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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 September 2011 (09.09.2011)

PCT

(10) International Publication Number
WO 2011/107903 A1

(51) International Patent Classification:
C07D 265/30 (2006.01) *A61P 1/00* (2006.01)
A61K 31/5375 (2006.01)

(21) International Application Number:
PCT/IB2011/050763

(22) International Filing Date:
23 February 2011 (23.02.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
495/DEL/2010 4 March 2010 (04.03.2010) IN

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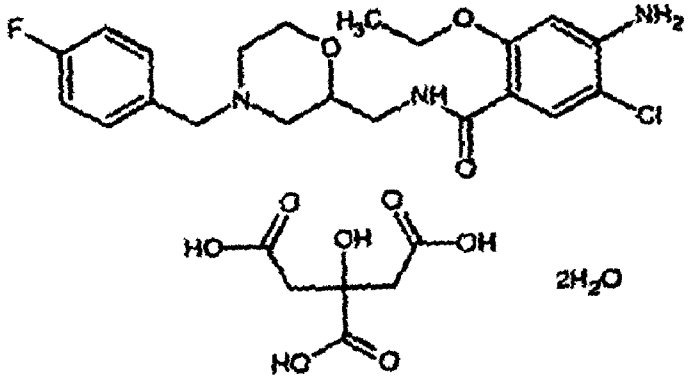
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, 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, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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

(54) **Title**: HIGHLY PURE MOSAPRIDE CITRATE DIHYDRATE AND PROCESSES FOR ITS PREPARATION



(57) **Abstract**: The present invention provides for highly pure mosapride citrate dihydrate and processes for its preparation. The present invention further provides a process for the preparation of mosapride citrate dihydrate substantially free of impurity D-II.

WO 2011/107903 A1

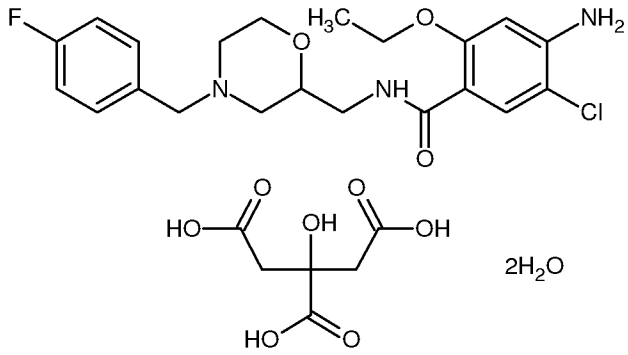
HIGHLY PURE MOSAPRIDE CITRATE DIHYDRATE AND PROCESSES FOR ITS PREPARATION

Field of the Invention

The present invention provides for highly pure mosapride citrate dihydrate and processes for its preparation. The present invention further provides a process for the preparation of mosapride citrate dihydrate substantially free of impurity D-II.

Background of the Invention

Mosapride citrate dihydrate of Formula A, chemically, (±)-4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide citrate dihydrate, is marketed under the brand name Gasmotin® and indicated for gastrointestinal symptoms associated with chronic gastritis (heartburn, nausea/vomiting).



Formula A

U.S. Patent No. 4,870,074 (hereinafter "the '074 patent") provides a process for the preparation of mosapride citrate dihydrate; which involves dissolving mosapride freebase in hot 10% aqueous citric acid solution and allowing the resulting solution to cool to provide mosapride citrate dihydrate.

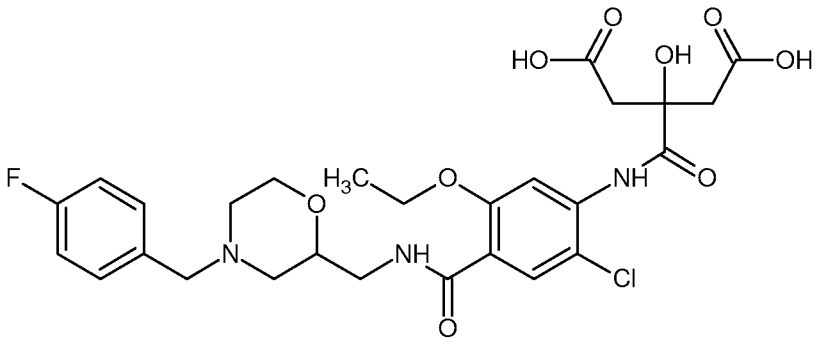
WO 03/106440 provides a process for the preparation of mosapride citrate dihydrate, which involves boiling mosapride free base with 10% aqueous citric acid solution with stirring and further cooling to 0°C to precipitate mosapride citrate dihydrate.

Korean Patent KR 750593 B1 provides a process for the preparation of mosapride citrate dihydrate by treating mosapride free base with a 10% citric acid solution in ethanol.

Drugs of the Future, 18(6): pp. 513-515 (1993), provides a process for the preparation of mosapride citrate dihydrate through the treatment of mosapride free base with citric acid.

Japan Application No. 2008/247753, Chinese Patent No. 1226295, Korean Application No. 2009/044694, *Heterocycles*, Vol. 38 Issue 5, pp. 1033-1040; *Journal of Medicinal Chemistry,* 34(2), pp. 616-24 (1991); and *Chem. Pharm. Bull.*, 42(4), pp. 877-82 (1994), provide various processes for the preparation of mosapride and its intermediates.

Mosapride citrate dihydrate obtained by the processes described in the art is not satisfactorily pure. Reproduction of the mosapride citrate dihydrate synthetic procedures as described in the prior art, wherein mosapride free base and citric acid are taken in the mole ratio of about 1:8 to about 1:2, does not provide mosapride citrate dihydrate in a high purity and there are unacceptable amounts of impurities. Among these impurities, 3-{[2-chloro-5-ethoxy-4-({[4-(4-fluorobenzyl)morpholin-2-yl]methyl}carbamoyl)phenyl]carbamoyl}-3-hydroxypentanedioic acid (hereinafter "impurity D-II") represented by the compound of Formula B is found to be present at a level of more than 0.25% when measured by HPLC.



Formula B

Impurities in mosapride citrate dihydrate, or any active pharmaceutical ingredient ("API"), are undesirable and, in extreme cases, might even be harmful to a patient being treated with a dosage form containing the API.

The purity of an API produced in a manufacturing process is critical for commercialization. The product of a chemical reaction is rarely a single compound with sufficient purity to comply with pharmaceutical standards. Side products and by-products

of the reaction and adjunct reagents used in the reaction will, in most cases, also be present in the final product. At certain stages during processing of an API, it must be analyzed for purity, typically, by high performance liquid chromatography ("HPLC") or thin-layer chromatography ("TLC"), to determine if it is suitable for continued processing and, ultimately, for use in a pharmaceutical product.

As known by those skilled in the art, the management of process impurities is greatly enhanced by understanding their chemical structures and synthetic pathways and by identifying the parameters that influence the amount of impurities in the final product.

Extensive experimentation has been carried out by the present inventors to reduce the level of the impurity D-II in mosapride citrate dihydrate. As a result, the present inventors found an improved method for the preparation of mosapride citrate dihydrate substantially free of impurity D-II by controlling the parameters such as quantity of citric acid and temperature. Thus, the present invention provides a process which results in mosapride citrate dihydrate having impurity D-II at a level less than 0.1%. The mosapride citrate dihydrate made by the process of the present invention is suitable for commercial scale production.

Summary of the Invention

In one general aspect, the present invention provides for a process for the preparation of mosapride citrate dihydrate. The process includes:

a) treating mosapride free base with citric acid, wherein the mosapride free base and the citric acid are taken in the mole ratio of about 1:0.5 to about 1:1.2; and

b) isolating mosapride citrate dihydrate.

Embodiments of this aspect may include one or more of the following features. For example, step a) is carried out in one or more solvents at a temperature of about 20°C to 85°C.

Suitable solvents are water, esters, alkanols, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents or mixtures thereof.

Suitable esters are one or more of ethyl acetate, n-propyl acetate, isopropyl acetate, and n-butyl acetate.

Suitable alkanols are methanol, ethanol, n-propanol, isopropanol and butanol.

Suitable halogenated hydrocarbons are dichloromethane, chloroform, and 1,2-dichloroethane.

Suitable ketones are acetone or methyl ethyl ketone.

Suitable ethers are diethyl ether or tetrahydrofuran.

Suitable polar aprotic solvents are one or more of N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

In another general aspect, the present invention provides for a process for the preparation of mosapride citrate dihydrate substantially free of impurity D-II. The process includes:

a) treating mosapride free base with citric acid, wherein the mosapride free base and the citric acid are taken in the mole ratio of about 1:0.5 to about 1:1.2; and

b) isolating the mosapride citrate dihydrate substantially free of impurity D-II.

Embodiments of this aspect may include one or more of the following features. For example, step a) is carried out in one or more solvents at a temperature of about 20°C to 85°C.

Suitable solvents are water, esters, alkanols, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents or mixtures thereof.

Suitable esters are one or more of ethyl acetate, n-propyl acetate, isopropyl acetate, and n-butyl acetate.

Suitable alkanols are methanol, ethanol, n-propanol, isopropanol and butanol.

Suitable halogenated hydrocarbons are dichloromethane, chloroform, and 1,2-dichloroethane.

Suitable ketones are acetone or methyl ethyl ketone.

Suitable ethers are diethyl ether or tetrahydrofuran.

Suitable polar aprotic solvents are one or more of N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

In yet another general aspect, the present invention provides for mosapride citrate dihydrate substantially free of impurity D-II.

In another general aspect, the present invention provides for mosapride citrate dihydrate having impurity D-II in an amount of 0.1% or less as determined by HPLC method.

In another general aspect, the present invention provides for mosapride citrate dihydrate substantially free of impurity D-II having impurity D-II in an amount of 0.05% or less as determined by HPLC method.

In another general aspect, the present invention provides for mosapride citrate dihydrate substantially free of impurity D-II having impurity D-II in an amount of 0.01% or less as determined by HPLC method.

In yet another general aspect, the present invention provides for mosapride citrate dihydrate substantially free of impurity D-II having impurity D-II undetectable as determined by HPLC method.

In another general aspect, the present invention provides for a process for the preparation of highly pure mosapride citrate dihydrate. The process includes:

a) treating mosapride free base with citric acid, wherein the mosapride free base and the citric acid are taken in the mole ratio of about 1:0.5 to about 1:1.2; and

b) isolating the highly pure mosapride citrate dihydrate.

Embodiments of this aspect may include one or more of the following features. For example, step a) is carried out in one or more solvents at a temperature of about 20°C to 85°C.

Suitable solvents are water, esters, alkanols, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents or mixtures thereof.

Suitable esters are one or more of ethyl acetate, n-propyl acetate, isopropyl acetate, and n-butyl acetate.

Suitable alkanols are methanol, ethanol, n-propanol, isopropanol and butanol.

Suitable halogenated hydrocarbons are dichloromethane, chloroform, and 1,2-dichloroethane.

Suitable ketones are acetone or methyl ethyl ketone.

Suitable ethers are diethyl ether or tetrahydrofuran.

Suitable polar aprotic solvents are one or more of N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

In another general aspect, the present invention provides for mosapride citrate dihydrate having purity of 100% as measured by HPLC method.

In yet another general aspect, the present invention provides for a pharmaceutical composition that includes mosapride citrate dihydrate having purity of 100% as measured by HPLC method or a mosapride citrate dihydrate substantially free of impurity D-II and one or more pharmaceutically acceptable excipients.

In yet another general aspect, the present invention provides for a method of treating gastrointestinal symptoms associated with chronic gastritis (heartburn, nausea/vomiting) in a patient in need thereof comprising administering an effective amount of mosapride citrate dihydrate having a purity of 100% as measured by HPLC method or mosapride citrate dihydrate substantially free of impurity D-II.

Detailed Description of the Invention

The term "mosapride citrate dihydrate substantially free of impurity D-II" in context to the present invention relates to mosapride citrate dihydrate having impurity D-II in an amount of 0.1% or less, preferably 0.05% or less, more preferably 0.01% or less, and most preferably undetectable as determined by HPLC method.

The term "highly pure mosapride citrate dihydrate" in context to the present invention relates to mosapride citrate dihydrate having purity more than 99.9%, preferably 99.95% or more, more preferably, more than 99.99% as measured by HPLC method.

One aspect of the present invention provides a process for the preparation of mosapride citrate dihydrate which includes:

a) treating mosapride free base with citric acid, wherein the mosapride free base and the citric acid are taken in the molar ratio of about 1:0.5 to about 1:1.2, and

b) isolating mosapride citrate dihydrate.

The mosapride free base may be prepared by any of the methods known in the art including those described in U.S. Patent No. 4,870,074, and WO 03/106440.

In one embodiment Step a) involves the addition of the citric acid to a solution of mosapride free base in one or more solvents at a temperature of about 20°C to 85°C, optionally under stirring. Preferably, the citric acid may be added at about 40°C to 60°C. The citric acid can be added all at once, it can be added in two or more portions, or it can be added incrementally. After the completion of addition, the resultant mixture may be stirred for about 15 minutes to about 3 hours at temperature of about 20°C to reflux.

In another embodiment Step a) involves the addition of mosapride free base to a solution of citric acid in one or more solvents at a temperature of about 20°C to 85°C, optionally under stirring. Preferably, it may be added at about 40°C to 60°C. The mosapride free base can be added all at once, it can be added in two or more portions, or it may be added incrementally. After the completion of addition the resultant mixture can be stirred for about 15 minutes to about 3 hours at temperature of about 20°C to reflux.

In another embodiment Step a) involves adding the solution of mosapride free base to citric acid solution or adding citric acid solution to the mosapride free base in one or more solvents in optional order of succession at a temperature of about 20°C to 85°C optionally under stirring. Preferably, it may be stirred at about 40°C to 60°C. The addition may be carried out dropwise for a time period of 15 minutes to 2 hours at a temperature of about 20°C to 70°C under stirring. After the completion of addition the resultant mixture may be stirred for about 15 minutes to about 3 hours at temperature of about 20°C to 70°C. Preferably, it may be stirred at about 40°C to 60°C.

The amount of mosapride free base to citric acid is taken in the molar ratio of about 1:0.5 to about 1:1.2, preferably, about 1:0.8 to about 1:1.1.

The solution of mosapride free base can be prepared by treating mosapride free base with one or more solvents at a suitable temperature of 20°C to reflux under stirring.

The solution of mosapride free base before treatment with citric acid can be optionally clarified to remove foreign particulate matter or treated with activated charcoal to remove coloring and other related impurities. The solution of mosapride free base may be optionally concentrated to reduce the amount of solvent.

The solution of citric acid can be prepared by contacting citric acid with one or more solvents at a suitable temperature of 20°C to reflux under stirring.

The term "solvents" includes any solvent or solvent mixture, including for example, water, esters, alkanols, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents or mixtures thereof in which both mosapride free base and citric acid are soluble.

The esters may include one or more of ethyl acetate, n-propyl acetate, isopropyl acetate, and n-butyl acetate. Examples of alkanol include those primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable alkanol solvents include methanol, ethanol, n-propanol, isopropanol and butanol. Examples of halogenated hydrocarbons include dichloromethane, chloroform, and 1,2-dichloroethane. Examples of ketones include acetone, methyl ethyl ketone and the like. Examples of ethers include diethyl ether, tetrahydrofuran, and the like. A suitable polar aprotic solvent includes one or more of N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

Isolation of the mosapride citrate dihydrate in Step b) involves common isolation techniques such as one or more of washing, crystallization, precipitation, cooling, filtration, filtration under vacuum, decantation and centrifugation, or a combination thereof.

The preferred method of isolation of mosapride citrate dihydrate involves cooling the mixture obtained in step a) to a temperature of 0°C to 15°C for a time period of 30 minutes to 2 hours under stirring; which may be optionally stirred further for a period of 15 minutes to 3 hours at a temperature of 0°C to 15°C. The solid thus precipitated can be filtered optionally under vacuum followed by subsequent washings to obtain mosapride citrate dihydrate.

The filtration and washings are preferably carried out at a temperature of 25°C to 50°C.

The isolated mosapride citrate dihydrate may be further dried at 40°C to 60°C under vacuum until the desired moisture content (~5-6 %) is obtained.

Another aspect of the present invention provides for a process for the preparation of mosapride citrate dihydrate substantially free of impurity D-II which includes:

a) treating mosapride free base with citric acid wherein the mosapride free base and citric acid are taken in the mole ratio of about 1:0.5 to about 1:1.2;

b) isolating the mosapride citrate dihydrate substantially free of impurity D-II.

The isolated mosapride citrate dihydrate is substantially free of impurity D-II and may be further dried at 40°C to 60°C under vacuum till the desired moisture content (5% to 6%) is obtained.

The term "mosapride citrate dihydrate substantially free of impurity D-II" in context to the present invention relates to mosapride citrate dihydrate having impurity D-II in an amount of 0.1% or less, preferably, 0.05% or less, more preferably, 0.01% or less, most preferably, undetectable as determined by HPLC method.

Still another aspect of the present invention provides a process for the preparation of highly pure mosapride citrate dihydrate which comprises:

a) treating mosapride free base with citric acid wherein mosapride free base and citric acid are taken in the mole ratio of about 1:0.5 to about 1:1.2,

b) isolating the highly pure mosapride citrate dihydrate.

The term "highly pure mosapride citrate dihydrate" in context to the present invention relates to mosapride citrate dihydrate having purity of more than 99.9%, preferably, 99.95% or more, more preferably, more than 99.99% as measured by HPLC method.

The isolated highly pure mosapride citrate dihydrate may be further dried at 40°C to 60°C under vacuum till the desired moisture content (5% to 6%) is obtained.

The present invention also provides for mosapride citrate dihydrate having purity of 100% as measured by HPLC method.

The mosapride citrate dihydrate having purity of 100% as measured by HPLC method or a mosapride citrate dihydrate substantially free of impurity D-II optionally may be manufactured into a pharmaceutical that also includes one or more pharmaceutically acceptable excipients.

Yet another aspect of the present invention provides a method of treating gastrointestinal symptoms associated with chronic gastritis (heartburn, nausea/vomiting) in a patient in need thereof which includes administering an effective amount of mosapride citrate dihydrate having purity of 100% as measured by HPLC method or mosapride citrate dihydrate substantially free of impurity D-II.

In still another aspect, the present invention provides a pharmaceutical composition comprising mosapride citrate dihydrate made by the process disclosed herein, and one or more pharmaceutically acceptable excipients.

Brief Description of the Drawing

Figure 1 depicts HPLC chromatogram of mosapride citrate dihydrate having purity of 100%.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

REFERENCE EXAMPLES

The procedure given in U.S. Patent No. 4,870,074 (Column 14, Lines 63-68, Example 1, Sub Example 4).

Reference Example 1:

Preparation of Mosapride Citrate Dihydrate

The mosapride free base (20.0 g) was dissolved in a hot 10% aqueous citric acid solution (800 ml) and the resulting solution was allowed to cool. The precipitate was collected to give the title compound.

Yield: 21.24 g (69%)

Impurity D II content: 1.59%

Reference Example 2:

The mosapride free base (20.0 g) was dissolved in a hot 10% aqueous citric acid solution (800 ml) and the resulting solution was allowed to cool. The precipitate was collected to give the title compound.

Yield: 21.44 g (70.8%)

Impurity D II content: 1.44%

EXAMPLES

Example 1: Preparation of Mosapride Citrate Dihydrate

Citric acid monohydrate (84.67 g) and water (850 ml) were charged at ambient temperature and stirred to dissolve the solid. The reaction mass was heated up to 80°C and mosapride free base (85 g) was charged at 80°C. The heterogeneous mass was stirred and heated up to reflux (95°C to 110°C). The clear solution was stirred at reflux temperature for 30 minutes. The reaction mass was cooled down to 0°C and was stirred at 0°C to 5°C for 30 minutes. The solid was filtered and washed with water (2 X 170 ml). The solid was suck dried and unloaded. The solid was dried at 60°C for 15 hours under vacuum to give the title compound.

Yield: 125 g (95.45%)

Water content: 6.28%

D-II Impurity: 0.269

Example 2: Preparation of Mosapride Citrate Dihydrate

Preparation of Solution A:

Methanol (1000 ml) and mosapride free base (100 g) were charged at ambient temperature. The reaction mass was heated to reflux at 65°C to 67°C and was stirred to get a clear solution. Activated carbon (5 g) was charged into the reaction mass and was stirred for 15 minutes to 20 minutes at reflux temperature. The clear solution was filtered

through a hyflo bed. The hyflo bed was washed with methanol (200 ml). The reaction mass was cooled to 40°C (Solution A).

Preparation of Solution B:

Deionised water (1000 ml) was charged in to another flask at ambient temperature. Citric acid monohydrate (59.77 g) was charged at ambient temperature and was stirred for 10 minutes to get a clear solution. The clear solution was filtered through a hyflo bed and the bed was washed with deionised water (200 ml) (Solution B).

Solution B was charged into Solution A over 30 minutes to 45 minutes at 40°C to 45°C. The reaction mass was stirred at 45°C to 50°C for 30 minutes and was further cooled down to 5°C over 60 minutes to 75 minutes. The reaction mass was stirred at 5°C for 60 minutes. The solid was filtered and the bed was washed with deionised water (200 ml) at ambient temperature. The solid was unloaded and dried at 50°C to 55°C under vacuum to obtain the title compound.

Yield: (130 g) 84.21%

Water content: 5.02%

D-II Impurity: Not detectable

Example 3: Preparation of Mosapride Citrate Dihydrate

Preparation of Solution A:

Methanol (120ml) and mosapride free base (10 g) were charged at ambient temperature. The reaction mass was heated to reflux (65°C to 67°C) to get a clear solution. Activated carbon (0.5 gm) was charged at reflux temperature and was stirred for 30 minutes at reflux temperature.

Preparation of Solution B:

Water (150 ml) and citric acid monohydrate (5.97 g) were charged in another flask at ambient temperature. The reaction mass was heated to 45°C.

The hot clear Solution (A) was transferred into the citric acid solution at 45°C to 55°C through a hyflo bed and the bed was washed with hot methanol (20 ml). The

reaction mass was stirred at 50°C to 55°C for 30 minutes. The reaction mass was filtered through a hyflo bed to another flask maintained at 45°C. The bed was washed with hot methanol (10 ml) and the reaction mass was cooled to 0°C in 90 minutes. The reaction mass was stirred at 0°C to 5°C for 30 minutes. The solid obtained was filtered and washed by making slurry with deionised water (50 ml). The solid was suck dried. The solid was then dried at 52°C under vacuum to obtain the title compound.

Yield: 13.2 g (85.7%)

Water content: 5.16%

D-II Impurity: 0.01%

Example 4: Preparation of Mosapride Citrate Dihydrate

Methanol (100 ml) was charged at an ambient temperature and was heated to 65°C. Mosapride free base (10 g) was charged at 65°C and stirred for 15 minutes at 65°C. The reaction mixture was cooled to 55°C.

A solution of citric acid (19.92 g in 80 ml water) was charged dropwise over 60 minutes at 53°C to 55°C. The reaction mixture was filtered through a sintered funnel and was heated up to 70°C. The reaction mixture was stirred at 72°C for 30 minutes. The reaction mixture was cooled to 0°C and was stirred at 0°C to 5°C for 30 minutes. The solid was filtered and washed with water (20 ml) at ambient temperature. The solid was suck dried. The solid was then dried under vacuum at 60°C to 65°C to give the title compound.

Yield: 14.5 (94.16%)

Water content: 5.16%

D-II Impurity: 0.61%

The results of experiments performed by varying the reaction conditions such as temperature, mole ratio of citric acid and the quantity of solvent for the preparation of mosapride citrate dihydrate following the procedure of Example 4 is summarized in the table below:

Mosapride free base (mole equiv.)	Citric acid (mole equiv.)	Water (T) (ml)	Methanol (T) (ml)	Reaction Temp (°C)	Addition Time (min)	Stirring Time (min)	Purity	Yield w/w	M/C	D-II impurity
1	1.2	40	10	70	60	30	100	1.43	5.38	ND
1	1.2	40	20	45	0	120	100	1.41	5.57	ND
1	1.2	8	10	45	0	30	99.94	1.36	5.12	ND
1	1.2	8	20	45	60	30	99.86	1.43	5.57	0.08
1	1.2	8	20	70	60	120	100	1.28	--	ND

ND- Not Detected

We claim:

1. A process for the preparation of mosapride citrate dihydrate comprising,

a) treating mosapride free base with citric acid, wherein the mosapride free base and the citric acid are taken in the mole ratio of about 1:0.5 to about 1:1.2; and

b) isolating mosapride citrate dihydrate.

2. A process according to claim 1, wherein step a) is carried out in one or more solvents at a temperature of about 20°C to 85°C.

3. A process according to claim 2, wherein the solvents are selected from the group consisting of water, esters, alkanols, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents or mixtures thereof.

4. A process according to claim 3, wherein the esters consist of one or more of ethyl acetate, n-propyl acetate, isopropyl acetate, and n-butyl acetate.

5. A process according to claim 3, wherein the alkanols consist of methanol, ethanol, n-propanol, isopropanol and butanol.

6. A process according to claim 3, wherein the halogenated hydrocarbons consist of dichloromethane, chloroform, and 1,2-dichloroethane.

7. A process according to claim 3, wherein the ketones consist of acetone, or methyl ethyl ketone.

8. A process according to claim 3, wherein the ethers consist of diethyl ether, or tetrahydrofuran.

9. A process according to claim 3, wherein the polar aprotic solvents consist of one or more of N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

10. A process for the preparation of mosapride citrate dihydrate substantially free of impurity D-II which comprises:

a) treating mosapride free base with citric acid, wherein the mosapride free base and the citric acid are taken in the mole ratio of about 1:0.5 to about 1:1.2; and

b) isolating the mosapride citrate dihydrate substantially free of impurity D-II.

11. A process according to claim 10, wherein step a) is carried out in in one or more solvents at a temperature of about 20°C to 85°C.

12. A process according to claim 11, wherein the solvents are selected from the group consisting of water, esters, alkanols, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents or mixtures thereof.

13. A process according to claim 12, wherein the esters consist of one or more of ethyl acetate, n-propyl acetate, isopropyl acetate, and n-butyl acetate.

14. A process according to claim 12, wherein the alkanols consist of methanol, ethanol, n-propanol, isopropanol and butanol.

15. A process according to claim 12, wherein the halogenated hydrocarbons consist of dichloromethane, chloroform, and 1,2-dichloroethane.

16. A process according to claim 12, wherein the ketones consist of acetone, or methyl ethyl ketone.

17. A process according to claim 12, wherein the ethers consist of diethyl ether, or tetrahydrofuran.

18. A process according to claim 12, wherein the polar aprotic solvents consist of one or more of N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

19. Mosapride citrate dihydrate substantially free of impurity D-II.

20. Mosapride citrate dihydrate having impurity D-II in an amount of 0.1% or less as determined by HPLC method.

21. Mosapride citrate dihydrate substantially free of impurity D-II having impurity D-II in an amount of 0.05% or less as determined by HPLC method.

22. Mosapride citrate dihydrate substantially free of impurity D-II having impurity D-II in an amount of 0.01% or less as determined by HPLC method.

23. Mosapride citrate dihydrate substantially free of impurity D-II having impurity D-II undetectable as determined by HPLC method.

24. A process for the preparation of highly pure mosapride citrate dihydrate which comprises:

a) treating mosapride free base with citric acid, wherein the mosapride free base and the citric acid are taken in the mole ratio of about 1:0.5 to about 1:1.2; and

b) isolating the highly pure mosapride citrate dihydrate.

25. A process according to claim 24, wherein step a) is carried out in one or more solvents at a temperature of about 20°C to 85°C.

26. A process according to claim 25, wherein the solvents are selected from the group consisting of water, esters, alkanols, halogenated hydrocarbons, ketones, ethers, polar aprotic solvents or mixtures thereof.

27. A process according to claim 26, wherein the esters consist of one or more of ethyl acetate, n-propyl acetate, isopropyl acetate, and n-butyl acetate.

28. A process according to claim 26, wherein the alkanols consist of methanol, ethanol, n-propanol, isopropanol and butanol.

29. A process according to claim 26, wherein the halogenated hydrocarbons consist of dichloromethane, chloroform, and 1,2-dichloroethane.

30. A process according to claim 26, wherein the ketones consist of acetone, or methyl ethyl ketone.

31. A process according to claim 26, wherein the ethers consist of diethyl ether, or tetrahydrofuran.

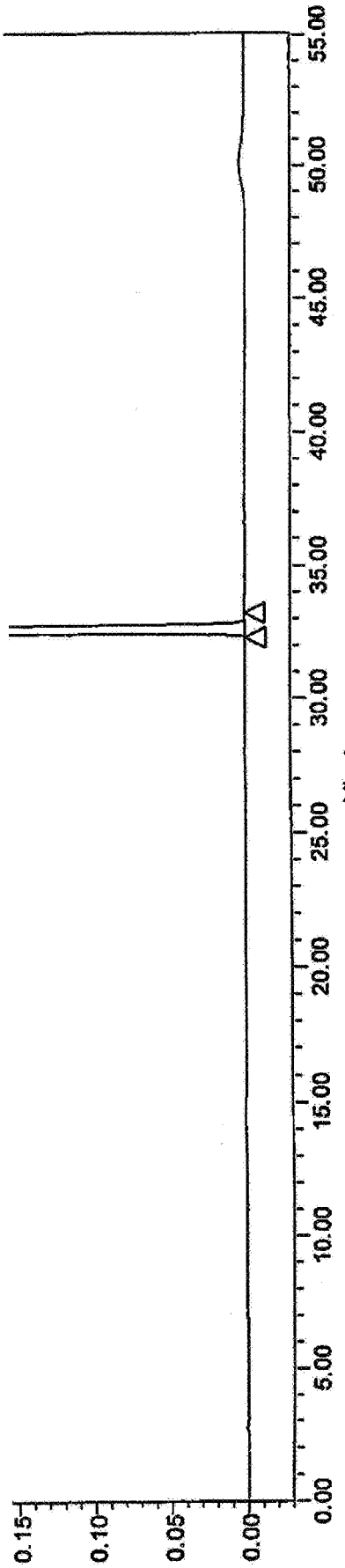
32. A process according to claim 26, wherein the polar aprotic solvents consist of N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile and N-methylpyrrolidone.

33. Mosapride citrate dihydrate having purity of 100% as measured by HPLC method.

34. A pharmaceutical composition comprising mosapride citrate dihydrate having purity of 100% as measured by HPLC method or a mosapride citrate dihydrate substantially free of impurity D-II and one or more pharmaceutically acceptable excipients.

35. A method of treating gastrointestinal symptoms associated with chronic gastritis (heartburn, nausea/vomiting) in a patient in need thereof comprising administering an effective amount of mosapride citrate dihydrate having a purity of 100% as measured by HPLC method or mosapride citrate dihydrate substantially free of impurity D-II.

FIGURE 1: HPLC CHROMATOGRAM OF MOSAPRIDE CITRATE DIHYDRATE HAVING PURITY OF 100%.



Peak Results

	Name	Retention Time (min)	Area (µV*sec)	% Area	Int Type
1	Peak1	32.53	7282978	100.00	BB

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2011/050763

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D265/30 A61K31/5375 A61P1/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KR 100 750 593 B1 (DONGWOO SYNTECH CO LTD [KR]) 13 August 2007 (2007-08-13) page 8	1-9, 19-23, 33-35
X	WO 03/106440 A2 (RICHTER GEDEON VEGYESZET [HU]; VUKICS KRISZTINA [HU]; FISCHER JANOS [H) 24 December 2003 (2003-12-24) page 1, line 5 - line 9; example 6	19-23, 33-35
X	US 4 870 074 A (KON TATSUYA [JP] ET AL) 26 September 1989 (1989-09-26) examples 1,158,186	19-23, 33-35

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 May 2011	27/05/2011

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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