarbonyl-9-(ethoxycarbonylmethyl)-9-azabicyclo-[3.3.1]nonan-3-ol (20) (480 g, 1.16 mole) and potassium t-butoxide (235 g, 2.09 mole) in toluene (4.5 L) was refluxed under nitrogen atmosphere for 2 hr. Acetic acid (140 mL) was added to the reaction mixture at 10-15^{0}C followed by water (500 mL). The reaction mixture was extracted with ethyl acetate (3.0 L), the ethyl acetate layer was separated, washed with water and concentrated to obtain endo-hexahydro-8-(t-butyldimethylsilyloxy)-2-ethoxycarbonyl-2,6-methano-2H-quinolizin-3-(4H)-one(21). Yield: 270 g, 92. 15%.

^{1}HNMR: 200MHz, $CDCl_3$; the chemical shifts expressed are in δ.

0.08 (s, 6H, 2 x CH_3); 0.89 (m, 12H, 4 x CH_3); 4.1 to 4.23 (m, 4H, 2 x CH_2); 1.23 to 4.2 & 4.81 to 5.3 (m, 12H, 5 x CH_2 + 2 x CH).

Example 8: Preparation of endo-hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3-(4H)-one **(11)**

To the oily compound, endo-hexahydro-8-(t-butyldimethylsilyloxy)-2-ethoxycarbonyl-2,6-methano-2H-quinolizin-3-(4H)-one **(21)** (100 g, 0.39 mole) in water

(200 mL) concentrated hydrochloric acid (50 mL) was added. The reaction mixture was refluxed for 16 hr, cooled to room temperature and basified with potassium carbonate till pH becomes 8-8.5. This solution was concentrated under reduced pressure to obtain a residue. This residue was treated with 50% methanol in dichloromethane to precipitate inorganic material. This inorganic material was separated by filtration and filtrate was concentrated to give endo-hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3-(4H)-one (11). Yield: 26 g, 36.34%.

Example 9: Preparation of endo-hexahydro-8-hydroxy-2,6-methano-2H-quinolizm-**3-(4H)-one (11)**

To the oily compound, endo-hexahydro-8-(t-butyldimethylsilyloxy)-2-ethoxycarbonyl-2,6-methano-2H-quinolizin-3-(4H)-one **(21)** (100 g, 0.39 mole) in water (200 mL) was added concentrated hydrochloric acid (50 mL). The reaction mixture was refluxed for 16 h cooled to room temperature and basified with potassium carbonate till pH becomes 8-8.5. This solution was extracted with n-butanol. The butanol layer was separated and concentrated under reduced to give endo-hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3-(4H)-one (11). Yield: 25.5 g, 35.64%.

Example 10: Preparation of endo-hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-**3-(4H)-one (11)**

To the oily compound endo-hexahydro-8-(t-butyldimethylsilyloxy)-2-ethoxycarbonyl-2,6-methano-2H-quinolizin-3-(4H)-one **(21)** (100 g, 0.39 mole) in water (200 mL) was added concentrated hydrochloric acid (50 mL). The reaction mixture was refluxed for 16 hr and cooled to room temperature and basified with potassium carbonate till pH becomes 8-8.5. This solution was saturated with sodium chloride and extracted with isopropanol. The isopropanol layer was separated and concentrated under reduced pressure to give residue. This residue was treated with dichloromethane and clear solution of dichloromethane was filtered and concentrated to provide endo-hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3-(4H)-one (11). Yield: 25.5 g, 35.64%.

EXAMPLE 11: Preparation of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-**methano-2H-quinoIizin-3(4H)-one (Dolasetron base).**

A solution of trifluoroacetic anhydride (413.7 g, 1.97 mole) in dichloromethane (1700 mL) was stirred under nitrogen atmosphere and to this, indole-3-carboxylic acid (302 g, 1.87 moles) was added in a portion wise manner for 30 min at -5 to 0^{0}C. The reaction mixture was stirred further 30 min at - 5 to 0^{0}C. Then endo-hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3-(4H)-one (Step VII) (170 g, 0.939 moles) in dichloromethane (850 mL) was added in a drop wise manner for 30 min at —5 to 0^{0}C and was added dimethyl amino pyridine (1.43 g). The reaction mixture was stirred further for 12 h at room temperature. The reaction mixture was filtered and the collected solid washed with dichloromethane (3 x 170 mL). The solid was stirred in water (2550 ml) and 10% sodium carbonate (1360 mL) for 30 min. The solid formed was filtered and washed with water. This solid was stirred with 5 % methanesulphonic acid (850 mL) for 1 h and filtered to remove excess undissolved indole 3-carboxylic acid. The filtrate was extracted with ethyl acetate (3 x 340 ml) and the ethyl acetate layer was separated. The aqueous acidic layer was basified with 10% sodium carbonate (850 mL), solid was separated, filtered and washed with water. Dried the wet solid (Dolasetron base).

Yield: 127 g, 42%.

Example 12: Preparation of endo-hexahydro-8-(3-indoly ïcarbonyloxy)-2,6-**methano-2H-quinolizin-3(4H)-one (Dolasetron base)**

A solution of trifluoroacetic anhydride (121.8 g, 0.57 mole) in dichloromethane (750 mL) was stirred under nitrogen atmosphere and to this, indole-3-carboxylic acid (88 g, 0.54 mole) was added in a portion wise manner for 30 min at 0 to 5^{0}C, The reaction mixture was stirred for further 30 min at 0-5^{0}C. Then endo-hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3-(4H)-one (11) (50 g, 0.27 mole) in dichloromethane (500 mL) and dimethyl amino pyridine (0.42 g, 0.0039 mole) were added in a drop wise manner for 30 min at 0-5^{0}C. The reaction mixture was stirred further for 12 h at room temperature. The reaction mixture was filtered and the collected solid washed with dichloromethane (100 mL). The solid was stirred in ethyl acetate (550 mL) and 10% sodium carbonate (500 mL) was further added. The ethyl acetate layer was separated, washed with water and concentrated to obtain crude Dolasetron base (60 g). The crude base was recrystallized from ethyl acetate-hexane to give pure Dolasetron base.

Yield: 50 g, 50.63%.

Example 13: Preparation of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-**methano-2H-quinoIizin-3(4H)-one** mesylate

Dolasetron base (50 g, 0.15 mole) was dissolved in acetone (1000 mL) and methane sulphonic acid was added (10.70 mL) drop wise over a period of 30 min at 20^{0}C. The reaction mixture was stirred further for 2 hr. The solid formed was filtered, washed with cold acetone (50 mL) and dried. Yield (crude) 59 g, 90.77%.

Example 14: Purification of endo-hexahydro-8-(3-indolylcarbonyIoxy)-2,6-methano-2H-quinolizin-3(4H)-one mesylate, Dolasetron mesylate.

Dolasetron mesylate crude (59 g) was dissolved in hot 5% aqueous isopropanol (500 mL) treated with charcoal and filtered hot. Diethyl ether (50 mL) was added to the filtrate, the solid formed was filtered and dried. Yield 50 g, 82.71%. Purity: 99.9% (HPLC).

Example 15: Preparation of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-**methano-2H-quinoIizin-3(4H)-one** mesylate hydrate.

To Dolasetron base (119 g, 0.368 moles) (Step VIII) was dissolved in acetone (2023 mL) and treated with activated charcoal (12 g). Filtered the mixture through hyflow and the clear solution was treated with water (24 ml) and methane sulphonic acid (38.96 g, 0.405 moles) at 25-30°C. The reaction mass was stirred further for 2 h at 0-5^{0}C. The solid formed was filtered, washed with acetone (3 x 120 mL) and dried. Yield (crude) 140 g, 87%.

Example 16: Purification of endo-hexahydro-8-(3-indoIylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)-one mesylate, **Dolasetron** mesylate hydrate.

The Dolasetron mesylate (140 g) (Step IX) was taken in water (900 ml) and extracted with ethyl acetate (3x280 ml). The aqueous layer was separated, basified with 10% sodium carbonate (320 mL). The solid obtained was filtered, washed with water and dried. This solid was dissolved in acetone (2 xlOO mL) and treated with activated charcoal (12 g). Filtered the mixture through hyfiow and clear solution was treated with water (20 mL) and methane sulphonic acid (32.72 g, 0.341 moles) at 25-30^{0}C. The reaction mass

was stirred further for 2 h at 0-5^{0}C. The solid formed was filtered, washed with acetone (3 xlOO niL) and dried. Yield 130 g, 93%. Purity: 99.9% (HPLC).

PREPARATION OF POLYMORPHIC **FORMS OF DOLASETRON MESYLATE**

Preparation of Dolasetron mesylate **Form I**

Example 17

0.5g of Dolasetron mesylate was dissolved in 30 mL of IPA at reflux temperature. The hot solution was allowed to cool to room temperature. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65^{0}C to get Dolasetron mesylate Form I. (Kf= 4.85%)

Example 18

0.5g of Dolasetron mesylate was dissolved in 20 mL of acetonitrile at reflux temperature. The hot solution was allowed to cool to room temperature. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65°C to get Dolasetron mesylate Form I. (K_f = 4.56%)

Example 19

0.5g of Dolasetron mesylate was dissolved in 20 mL of acetone at reflux temperature. The hot solution was allowed to cool to room temperature. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65^{0}C to get Dolasetron mesylate Form I. (K_f = 5.32%)

Example 20

0.5g of Dolasetron mesylate was dissolved in 50 mL of ethyl acetate at reflux temperature. The hot solution was allowed to cool to room temperature. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65^{0}C to get Dolasetron mesylate Form I. (K_f = 4.96%)

Example 21

0.5g of Dolasetron mesylate was dissolved in 2 mL of DMF at room temperature. To this clear solution 10 mL of THF was added. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65^{0}C to get Dolasetron mesylate Form I. (K_f = 4.81%)

Example 22

0.5g of Dolasetron mesylate was dissolved in 2 mL of DMF at room temperature. To this clear solution 10 mL of toluene was added. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65°C to get Dolasetron mesylate Form I. (K_f = 5.28%)

Example 23

0.5g of Dolasetron mesylate was dissolved in 2 mL of DMF at room temperature. To this clear solution 10 mL of IPA was added. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65°C to get Dolasetron mesylate Form I. (K_f = 4.75%)

Example 24

0.5g of Dolasetron mesylate was dissolved in 2 mL of DMSO at room temperature. To this clear solution 10 mL of THF was added. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65^0C to get Dolasetron mesylate Form I. (K_f = 5.32%)

Example 25

0.5g of Dolasetron mesylate was dissolved in 2 mL of DMSO at room temperature. To this clear solution 10 mL of toluene was added. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65^0C to get Dolasetron mesylate Form I. (K_f = 5.68%)

Example 26

0.5g of Dolasetron mesylate was dissolved in 2 mL of DMSO at room temperature. To this clear solution 10 mL of IPA was added. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65^0C to get Dolasetron mesylate Form I. (K_f = 4.52%)

Example 27

0.5g of Dolasetron mesylate was dissolved in 2 mL of N,N-dimethyl acetamide at room temperature. To this clear solution 10 mL of THF was added. The solution was

stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65^{0}C to get Dolasetron mesylate Form I. (K_f = 4.95%)

Example 28

0.5g of Dolasetron mesylate was dissolved in 2 mL of N,N-dimethyl acetamide at room temperature. To this clear solution 10 mL of toluene was added. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65^{0}C to get Dolasetron mesylate Form I. (K_f = 5.12%)

Example 29

0.5g of Dolasetron mesylate was dissolved in 2 mL of N, N-dimethyl acetamide at room temperature. To this clear solution 10 mL of IPA was added. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65^{0}C to get Dolasetron mesylate Form **I.** (K_f = 4.82%)

Preparation of Dolasetron mesylate **Form II**

Example **30**

0.5g of Dolasetron mesylate was dissolved in 5 mL of methanol at reflux temperature. The hot solution was allowed to cool to 5^{0}C. The solution was stirred at the same temperature for 12 hr. The solid obtained was filtered and dried at 65°C to get Dolasetron mesylate Form II. (K_f = 2.60%)

Preparation of Dolasetron mesylate **Form III**

Example **31**

0.5g of Dolasetron mesylate was dissolved in 10 mL of ethanol at reflux temperature. The hot solution was allowed to cool to 5°C for 2 hr and the solution was stirred at the same temperature for 12 hr. The solid obtained was filtered and dried at 65^{0}C to get Dolasetron mesylate Form III. (K_f = 5.48%)

Example 32

0.5g of Dolasetron mesylate was dissolved in 20 mL of ethanol at reflux temperature. The hot solution was allowed to cool to 45°C and to this was added 50 mL of n-hexane. The resultant slurry was stirred for 2 hr and the solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65^{0}C to get Dolasetron mesylate Form III. (K_f = 4.81%).

Preparation of Dolasetron mesylate **Form IV**

Example 33

0.5g of Dolasetron mesylate was dissolved in 5 mL of n-propanol at reflux temperature. The hot solution was allowed to cool to 5°C for 2 hr and the solution was stirred at the same temperature for 12 hr. The solid obtained was filtered and dried at 65°C to get Dolasetron mesylate Form IV. (K_f = 5.66%).

Preparation of Dolasetron mesylate **Form V**

Example 34

0.5g of Dolasetron mesylate was dissolved in 75 mL of chloroform at reflux temperature. The hot solution was maintained at the same temperature for 30 min. The hot solution was allowed to cool to room temperature and was stirred for 3 hr at the same temperature. The solid obtained was filtered and dried at 65^0C to get Dolasetron mesylate Form V. (K_f = 5.83%)

Example 35

0.5g of Dolasetron mesylate was dissolved in 75 mL of methylene dichloride at reflux temperature. The hot solution was maintained at the same temperature for 30 min. The hot solution was allowed to cool to room temperature and was stirred for 3 hr at the same temperature. The solid obtained was filtered and dried at 65°C to get Dolasetron mesylate Form V. (K_f = 7.69%)

Preparation of Dolasetron mesylate **Form VI**

Example 36

0.5g of Dolasetron mesylate was dissolved in 2 mL of DMF at room temperature. To this solution 20 mL of 1,4-dioxane was added at room temperature. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65°C to get Dolasetron mesylate Form VI. (K_f = 4.69%)

Example 37

0.5g of Dolasetron mesylate was dissolved in 2 mL of DMSO at room temperature. To this solution 10 mL of 1,4-dioxane was added at room temperature. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65^0C to get Dolasetron mesylate Form VI. (K_f = 4.46%)

Preparation of Dolasetron mesylate **Form VII**

Example 38

0.5g of Dolasetron mesylate was dissolved in 2 mL of N,N-dimethyl acetamide at room temperature. To this solution 20 mL of 1,4-dioxane was added at room temperature. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65^{0}C to get Dolasetron mesylate Form VII. (K_f = 4.80%)

Preparation of Dolasetron mesylate **Form VIII**

Example 39

0.5g of Dolasetron mesylate was suspended in 20 mL of ethyl methyl ketone and the solution was heated to reflux for 1 hr. The solution was cooled to room temperature. The solution was stirred at the same temperature for 3 hr. The solid obtained was filtered and dried at 65°C to get Dolasetron mesylate Form VIII. (K_f = 8.01%)

Preparation of Dolasetron mesylate **Form IX**

Example 40

0.5g of Dolasetron mesylate was suspended in 20 mL of ethanol and the solution was heated to reflux for 1 hr. The solution was cooled to 45°C temperature. To this hot solution, 50 mL of diisopropyl ether was added and the solution was stirred at 3O^{0}C for 3 hr. The solid obtained was filtered and dried at 65°C to get Dolasetron mesylate Form IX. (K_f = 5.04%).

Preparation of amorphous form of Dolasetron mesylate

Example 41

0.5g of Dolasetron mesylate was suspended in 20 mL of methanol, The solution was warmed to 60^{0}C to get a clear solution. The hot solution was distilled under vacuum at 55-60^{0}C under pressure. The solid obtained by this method was maintained at same temperature and pressure to remove any traces of solvent. The solid obtained was amorphous form of Dolasetron mesylate. (Kf= 4.81%)

Example 42

0.5g of Dolasetron mesylate was suspended in 10 mL of water. The solution was warmed to 6O^{0}C to get a clear solution. The hot solution was distilled under vacuum at 55-60^{0}C under pressure. The solid obtained by this method was maintained at same

temperature and pressure to remove any traces of solvent. The solid obtained was amorphous form of Dolasetron mesylate. (K_f = 4.96%)

Example 43

0.5g of Dolasetron mesylate was suspended in clean and dry 100 mL round bottom flask and the flask was heated to 160^{0}C to melt the solid in to liquid. The melt solid was heated to 120° for 3 hr. The solid obtained was amorphous form of Dolasetron mesylate. (K_f = 4.92%)

Example 44

A 50 mL aqueous solution of Dolasetron mesylate was frozen using dry ice bath and dried by lyophilization for 24 hr.

Example 45

A 50mL aqueous solution of Dolasetron mesylate at a concentration of 20% weight/volume and at a temperature of 30^{0}C was spray dried by a spray gun (PSD 00 Pilot, Hemraj, India at pressure 500 to 600 psi and flow rate of 2 L/hr) at an inlet temperature of 165^{0}C and outlet temperature of 105^{0}C of the spray gun.

Example 46

The procedure of Example 45 was carried out at inlet temperature of 155^{0}C and outlet temperature of 95^{0}C of the spray gun.

What is claimed is:

1. A process for producing polymorphic Form I of Dolasetron mesylate comprising: dissolving Dolasetron mesylate in a solubilizing solvent at a temperature in the range of 30^0C to 80^0C, cooling at a temperature in the range of 0^0C to 30^0C, isolating and drying the product at a temperature in the range of 30^0C to 90^0C.

2. The process as claimed in claim 1 , wherein the solubilizing solvent is selected from isopropanol, acetonitrile, ethyl acetate, acetone or mixture thereof.

3. A process for producing polymorphic Form I of Dolasetron mesylate comprising: dissolving Dolasetron mesylate in a solubilizing solvent, adding an anti-solvent, stirring the suspension with or without cooling for about one hour to about eight hours, isolating and drying the product at a temperature range of 30^0C to $9O^0$C.

4. The process as claimed in claim 3, wherein the solubilizing solvent is selected from polar aprotic solvents.

5. The process as claimed in claim 4, wherein the polar aprotic solvent is selected from dimethyl formamide, dimethyl sulfoxide, N, N-dimethyl acetamide or mixture thereof.

6. The process as claimed in claim 3, wherein the anti-solvent is selected from a group of tetrahydrofuran, toluene, isopropanol or mixture thereof.

7. A crystalline polymorphic Form II of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)-one methanesulfonate, Dolasetron mesylate characterized by the X-ray powder diffraction pattern as given below:

Peaks in the powder X-ray diffraction pattern are at about 2Θ: 8.5677, 14.3549, 15.3566, 16.1189, 17.4727, 17.9848, 18.2788, 19.9142, 20.3327, 20.7258, 21.4927, 24.4864, 27.5344 and 28.2995 ± 0.2 degrees.

8. A process for producing polymorphic Form II of Dolasetron mesylate of claim 7 comprising: dissolving Dolasetron mesylate in methanol at a temperature in the range of $3O^0$C to $8O^0$C, cooling to a temperature in the range of 2°C to 7°C, isolating a residue and drying the residue at a temperature in the range of 30^0C to 90^0C.

9. A crystalline polymorphic Form III of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)-one methanesulfonate, Dolasetron mesylate characterized by the X-ray powder diffraction pattern as given below:

Peaks in the powder X-ray diffraction pattern are at about 2Θ: 6.9327, 12.6509, 13.7701, 16.6416, 17.5613, 18.1133, 19.4364, 19.6530, 20.5969, 21.2122, 22.1215, 22.3203, 22.9997, 27.9040 and 29.5991 ± 0.2 degrees.

10. A process for producing polymorphic Form III of Dolasetron mesylate of claim 9 comprising: dissolving Dolasetron mesylate in ethanol at a temperature in the range of 30^0C to 80^0C, cooling to a temperature in the range of - 5^0C to 30^0C, isolating a product and diying the product at a temperature in the range of $3O^0$C to 90^0C.

11. A process for producing polymorphic Form III of Dolasetron mesylate of claim 9 comprising: dissolving Dolasetron mesylate in a solubilizing solvent at an elevated temperature in the range of $6O^0$C to 80^0C, adding an anti-solvent at a temperature in the range of $3O^0$C to 55°C, isolating a product and drying the product at a temperature in the range of30°C to 90°C.

12. The process as claimed in claim 11, wherein the solubilizing solvent is selected from methanol, ethanol, n-propanol and isopropanol.

13. The process as claimed in claim 11, wherein the solubilizing solvent is ethanol.

14. The process as claimed in claim 11, wherein the anti-solvent is an aliphatic hydrocarbon.

15. The process as claimed in claim 14, wherein the aliphatic hydrocarbon is selected from n-pentane, n-hexane and n-heptane.

16. The process as claimed in claim 14, wherein the aliphatic hydrocarbon is n-hexane.

17. A crystalline polymorphic Form IV of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)-one methanesulfonate, Dolasetron mesylate characterized by the X-ray powder diffraction pattern as given below:

Peaks in the powder X-ray diffraction pattern are at about 2Θ: 8.9231, 12.1275, 12.5348, 12.7100, 14.0712, 14.8069, 16.6676, 17.3884, 18.9666, 19.2953, 19.9217, 20.81 15, 22.0471 and 22.4082 ± 0.2 degrees.

18. A process for producing polymorphic Form IV of Dolasetron mesylate of claim 17 comprising: dissolving Dolasetron mesylate in n-propanol at a temperature in the range of 30^0C to 100^0C, cooling to a temperature in the range of -5°C to $3O^0$C, isolating a product and drying the product at a temperature in the range of 30^0C to 90^0C.

19. A crystalline polymorphic Form V of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)-one methanesulfonate, Dolasetron mesylate characterized by the X-ray powder diffraction pattern as given below:

Peaks in the powder X-ray diffraction pattern are at about 2Θ: 7.0234, 9.4499, 11.2346, 12.3990, 13.5899, 14.2116, 14.9901, 16.4007, 18.7313, 20.3109, 20.7126, 21.2339, 22.2956, 23.8661, 24.2519, 24.8389, 28.8706 ± 0.2 degrees.

20. A process for producing polymorphic Form V of Dolasetron mesylate of claim 19 comprising: dissolving Dolasetron mesylate in a solubilizing solvent at a temperature at a temperature in the range of $3O^0$C to 80^0C, cooling to a temperature in the range of - 5^0C to $3O^0$C, isolating a product and drying the product at a temperature in the range of $3O^0$C to 90^0C.

21. The process as claimed in claim 20, wherein the solubilizing solvent is a chlorinated hydrocarbon.

22. The process as claimed in claim 20, wherein the chlorinated hydrocarbon is either chloroform or methylene dichloride.

23. A crystalline polymorphic Form VI of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)-one methanesulfonate, Dolasetron mesylate characterized by the X-ray powder diffraction pattern as given below:

Peaks in the powder X-ray diffraction pattern are at about 2Θ: 7.4433, 9.5049, 9,9496, 10.5039, 12.6288, 13.3801, 13.7613, 16.6316, 17.8499, 19.0352, 19.3432, 20.4909 and 21.8514 ± 0.2 degrees.

24. A process for producing polymorphic Form VI of Dolasetron mesylate of claim 23 comprising: dissolving Dolasetron mesylate in a solubilizing solvent at a temperature in the range of $2O^0$C to 35°C, adding an anti-solvent at a temperature range of 20^0C to 45^0C, isolating and drying the product at a temperature in the range of $3O^0$C to 90^0C.

25. The process as claimed in claim 24, wherein the solubilizing solvent is a polar aprotic solvent.

26. The process as claimed in claim 25, wherein the polar aprotic solvent is either dimethyl formamide or dimethyl sulfoxide.

27. The process as claimed in claim 24, wherein the anti-solvent is 1, 4-dioxane.

28. A crystalline polymorphic Form VII of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)-one methanesulfonate, Dolasetron mesylate, characterized by the X-ray powder diffraction pattern as given below:

Peaks in the powder X-ray diffraction pattern are at about 2Θ: 9.4384, 12.5519, 13.3180, 16.5925, 17.2066, 17.7820, 18.9901, 19.2914, 20.5000, 20.9102, 21.2835, 21.7867, 22.0779, 22.7162, 27.1538 and 29.0636 ± 0.2 degrees.

29. A process for producing polymorphic Form VII of Dolasetron mesylate of claim 28 comprising: dissolving Dolasetron mesylate in N,N-dimethyl acetamide at a temperature in the range of 20^0C to 35°C, adding an anti-solvent at a temperature in the range of 20^0C to 45°C, isolating and drying the product at a temperature in the range of 30^0C to $9O^0$C.

30. The process as claimed in claim 29, wherein the anti-solvent is 1, 4-dioxane.

31. A crystalline polymorphic Form VIII of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3 (4H)-one methanesulfonate, Dolasetron mesylate, characterized by the X-ray powder diffraction pattern as given below:

Peaks in the powder X-ray diffraction pattern are at about 2Θ: 9.3846, 12.3236, 14.1731, 15.0400, 16.2205, 18.3240, 20.7258, 21.0127, 22.0929, 22.5425 and 23.7057 ± 0.2 degrees.

32. A process for producing polymorphic Form VIII of Dolasetron mesylate of claim 31 comprising: suspending Dolasetron mesylate in ethyl methyl ketone, heating at an elevated temperature in the range of $4O^0$C to 80^0C for one hour, stirring the solution with cooling to a temperature in the range of - 5^0C to 30^0C, isolating a product and drying the product at a temperature in the range of $3O^0$C to $9O^0$C.

33. A crystalline polymorphic Form IX of endo-hexahydro-8-(3-indolylcarbonyloxy)-2,6-methano-2H-quinolizin-3(4H)-one methanesulfonate, Dolasetron mesylate, characterized by the X-ray powder diffraction pattern as given below:

Peaks in the powder X-ray diffraction pattern are at about 2Θ: 8.9186, 9.5043, 9.9342, 12.2006, 13.0074, 13.5809, 14.2218, 15.1831, 19.0277, 19.7369, 20.3022, 21.2529 and 22.5030 ± 0.2 degrees.

34. A process for producing polymorphic Form IX of Dolasetron mesylate of claim 33 comprising: dissolving Dolasetron mesylate in a solubilizing solvent at a temperature in the range of 60^0C to 80^0C, adding an anti-solvent at a temperature in the range of 30^0C to 55°C, isolating and drying the product at a temperature in the range of $3O^0$C to $9O^0$C.

35. The process as claimed in claim 34, wherein the solubilizing solvent is selected from a group consisting of methanol, ethanol and n-propanol.

36. The process as claimed in claim 34, wherein the solubilizing solvent is ethanol.

37. The process as claimed in claim 34, wherein the anti-solvent is aliphatic ether.

38. The process as claimed in claim 37, wherein the aliphatic ether is selected from a group consisting of diethyl ether, diisopropyl ether and methyl tert-butyl ether.

39. The process as claimed in claim 37, wherein the aliphatic ether is diisopropyl ether.

40. An amorphous form of endo-hexahydro-8-(3-indolylcarbonyloxy)-2, 6-methano-2H-quinolizin-3 (4H)-one methanesulfonate (Dolasetron mesylate).

41. A process for preparation of amorphous form of Dolasetron mesylate of claim 40 comprising: dissolving Dolasetron mesylate in polar protic solvents and vacuum evaporating the solution.

42. The process claimed in claim 41, wherein the polar protic solvent is selected from methanol, ethanol, n-propanol and water.

43. . A process for preparation of amorphous form of Dolasetron mesylate of claim 40 comprising: dissolving Dolasetron mesylate in polar protic solvents and lyophilizing the solution.

44. The process as claimed in claim 43, wherein the polar protic solvent is selected from methanol, ethanol, n-propanol and water.

45. The process as claimed in claim 43, wherein the polar protic solvent is water.

46. A process for preparation of amorphous form of Dolasetron mesylate of claim 40, comprising: dissolving Dolasetron mesylate in polar protic solvents and spray drying the solution.

47. The process as claimed in claim 46, wherein the polar protic solvent is selected from methanol, ethanol, n-propanol and water.

48. The process as claimed in claim 46, wherein the solution is spray dried at an inlet temperature in the range of 120^0C to 180^0C.

49. The process as claimed in claim 46, wherein the solution is spray dried at an inlet temperature in the range of 155° C to 165°C.

50. The process as claimed in claim 46, wherein the solution is spray dried at an outlet temperature in the range of 60^0C to 110^0C.

51. The process as claimed in claim 46, wherein the solution is spray dried at an outlet temperature in the range of 95^0C to 105^0C.

52. A process for preparation of amorphous form of Dolasetron mesylate of claim 40 comprising: melting Dolasetron mesylate at a temperature in the range of $15O^0$C to 170^0C and cooling the melt at a temperature in the range of 25°C to 45^0C.

53. A process for preparation of amorphous form of Dolasetron mesylate of claim 40 comprising: dissolving Dolasetron mesylate in water and lyophilizing the solution.

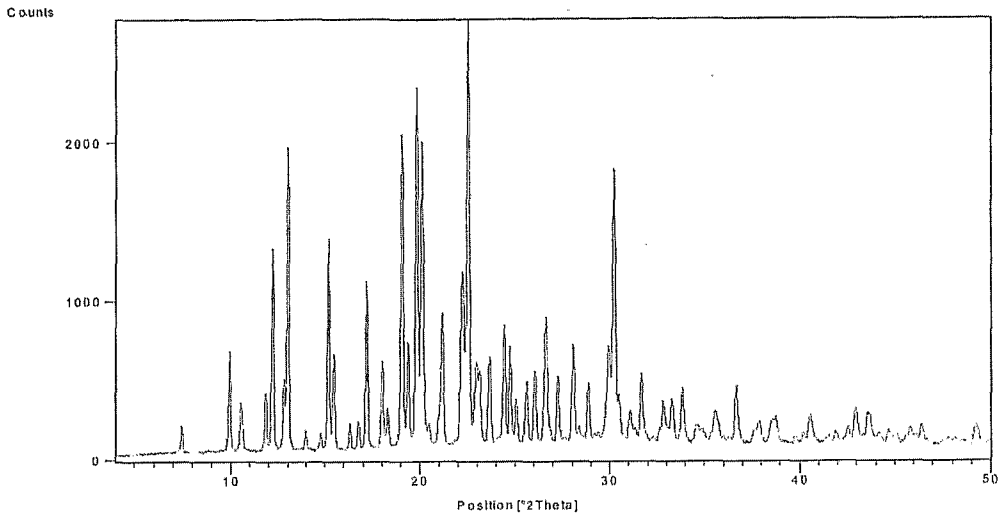


Figure 1

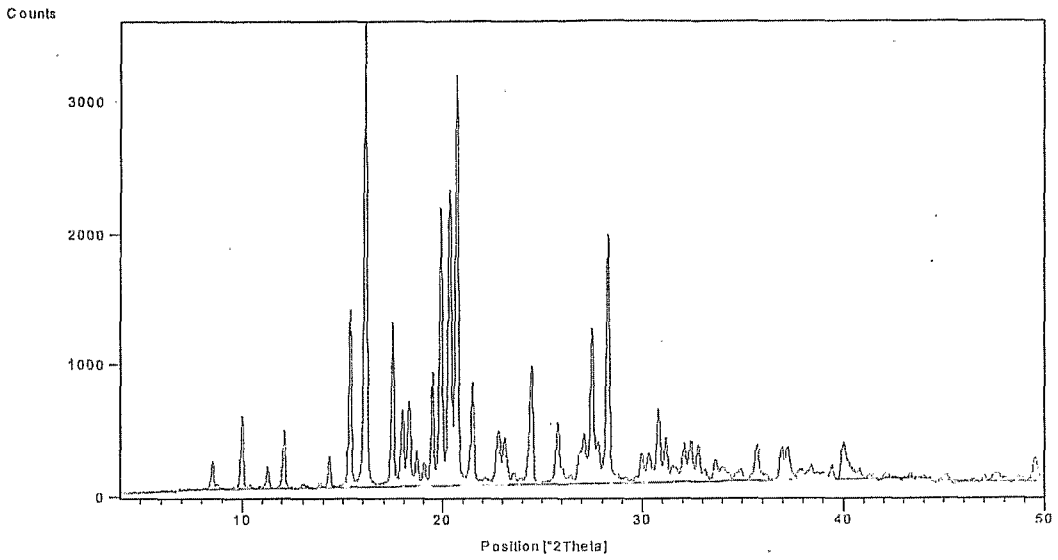


Figure 2

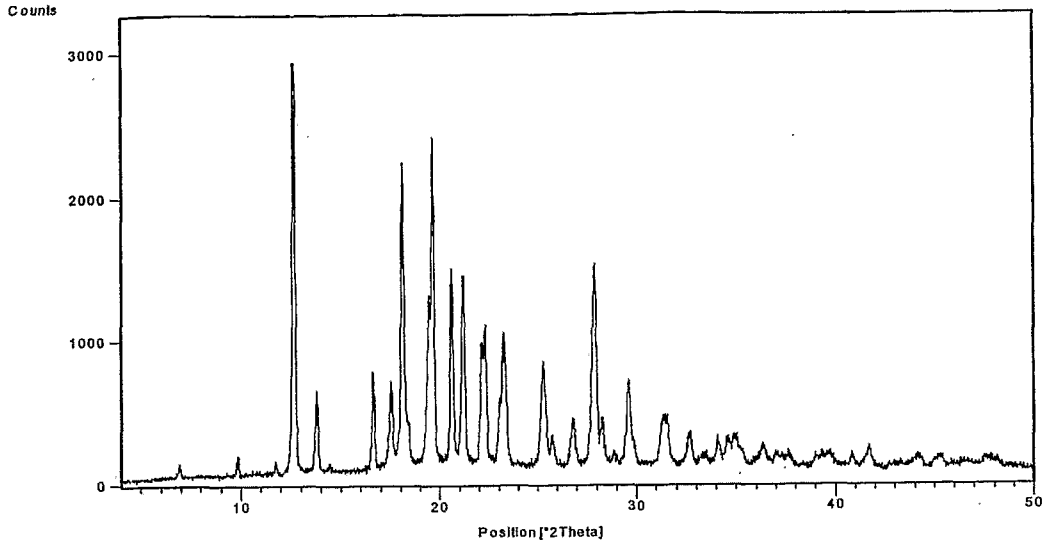


Figure 3

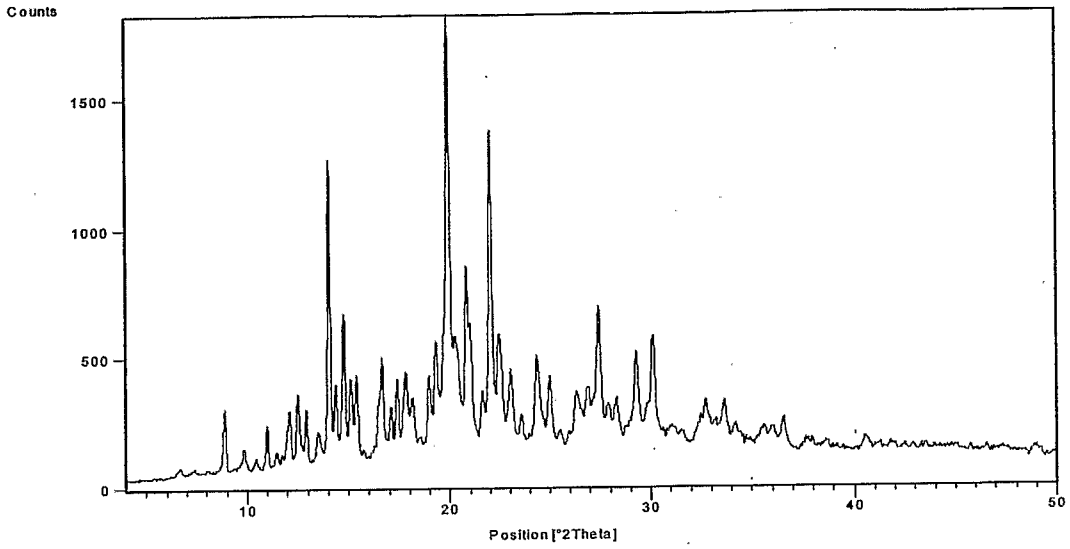


Figure 4

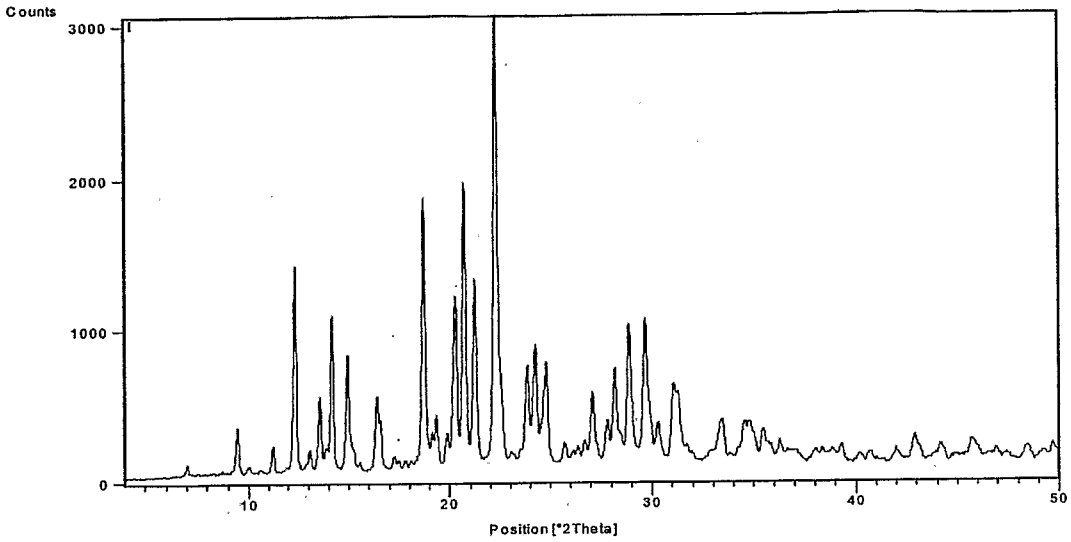


Figure 5

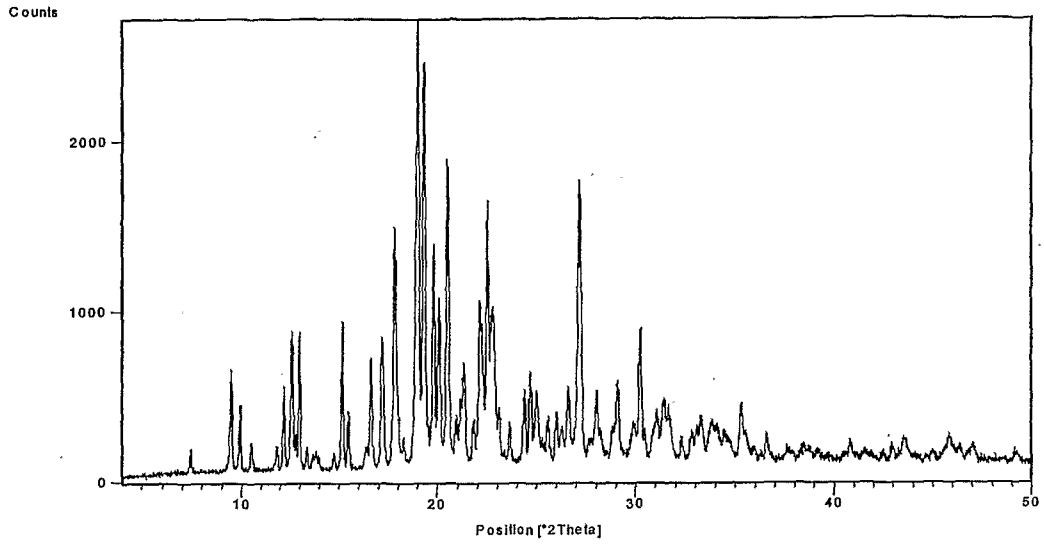


Figure 6

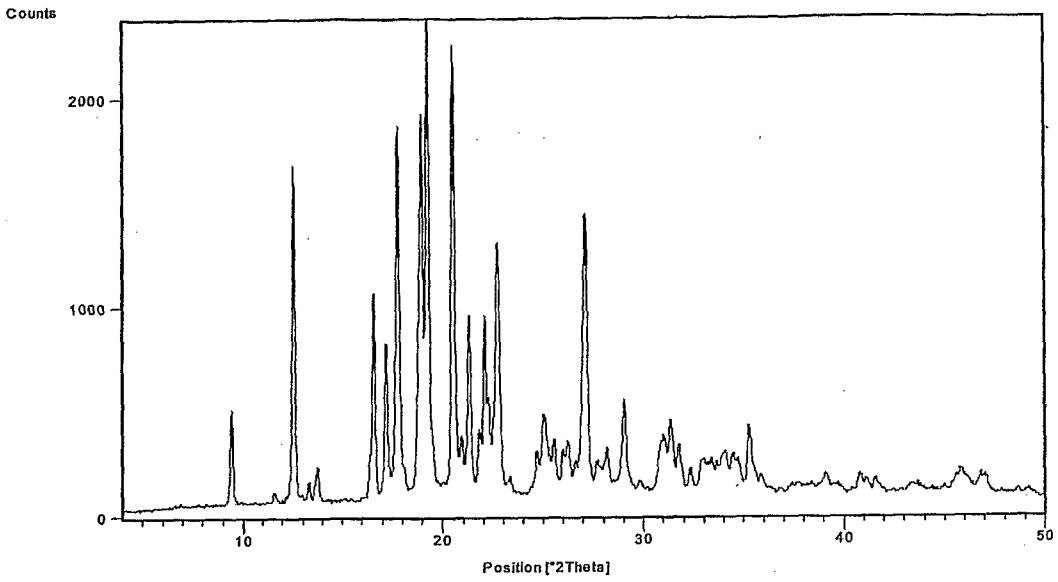


Figure 7

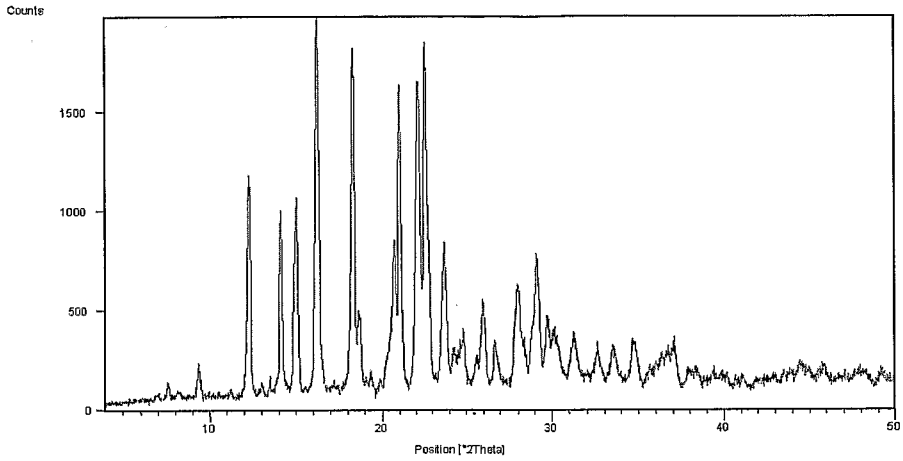


Figure 8

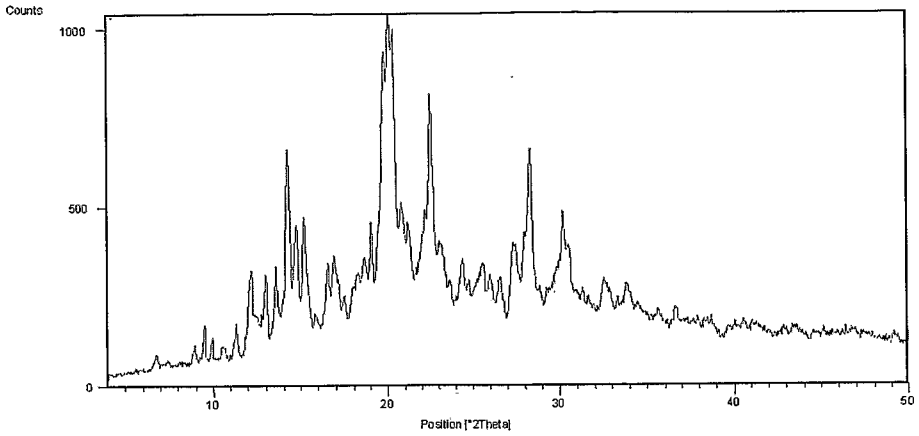


Figure 9

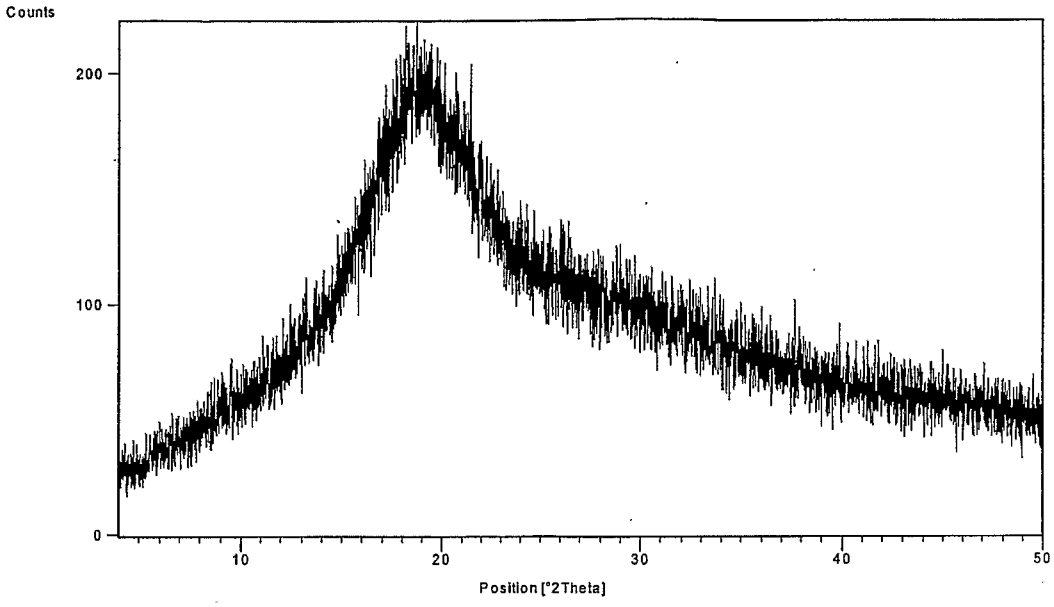


Figure 10