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

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
18 January 2007 (18.01.2007)

(10) International Publication Number
WO 2007/007347 A1

(51) International Patent Classification:
C07D 211/22 (2006.01)

(21) International Application Number:
PCT/IN2005/000241

(22) International Filing Date: 13 July 2005 (13.07.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
809/MUM/2005 7 July 2005 (07.07.2005) IN

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

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

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— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(Ui)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, Fl, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

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

(54) **Title:** INDUSTRIAL PROCESS OF FEXOFENADINE HYDROCHLORIDE WITH CONTROLLED SIDE PRODUCTS

(57) **Abstract:** The present invention relates to a process for the preparation of Anhydrous Fexofenadine Hydrochloride with controlled level of side products. Another aspect of the present invention is purification of Fexofenadine base free of meta isomer of fexofenadine base and fexofenadinone.

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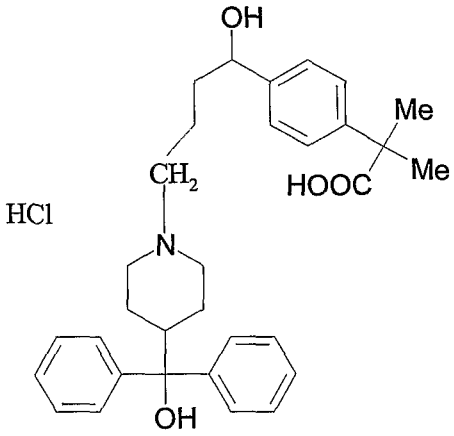
INDUSTRIAL PROCESS OF FEXOFENADINE **HYDROCHLORIDE WITH** CONTROLLED **SIDE** PRODUCTS

FIELD **OF** THE INVENTION

The present invention relates to the robust, economically feasible and environmentally friendly manufacturing process of Anhydrous Fexofenadine Hydrochloride (I) with controlled level of side products. There are two aspects of present invention. First, to get the required regio-isomer, i.e., para-isomer (Fexofenadine) by repeated purifications of the crude product. The second aspect of the present invention is to furnish Fexofenadine Hydrochloride with controlled level of water content, i.e., not more than 0.5% using acetone as a solvent of choice for dehydration.



Anhydrous Fexofendine Hydrochloride (I)

BACKGROUND OF THE INVENTION

4-[4-[4-(Hydroxydiphenylmethyl)-l-piperidinyl]-l-hydroxybutyl]- α, α-dimethylbenzene acetic acid of formula (I) (Fexofenadine) hydrochloride is a useful antihistamine, antiallergic agent and bronchodilator (U.S. Patents 4,254,129; 4,254,130 and 4,285,958).

A number of patents disclose the syntheses of Fexofenadine Hydrochloride, e.g., U.S. Patents 3,878,217; 3,931,197; 3,941,795; 3,946,022; 4,254,129; 4,254,130; 4,285,957; 4,443,460; 5,375,693; 5,578,610; 5,581,011; 5,589,487; 5,631,375; 5,663,412; 5,750,703; 5,925,761 and 5,990,127. A thorough review of the available literature information reveals that there are two ways to furnish fexofenadine as its pharmaceutically acceptable salt, one is by purification of the intermediates involved hi the synthesis of fexofendine and also the final crude product and the other is by derivatization of the intermediate in such a way that the unrequired product will not contaminate the required isomer of fexofenadine (U.S. Patents 4,254,129; 4,254,130 and 5,578,610).

The present invention relates to a purification method of the crude product to get acceptable quality of Fexofenadine Hydrochloride.

SUMMARY OF THE INVENTION

The present invention reports the robust manufacturing process for the production of Fexofenadine Hydrochloride having less than 1.0% of total impurities and moisture content less than 0.5 %. The characterization of the known impurities, i.e. , Fexofenadone and meta-isomer of Fexofenadine has been done by IR, NMR (^{1}H and C^{13}), LC MS MS and HPLC impurity profile gradient method.

The manufacturing process starts from the α,α-Dimethylphenyl acetic acid. α,α-Dimethylphenyl acetic acid on treatment with methanol in presence of concentrated sulfuric acid in catalytic amount provides the methyl ester of α,α-Dirnethylphenyl acetic acid, i.e., methyl-α,α-Dimethylphenyl acetate.

Further this ester on Fridel - Crafts' , acylation with 4-Chlorobutyryl chloride in presence of anhydrous aluminium chloride in ethylenedichloride (EDC) solvent furnishes the

corresponding acylated methyl-α,α-Dimethylphenyl acetate, i.e., ketone intermediate as a mixture having para and meta isomer.

This ketone intermediate on condensation with Azacyclanol in presence of potassium bicarbonate and potassium iodide in aromatic hydrocarbon or dimethylformamide gives the corresponding para and meta isomer of Fexofenadone methyl ester.

The Fexofenadone methyl ester is reduced with sodium borohydride in methanol, which on subsequent alkaline hydrolysis in water methanol mixture gives Fexofenadine having para and meta isomer.

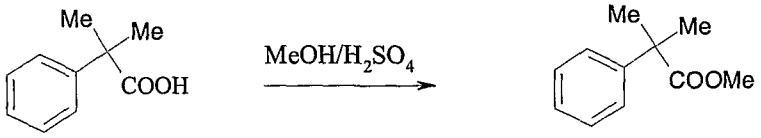
The exclusive separation of para isomer from this isomeric mixture has been done with just two to three times suspensions in methanol : methylethylketone mixture having specific ratio of ingredients. Finally refluxing the material in methanol : dimethylformamide provides Fexofenadine Base having total impurities not more than 1.0% and having moisture content in the range of 2.5 to 6.0%.

Fexofenadine base with moisture content 2.5 to 6.0% on treatment with methanol and aqueous hydrochloric acid gives the corresponding hydrochloride salt which on treatment with acetone at reflux and then cooling provides Anhydrous Fexofenadine Hydrochloride. The product meets all the requirement of the International Conference on Harmonization (ICH) guidelines.

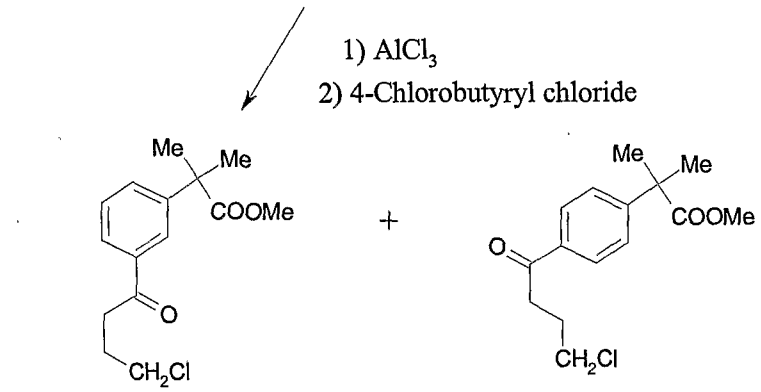
DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for the efficient purification method of Fexofenadine and its hydrochloride salt having less than **1.0%** of total impurities and moisture content less than **0.5%.** The characterization of the known impurities, i.e., Fexofenadone and meta-isomer of Fexofenadine has been done by IR, **NMR (**^{1}**H** and C^{13}), LC **MS MS** and HPLC impurity profile gradient method.

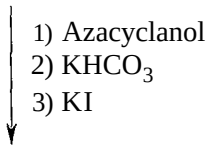
According to one embodiment, the present invention is directed to a manufacturing process of 4-[4-[4-(hydroxydiphenylmethyl)-l-piperidinyl]-l-hydroxybutyl]- α, α-dimethylbenzene acetic acid hydrochloride in pure form. The schematic presentation of synthetic process of fexofenadine hydrochloride is shown in Scheme I.

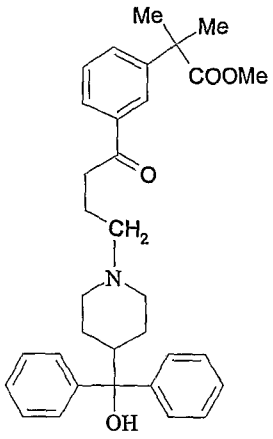


Alpha-alpha-Dimethyl phenylacetic acid Methyl-alpha-alpha-Dimethyl phenylacetic acid



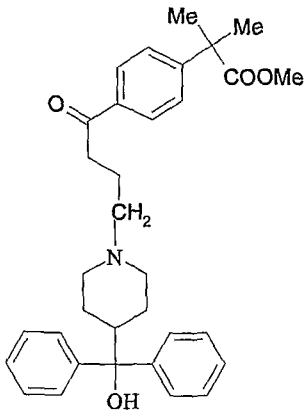
Ketone (Meta-isomer) Ketone (Para-isomer)





(Meta-isomer)
Methyl ester of Fexofenadine

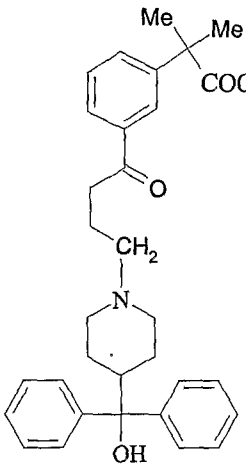
+



(Para-isomer)
Methyl ester of Fexofenadine

Methyl ester of Fexofenadine (meta and para isomers)

1) Aq. NaOH
2) MeOH/H_2O



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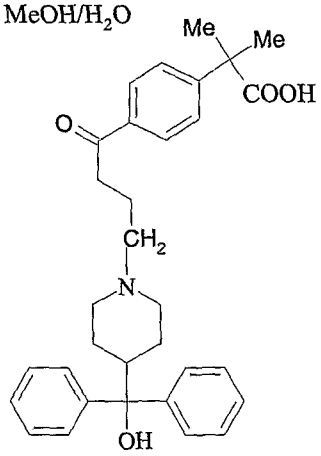
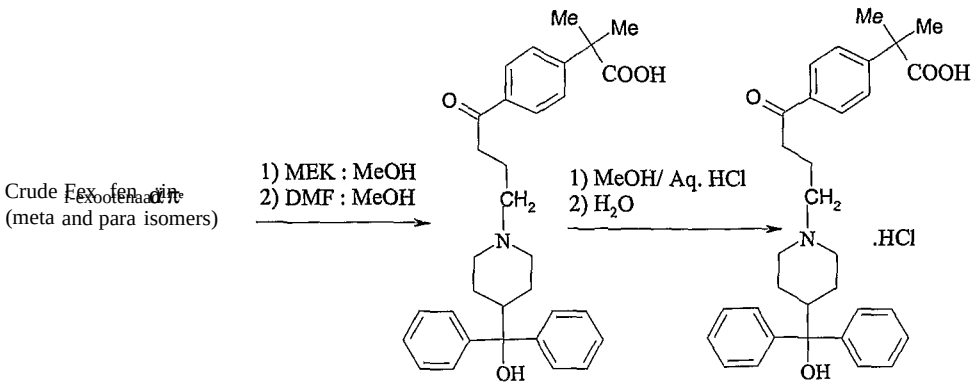
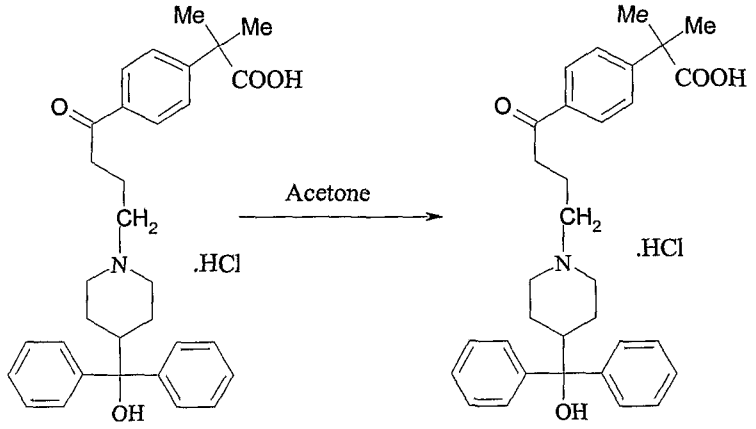


Crude Fexofenadine(Meta-isomer) Crude Fexofenadine(Para-isomer)



Fexofenadine (Para-isomer) Fexofenadine hydrochloride



Fexofenadine hydrochloride Anhydrous Fexofenadine hydrochloride

In the present invention it is observed that crude fexofenadine (meta and para isomers) may be purified by heating it in a mixture of methylethyl ketone and methanol followed by second treatment with dimethylformamide and methanol.

A detailed synthetic process of fexofenadine hydrochloride, an efficient purification method of fexofenadine base and process for making anhydrous fexofenadine hydrochloride are disclosed herein:

(a) Reaction of α,α-Dimethyl phenyl acetic acid and methanol

α,α-Dimethylphenyl acetic acid was reacted with methanol in presence of cone, sulfuric acid between about 25 to 45°C. Reaction mixture was refluxed for about 4 hours. Methanol was distilled off after the said time to give thick oily slurry of Methyl- α,α-dimethylphenyl acetic acid. Water was added to the pre-cooled reaction mixture and extracted with chloroform

followed by washing with aqueous sodium bicarbonate solution and finally with potable water. Removal of chloroform under reduced pressure yielded title compound as oily mass in about 98 % HPLC purity.

(b) Reaction of Methyl-α,α-dimethylphenyl acetic acid with 4-Chlorobutyryl chloride

Methyl-α,α-dimethylphenylacetic acid on Fridel-Craft's acylation with 4-chlorobutyryl chloride in presence of anhydrous aluminum chloride in ethylene dichloride produced acylated Methyl-α,α-dimethylphenyl acetic acid, i.e., ketone intermediate as meta and para- isomers.

More particularly, aluminum chloride was taken in dichloroethane and cooled in between about 0 to $2O^0C$. To the above pre cooled solution, Methyl-α,α-dimethylphenyl acetic acid was added at low temperature. To the reaction mixture, 4-chlorobutyryl chloride was added between about 0 to 20°C. After addition of acid chloride the reaction mixture was stirred for about 8 to 10 hours at the same temperature. After completion of the reaction, mixture was quenched over chilled mixture of potable water and cone. hydrochloric acid followed by stirring the reaction mixture for another 4 hours. The reaction mixture was washed with aqueous solution of sodium bicarbonate and finally with water. Removal of dichloromethane provided Methyl-4-(4-chloro-l-oxobutyryl)- α,α-dimethylphenyl acetate (Ketone) in about 95 % HPLC purity.

c) Reaction of Methyl-4-('4-chloro-l-oxobutyryl')-α,α-dimethylphenyl acetate with azacyclanol

Two methods were employed for this reaction which are as follows,

Method (I)

Methyl-4-(4-chloro-l-oxobutyryl)- α,α-dimethylphenyl acetate (Ketone) (meta and para isomers) was dissolved in toluene followed by addition of Azacyclanol and water in presence of potassium carbonate and potassium iodide. Reaction mixture was refluxed for about 30 to 40 hours. After the reaction was completed, reaction mixture was cooled to room temperature and aqueous layer was discarded. Organic layer was filtered through Nutsche and distilled under reduced pressure and degassed for 2 hours to get the oily mass of carbinol, i.e., Methyl-4{4-[4-(hydroxydiphenylmethyl)-l-piperidinyl}-l-oxobutyl]- α, α-diphenylmethyl benzene acetate.

Method 2

Methyl-4-(4-Chloro-l-oxobutyryl)- α, α-dimethylphenyl acetate, (Ketone) (meta and para isomers) was dissolved in dimethyl formamide followed by addition of Azacyclnol, potassium carbonate and potassium iodide. The reaction mixture was heated at 90°C for about 7 to 12 hours. Reaction was monitored by HPLC. After the reaction was completed it was cooled to room temperature and the product was extracted with chloroform and was well washed with water. Removal of the organic solvent at reduced pressure yielded thick oily carbinol.

d) Reduction of Carbinol viz, (Methyl-4{4-r4-(hvdroxydiphenyhnetyl)-l-piperidinyl}-l-hydroxybutyll-α,α-dimethylbenzene acetate)

Methyl-4{4-[4-(hydroxydiphenylmetyl)-l-piperidinyl}-l-hydroxybutyl]- α,α-dimethylbenzene acetate (carbinol) obtained as oily mass in example 3 was dissolved in methanol and cooled to about 0 to 20°C followed by addition of sodium borohydride. At the same temperature reaction mass stirred for 2 to 5 hours. After the reduction was completed the reaction mass was stirred at room temperature in presence of water and chloroform. Organic layer was separated followed by rewashing with aqueous layer. Combined organic layer was pooled and washed with potable water and submitted for chloroform distillation under reduced pressure to get thick oily mass of dicarbinol, i.e., Methyl-4{4-[4-(hydroxydiphenylmetyl)-l-piperidinyl}-l-hydroxybutyl]- α,α-dimethyl benzene acetate.

e) Deprotection of carboxyl function of Methyl-4{4-r4-(hydroxydiphenylmetyl)-l-piperidinyl}-l-hvdroxybutyll- α,α-dimethyl benzene acetate to yield crude isomer of Fexofenadine base

The dicarbinol prepared in example 3 was dissolved in methanol followed by addition of sodium hydroxide in potable water followed by refluxed for about 3 to 6 hours. Methanol was distilled off, once the reaction deprotection was completed. The reaction mixture was cooled to room temperature and to it chloroform was added. Reaction mixture was cooled to about 0 to $2O^0C$. pH of the reaction mass was adjusted to about 6.4 to 6.8 with 50 % aqueous hydrochloric acid solution. Reaction mixture was stirred for 1 hour at the same pH.

Chloroform was separated and aqueous layer was washed twice with chloroform. Organic layer was pooled and submitted for distillation under reduced pressure. To the above mass methanol was added and heated 45 to 50°C for about half an hour. The mass was cooled to room temperature and methylethyl ketone was added to it. The crystallized mass was stirred for about 30 to 35 hours at room temperature and centrifuged to get crude fexafenadine base.

f) Purification of Fexofenadine

Fexofenadine (40 Kg) thus isolated from the above step was charged to about 60 to 100 Ltr of a mixture of methanol in methylethyl ketone in volume ratio of 0.3 to 5.0. More particularly, the volume ratio of methanol in methylethyl ketone was 0.4 to 2.0, specifically about 0.4 to 0.6. The reaction mass was refluxed for about 10 minutes to 2 hours, more particularly between about 20 minutes to 40 minutes. After the said time reaction mass was cooled to room temperature followed by stirring for another 1 hour at room temperature. The reaction mixture was centrifuged. The same treatment was repeated twice followed by treatment with dimethyl formamide-methanol and water.

Three times treated fexofenadine base in the above step was charged to about 120 to 180 Ltr of a mixture of methanol in DMF volume ratio of 0.3 to 5.0. More particularly, the volume ratio of methanol was 0.4 to 2.0. More particularly, the volume ratio of methanol in DMF was about 0.4 to 0.6. The reaction mixture was refluxed for about 10 minutes to 2 hours, more particularly between about 30 minutes to 1.5 hours. After the said time reaction mixture was cooled to room temperature and centrifuged.

The wet cake obtained in the above process was taken in water and heated to 50 to 100^0C, more particularly between 65 to 85^0C. The mixture was stirred for about 1 hour and cooled to room temperature. The centrifuged material was centrifuged and dried in fluid bed dryer at 60 to $8O^0$C for about 5 to 7 hours. Fexofenadine Base (para isomer) having total impurities not more than 1.0% and having moisture content in the range of 2.5 to 6.0% was obtained after employing these purification steps.

g) Fexofenadine hydrochloride

Fexofenadine base having moisture content about 2.5 to 6% was taken in methanol and treated with 50 % aqueous HCl to make the pH of the solution between 2.4 to 2.6. The clear solution was filtered to remove any solid contaminant. Chilled potable water was added to the solution at 0 to 20°C. The hydrochloride salt of fexofenadine was obtained as white crystals. Additional volume of water was added to the reaction mixture at the same temperature and stirred for 2 hours. Material was centrifuged and dried.

h) Anhydrous Fexofenadine Hydrochloride

The fexofenadine hydrochloride obtained in the above step was treated with acetone for about 30 minutes to 2 hours between about 40^0C to reflux temperature. The reaction mixture was cooled to 0 to 5°C and centrifuged. Centrifuged material was dried in FBD for 6 to 8 hours at 60 to 80^0C to get the title product having moisture content between about 0.2 to 0.5%.

Examples

The following examples illustrate the invention, but is not limiting thereof,

EXAMPLE 1

Methyl-a,a-Dimethyl phenyl acetate (ester)

51 Kg (0.3109 Kmole) of α,α-Dimethyl acetic acid was dissolved in 100 to 150 Ltr methanol and to it was added concentrated sulfuric acid, 6 to 9 Kg maintaining temperature 25 to 45^0C. After complete addition of sulfuric acid reaction mixture was refluxed for 4 hours. After completion of the reaction methanol was distilled off under vacuum to obtain thick slurry which was cooled to room temperature and to it was added water. Reaction mixture was then extracted with chloroform and washed with 10% w/v sodium bicarbonate aqueous solution. Finally, chloroform layer was washed with potable water. On removal of chloroform under vacuum, Methyl-α,α-Dimethyl phenyl acetate as oily mass was obtained. HPLC Purity = 98%. Yield = 40 to 50 Kg.

EXAMPLE 2

Methyl-4-(4-chloro-l-oxobutyryl)- a,a-dimethyl phenyl acetate (Ketone)

95 Kg (0.7124 Kmole) of aluminium chloride was taken in 120 Ltr dichloroethane and reaction mixture was cooled to 0 to 2O^{0}C. To it was added ester of example 1, 46 Kg (0.2584 Kmole) through addition flask, maintaining the temperature 0 to 20^{0}C. Finally, to the reaction mixture was added 80 Kg (0.5673 Kmoles) of 4-chlorobutyryl chloride through addition flask maintaining the temperature 0 to 20^{0}C. After addition of acid chloride stirred the reaction mixture at 0 to 20^{0}C for 8 to 10 hours. After completion it was quenched over chilled mixture of potable water and concentrated hydrochloric acid. Then stirred the reaction mixture at 0 to 20^{0}C for 4 hours and finally extracted in dichloroethane. It was washed with 10% w/v aqueous solution of sodium bicarbonate and finally with water. Removal of the solvent under vacuum provides thick oily mass of Methyl-4-(4-chloro-l-oxobutyryl)- α-α-dimethyl phenyl acetate (Ketone). HPLC purity = 95%. Yield = 65 to 70 Kg.

EXAMPLE 3

Fexofenadine Base Crude

A) *Carbinol:(Methyl-4{4-[4-(hydroxydiphenylmetyl)-l-piperidinyl}-l-oxobutyl]- a,a-dimethylbenzene acetate) Method (I)*

Methyl-4-(4-chloro-l-oxobutyryl)- α,α-dimethyl phenyl acetate (Ketone), 70 Kg (0.2482 Kmole) was dissolved in 500 to 700 Ltr toluene and to it was added Azacyclanol, 50 to 60 Kg followed by potassium bicarbonate, 74 Kg (0.7391 Kmole) and potassium iodide, 0.50 to 1.20 Kg. Finally, to it was added 53 Ltr water. Reaction mixture was refluxed for 30 to 40 Hours. Completion of the reaction was monitored by HPLC. On completion the reaction mixture was cooled to room temperature and aqueous layer was discarded. Toluene layer was filtered through Nutsche. Finally toluene was distilled under reduced pressure and degassed for 2 hours to get the oily mass of carbinol.

Carbinol:(Methyl-4{4-[4-(hydroxydiphenyhnetyl)-l-piperidinyl}-l-oxobutyl]-a, a-dimethylbenzene acetate) Method (H)

Methyl-4-(4-chloro-l-oxobutyryl)- α,α-dimethyl phenyl acetate (Ketone), 0.50 Kg (0.001769 mole) was dissolved in 400 nil dimethylformamide and to it was added Azacyclanol, 0.428 Kg (0.00160 mole) followed by potassium bicarbonate, 0.528 Kg (0.00528 mole) and potassium iodide, 0.00357 Kg. Reaction mixture was heated at 9O^{0}C for 7 to 2 Hours. Completion of the reaction was monitored by HPLC. On completion the reaction mixture was cooled to room temperature and the product was extracted twice with chloroform and finally washed with water. Removal of the solvent at reduced pressure provides thick oily carbinol.

B) *Dicarbinol (Methyl-4{4-[4-(hydroxydiphenylmetyl)-l-piperidinyl}-l-hydroxybutylJ-a, a-dimethylbenzene acetate)*

Above oily mass of Carbinol was dissolved in 600 Ltr methanol and it was cooled to 0 to 20^{0}C. To it was added Sodium borohydride, 10 Kg (0.2645 Kmole) in lots. After complete addition, reaction mass was stirred at 0 to 2O^{0}C for 2 to 5 hours. After completion, the reaction mass was stirred at room temperature with 400 Ltr potable water and 200 Ltr Chloroform for 1 hour. Separated chloroform layer. The aqueous layer was again washed with 100 Ltr Chloroform. Combined chloroform extract was washed with potable water and then submitted for chloroform distillation under vacuum to get thick oily mass of dicarbinol.

C) *Fexofenadine* (Methyl-4{4-r4-(hydroxydiphenylmetyl)-l-piperidmyl}-l-hydroxybutyll-α,α-dimethylbenzene acetate)

The above oily mass of Dicarbinol was dissolved in 300 Ltr methanol and to it was added 120 to 130 Kg Sodium hydroxide dissolved in 400 Ltr potable water. Reaction mixture was refluxed for 3 to 6 hours. On completion of the reaction the methanol was distilled out under vacuum. Cooled the reaction mixture to room temperature and added 200 to 400 Ltr Chloroform. Finally the reaction mass was cooled to 0 to 20^{0}C. Adjusted the pH of the reaction mass 6.4 to 6.8 with 50% aqueous hydrochloric acid solution. At pH 6.4 to 6.8 the reaction mass was stirred for 1 hour and chloroform layer was separated. The aqueous layer was again washed twice with chloroform. Finally chloroform layer was submitted for distillation under vacuum. To the above mass added 30 Ltr methanol and heated at 45 to 5O^{0}C temperature for half an hour. Then cooled the mass to room temperature and added 60 Ltr

methylethyl ketone. The crystallization mass was stirred for 30 to 35 hours at room temperature. Then centrifuged the material. The sample was submitted for loss on drying and impurity profile. Yield = 40 to 45 Kg

EXAMPLE 4

Fexofenadine Base Pure

Purification

40 Kg of Crude Fexofenadine Base was charged to a mixture of 30 Ltr methanol and 60 Lr methylethyl ketone. The reaction mass was refluxed for 30 minutes followed by cooling to room temperature. Stirring of the reaction mixture was done at room temperature for 1 hour and was centrifuged the material. Sample was submitted for loss on drying and impurity profile.

Note: The above purification process was repeated twice and finally material was given the treatment with dimethylformamide and methanol followed by water to meet the impurity profile.

Dimethylformamide - Methanol treatment

Fexofenadine base obtained after third purification was treated with a mixture of 100 Ltr dimethylformamide and 50 Ltr methanol and heated at reflux for an hour. Then cooled to room temperature and centrifuged.

The wet cake obtained above was suspended in 300 Ltr potable water and heated to 70 to 75 ^{0}C temperature. The material was stirred for an hour and then cooled to room temperature. Centrifuged the material and dried in fluid bed dryer (FBD) at 60 to 8O^{0}C for 5 to 7 hours. Moisture content = 2.0 to 5.0%. HPLC Purity = 99%. Yield = 25 Kg.

EXAMPLE 5

Fexofenadine Hydrochloride

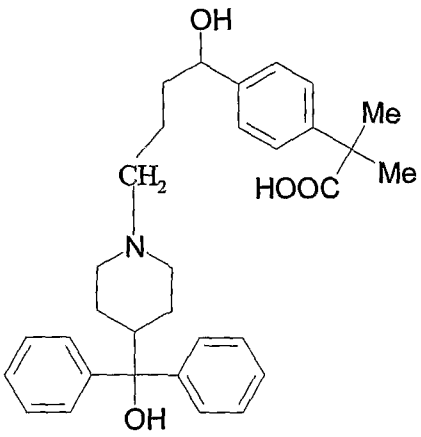
Fexofenadine Base pure, 25 Kg was suspended in 65 Ltr methanol on reaction mixture was cooled 0 to 2O^{0}C. Then it was added 50% aqueous hydrochloric acid solution to adjust

pH 2.4 to 2.6. At pH 2.4 to 2.6 the solution was clear and was filtered through module. To this solution *65* Ltr chilled potable water was added at 0 to 20^{0}C. pH was found 2.5. Material was thrown out as white crystals. Again to it 100 Ltr chilled water was added at temperature 0 to 20^{0}C. The reaction mixture was stirred for 2 hours. Centrifuged the material. It was dried in FBD at 60 to 80^{0}C for 7 to 8 hours till moisture content 2.0 to 6.0% . HPLC purity = 99%. Yield = 24 Kg.

The above material, 24 Kg was treated with acetone, 140 Ltr at reflux for an hour. Then it was cooled 0 to 5^{0}C. The material was stirred for 1 hour at 0 to 5^{0}C. Centrifuged the material and dried in FBD for 6 to 8 hours at 60 to 8O^{0}C. HPLC purity = 99% . Moisture content = 0.3%. Yield = 23 Kg.

Claims:

1. A process for purification of a compound of the formula



contaminated with meta isomer and fexofenadinone.

2. The process of claim 1, wherein contaminated fexofenadine base is purified with an organic solvent or mixtures thereof.
3. The process according to claim 2, wherein organic solvents are aliphatic alcohol, amide or ketone.
4. The process according to claim 3, wherein aliphatic alcohols are methanol, ethanol, propanol, isopropanol or n-butanol.
5. The process according to claim 4, wherein more preferable solvent is methanol.
6. The process according to claim 3, wherein amide is dimethyl formamide or dimethyl acetamide.
7. The process according to claim 6, wherein more preferably amide is dimethyl formamide.
8. The process according to claim 3, wherein more preferable ketone is methylethyl ketone.
9. The process according to claim 2, wherein said mixture of organic solvents are methylethyl ketone and methanol.
10. The process according to claim 9, wherein volume ratio of methanol in methylethyl ketone is between about 0.3 to 5.0.

11. The process according to claim 10, more preferably said methanol ratio is between about 0.4 to 0.6.

11. The process according to claim 3, wherein said mixture of organic solvents are aliphatic alcohols and amides.

12. The process according to claim 11, wherein said mixture of organic solvents are methanol and dimethyl formamide.

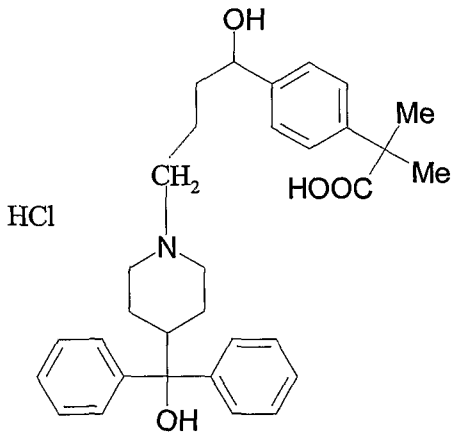
13. The process according to claim 12, wherein volume ratio of methanol in dimethyl formamdie is between about 0.3 to 5.0.

11. The process according to claim 13, more preferably said methanol ratio is between about 0.4 to 0.6.

12. The process according to claim 2-11, wherein said solid mass is refluxed with water after treatment with organic solvent or mixtures thereof.

13. The process according to claim 1, wherein purified fexofenadine contains less than 0.2 % Fexofenadinone and less than 0.1 % fexofenadine meta isomer.

14. A process of preparing anhydrous form of a compound of formula II



Fexofendine Hydrochloride (II)

15. The process according to claim 14, wherein a compound of formula (II) is refluxed with acetone to get anhydrous compound (II).

16. The process according to claim 14, wherein said anhydrous product of formula (II) obtained in about 0.2 to 0.5 % moisture.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN05/00241

A. CLASSIFICATION OF SUBJECT MATTER
IPC: **C07D 211/22(** 2006.0 1)

USPC: 546/236,239,240,241
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)
U.S. : 546/236, 239, 240, 241

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

Elec Üonic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/102777 A2 (Reddy et al.) 27 December 2002, see entire article, especially page 2	1-5
---	forth paragraph, page 9 example 1.	---
Y		1-16
Y	US 6,797,826 B2 (D'Ambra) 28 September 2004, see entire article, especially col. 16, lines 55-65 solvents variation.	1-16
X	US 6,903,232 B2 (Dandala et al.) see enitre reference, especially col. 12, lines 1-5.	1
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Y		1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents

'A" document defining the general state of the art which is not considered to be of particular relevance

'E" earlier application or patent published on or after the International filing date

"L" document which may throw doubts on priority claim(sj or which is cited to establish the publication date of another citation or other special reason (as specified)

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

"P" document published pπor 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
10 May 2006 (10.05.2006)

Date of mailing of the intern; aπonal search report
06 SEP 2006

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN05/00241

Continuation of B. FIELDS SEARCHED Item 3:
CAS--structure, purity
EAST/WEST--irnage, purity