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(71) Applicant *(for all designated States except US):* **ALEM¬ BIC PHARMACEUTICALS LIMITED** [IN/IN]; Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only):* **JAYARAMAN, Venkatraman** [IN/IN]; Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN). **BALAJL Sundara Kalyana** [IN/IN]; Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN). **KADIA, Jagadish** [IN/IN]; Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN). **PATEL, Ajay** [IN/IN]; Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN).

(74) Agent: **PATHAK, Alpesh;** Alembic Research Centre (arc), Patent Cell, Alembic Road, Gujarat, Vadodara 390003 (IN).

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(in))*

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WO 2013/024415 A1

(54) **Title:** AN IMPROVED METHOD FOR THE QUANTITATIVE DETERMINATION OF FESOTERODINE FUMARATE

(57) **Abstract:** An improved reversed-phase liquid chromatographic (RP-LC) method for the quantitative determination of fesoterodine fumarate is provided. A stability indicating analytical method using the samples generated from forced degradation studies is further provided.

Description

Title of Invention: AN IMPROVED METHOD FOR THE QUAN¬TITATIVE DETERMINATION OF FESOTERODINE FUMARATE

FIELD OF THE INVENTION

[1] The present invention relates to an improved reversed-phase liquid chromatographic (RP-LC) method for the quantitative determination of Fesoterodine fumarate. The present invention further provides a stability indicating analytical method using the samples generated from forced degradation studies.

[2]

BACKGROUND OF THE INVENTION

[3] Fesoterodine fumarate is chemically known as R-(+)-2-(3-Diisopropylamino-l-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrogen fumarate.

[4] Fesoterodine is a competitive muscarinic receptor antagonist. After oral administration, fesoterodine is rapidly and extensively hydrolyzed by nonspecific esterases to its active metabolite, 5-hydroxymethyl tolterodine, which is responsible for the antimuscarinic activity of fesoterodine.

[5] Muscarinic receptors play a role in contractions of urinary bladder smooth muscle and stimulation of salivary secretion. Inhibition of these receptors in the bladder is presumed to be the mechanism by which fesoterodine produces its effects.

[6] The product mixture of a reaction rarely is a single compound pure enough to comply with pharmaceutical standards. Side products and byproducts of the reaction and adjunct reagents used in the reaction will, in most cases, be present. At certain stages during processing of the fesoterodine fumarate contained in the product mixture into an active pharmaceutical ingredient (API), the fesoterodine fumarate must be analyzed for purity, typically by UPLC, HPLC or GC analysis, to determine if it is suitable for continued processing or ultimately for use in a pharmaceutical product.

[7] The U.S. Food and Drug Administration's Center for Drug Evaluation and Research (CDER) has promulgated guidelines recommending that drug applicants identify organic impurities of 0.1% or greater in the active ingredient. 'Guideline on Impurities in New Drug Substances,' 61 Fed. Reg. 371 (1996); 'Guidance for Industry ANDAs: Impurities in Drug Substances,' 64 Fed. Reg. 67917 (1999). Unless an impurity has been tested for safety, is in a composition proven to be safe in clinical trials, or is a human metabolite, the CDER further recommends that the drug applicant reduce the amount of the impurity in the active ingredient to below 0.1%. In order to obtain

marketing approval for a new drug product, manufacturers must submit to the regulatory authority evidence that the product is acceptable for administration to humans. Such a submission must include, among other things, analytical data showing the impurity profile of the product to demonstrate that the impurities are either absent, or present in a negligible amount. Therefore, there is a need for analytical methods to detect impurities to identify and assay those impurities.

[8] Generally, impurities (side products, byproducts, and adjunct reagents) are identified spectroscopically and by other physical methods and then the impurities are associated with a peak position in a chromatogram (or a spot on a TLC plate). Thereafter, the impurity can be identified by its position in the chromatogram, which is conventionally measured in minutes between injection of the sample on the column and elution of the particular component through the detector, known as the 'retention time' ('Rt'). This time period varies daily based upon the condition of the instrumentation and many other factors. To mitigate the effect that such variations have upon accurate identification of an impurity, practitioners use 'relative retention time' ('RRt') to identify impurities.

[9]

SUMMARY OF THE INVENTION

[10] In one aspect, the present invention provides a reversed-phase liquid chromatographic (RP-LC) method for the quantitative determination of fesoterodine fumarate.

[11] In another aspect, the present invention provides an UPLC method for fesoterodine fumarate containing less than about 5% area by UPLC, preferably less than about 3% area by UPLC, more preferably less than 1% area by UPLC, of total impurities.

[12] In another aspect, the present invention further provides a stability indicating analytical method using the samples generated from forced degradation studies.

[13] In yet another aspect, the present invention provides a simple, accurate and well-defined stability indicating an Ultra performance liquid chromatography (UPLC) method for the determination of fesoterodine fumarate in the presence of degradation products.

[14] In one aspect, the UPLC method described in the present invention has the following advantages when compared with prior art methods for determining the fesoterodine fumarate and its related impurities:

1. All the impurities were well separated with a minimum resolution 1.5 (limit: Not less than 1.2);
2. Gradient profile to elute all related impurities and organic phase is 70% which ensure the elution and detection of non polar impurities forming during the process or stress study;

3. The present method mobile phase pH is about 8.0 which is more stable in all C18 UPLC columns;
4. Consistency in specificity, precision & reproducibility with good peak shape; and
5. The degradation impurities from stress studies are well separated from the known impurities.

[15]

BRIEF DESCRIPTION OF DRAWINGS

[16] Fig. 1 illustrates the UPLC chromatogram of spiked (Impurity-A, impurity-B, impurity-C, impurity-E, impurity-F, impurity-G, impurity-H and impurity-I spiked in fesoterodine fumarate) sample.

[17]

DETAILED DESCRIPTION OF THE INVENTION

[18] As used herein, 'limit of detection (LOD)' refers to the lowest concentration of analyte that can be clearly detected above the base line signal, is estimated is three times the signal to noise ratio.

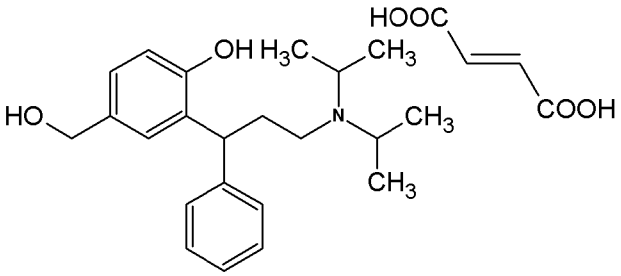
[19] As used herein, 'limit of quantization (LOQ)' refers to the lowest concentration of analyte that can be quantified with suitable precision and accuracy, is estimated as ten times the signal to noise ratio.

[20] As used herein, 'gradient elution' refers to the change in the composition of the gradient eluent over a fixed period of time, stepwise or at a constant rate of change, as the percentage of the first eluent is decreased while the percentage of the second eluent is increased.

[21] As used herein, 'gradient eluent' refers to an eluent composed of varying concentrations of first and second eluents.

[22] The eight main known impurities of fesoterodine fumarate are:

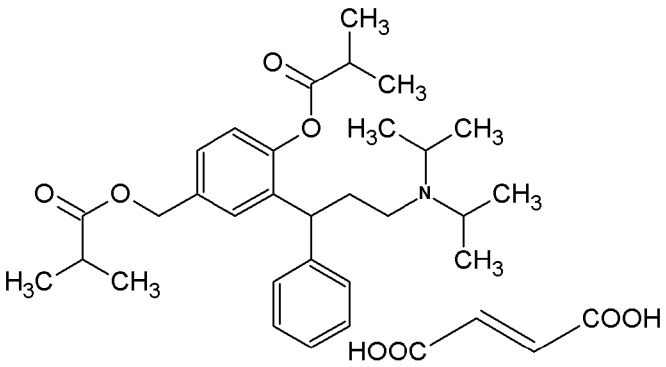
- (i) (R)-2-(3-diisopropylamino-l-phenylpropyl)-4-hydroxymethyl phenol hydrogen fumarate (Impurity-A) which has the following structure:



The impurity-A is detected and resolved from fesoterodine fumarate by UPLC with an relative retention time (hereafter referred as RRT) of 0.25.

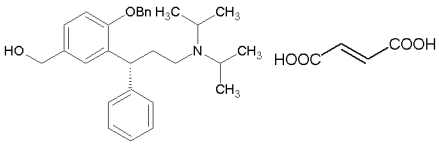
- (ii)

(+)-Isobutyrate-2-(3-diisopropylamino-l-phenylpropyl)-4-isobutyrylloxymeth ylphenylester hydrogen fumarate (Impurity-B), which has the following structure:



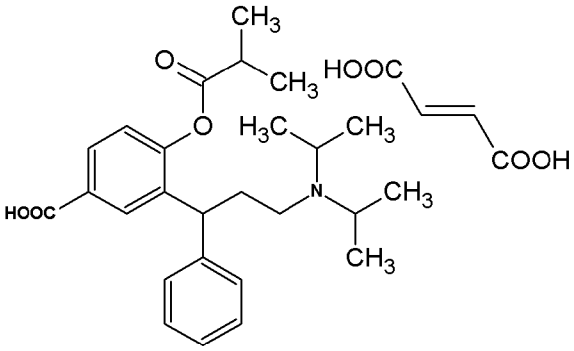
Impurity-B is detected and resolved from fesoterodine fumarate by UPLC with an RRT of 2.28.

- (iii) (R)-[4-Benzyloxy-3-(3-diisopropylamino-l-phenylpropyl) - phenyl]-methanol hydrogen fumarate. (Impurity-C), which has the following structure:



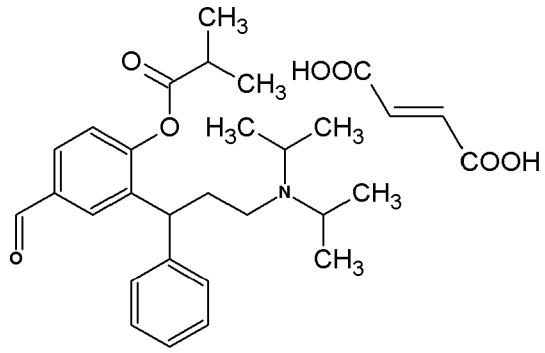
The impurity-C is detected and resolved from fesoterodine fumarate by UPLC with an RRT of 1.16.

- (iv) (+)3-(3-(diisopropylamino) - 1-phenylpropyl) -4- (isobutyryloxy) benzoic acid hydrogen fumarate (Impurity-E), which has the following structure:



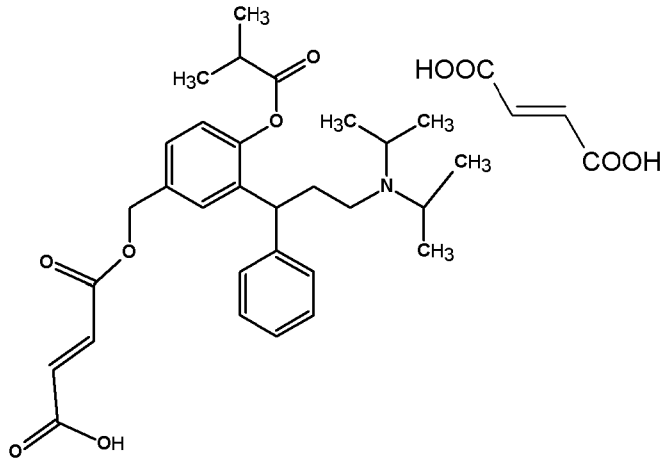
The impurity-E is detected and resolved from fesoterodine fumarate by UPLC with an RRT of 0.18.

- (v) (+)-2-(3-(diisopropylamino)-l-phenylpropyl)-4-formylphenyl isobutyrate hydrogen fumarate (Impurity-F), which has the following structure:



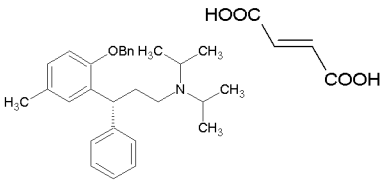
The impurity- F is detected and resolved from fesoterodine fumarate by UPLC with an RRT of 1.46.

- (vi) 4-[(3-(3-diisopropylamino-l-phenylpropyl)-4-(2-isobutyroyloxyphenyl)-methoxy]-4-oxobut-2-enoic acid hydrogen fumarate (Impurity-G) , which has the following structure:



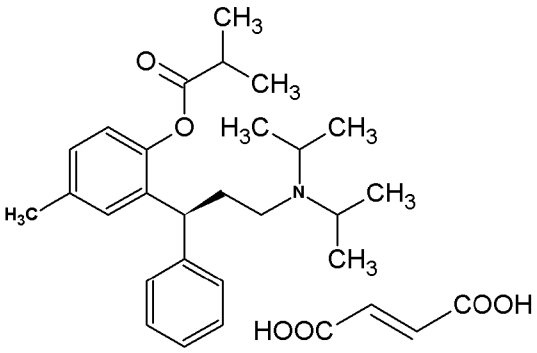
The impurity-G is detected and resolved from fesoterodine fumarate by UPLC with an RRT of 0.27.

- (vii) R-(+)-N,N-disiopropyl amine-3-(2-Benzyloxy-5-Methylphenyl)-3-Phenylpropylamine hydrogen fumarate (Impurity-H) which has the following structure:



Impurity-H is detected and resolved from fesoterodine fumarate by UPLC with an RRT of 2.67.

- (viii) (R)-2-(3-(diisopropylamino)-l-phenylpropyl)-4-methylphenyl isobutyrate hydrogen fumarate (Impurity-I) which has the following structure:



Impurity-I is detected and resolved from fesoterodine fumarate by UPLC with an RRTof 1.93.

[23] According to one aspect of the present invention, there is provided a reversed-phase liquid chromatographic (RP-LC) method for quantifying, by area percent, the amounts of fesoterodine fumarate and all impurities, preferably, Impurity-A, impurity-B, impurity-C, impurity-E, impurity-F, impurity-G, impurity-H and impurity-I present in a sample of fesoterodine fumarate.

[24] According to another aspect of the present invention, there is provided a stability indicating analytical method using the samples generated from forced degradation studies.

[25] According to another aspect of the present invention, there is provided an accurate and well-defined stability indicating UPLC method for the determination of fesoterodine fumarate in the presence of degradation products.

[26] Preferably, the method for determining the amount of impurities in a fesoterodine fumarate sample comprises the steps of:

- a) combining a Fesoterodine fumarate sample with buffer and acetonitrile in the ratio of 50:50 (v/v) to obtain a solution;
- b) injecting the sample solution into a 100mmx2.1 mm column with 1.7 μιη Acquity BEH C18 column;
- c) gradient eluting the sample with a mixture of A Eluent and B Eluent in the ratio of 50:50 (v/v) initial and progressively increased to 30:70(v/v) in 16 minutes.
- d) Preparing Eluent A by dissolving 1.4 g of Disodium hydrogen phosphate in 1000 mL of water and the pH adjusted was about 8.0 with diluted orthophosphoric acid and filter through 0.22 micron filter paper.
- e) Measuring of the amounts of fesoterodine and each impurity at 220nm wavelength with a UV detector (having an appropriate recording device).

[27] Preferably, the initial ratio of eluent A and eluent B in step-(c) may be continued at the same ratio for 2 minutes then changed linearly to 30:70 (v/v) within 5 minutes followed by same ratio for 9 minutes. After 1.5 minutes the initial gradient of 50:50 is

for 2.5 minutes to be conditioned for every analysis. The column temperature may be maintained at about 45°C.

[28] The LOD /LOQ values of fesoterodine fumarate and its related impurities, Impurity-A, impurity-B, impurity-C, impurity-E, impurity-F, impurity-G, impurity-H and impurity-I are summarized in Table 1.

[Table 1]

S. No	Components	LOD (%)	LOQ (%)
1	Impurity-A	0.0011	0.0034
2	Impurity-B	0.0032	0.0096
3	Impurity-C	0.0035	0.0105
4	Impurity-D	0.0018	0.0054
5	Impurity-E	0.0026	0.0080
6	Impurity-F	0.0017	0.0051
7	Impurity-G	0.0023	0.0071
8	Impurity-H	0.0026	0.0079
9	Fesoterodine fumarate	0.0032	0.0098

[29] Specificity is the ability of the method to measure the analyte response in the presence of its potential impurities and degradation products. The specificity of the LC method for fesoterodine fumarate. Intentional degradation was attempted to stress conditions of acid hydrolysis (using 1.0M HC1), base hydrolysis (using 0.1M NaOH), and oxidative degradation (using 3.0% H_20_2), thermal and photo degradation to evaluate the ability of the proposed method to separate fesoterodine fumarate from its degradation products. To check and ensure the homogeneity and purity of fesoterodine peak in the stressed sample solutions, PDA-UV detector was employed.

[30] Preferably, the limit of detection (LOD) and limit of quantification (LOQ) were estimated by signal to noise ratio method, by injecting a diluted solution with known concentration.

[31] The accuracy of the related substances method with the spiked impurities was evaluated at 0.15 % and 0.70 % of concentration levels.

[32] According to another aspect of the present invention, there is provided a chromatographic method to get the separation of all impurities and stress studies degradants from analyte peak. Satisfactory chromatographic separation was achieved using the mobile phase consists of buffer (1.4 g of Disodium hydrogen phosphate in 1000 mL of water. Adjust the pH to 8.0 + 0.05 with diluted orthophosphoric acid)In the optimized

conditions the fesoterodine fumarate, Impurity-A, impurity-B, impurity-C, impurity-E, impurity-F, impurity-G, impurity-H and impurity-I were well separated with a resolution of 1.5 and the typical retention times (RT) of fesoterodine fumarate, Impurity-A, impurity-B, impurity-C, impurity-E, impurity-F, impurity-G, impurity-H and impurity-I were about 6.00, 1.50, 13.64, 6.93, 1.08, 8.76, 1.64, 16.03 and 11.60 minutes respectively, and typically shown in Figure 1. The system suitability results and the developed LC method was found to be specific for fesoterodine and its eight impurities, namely Impurity-A, impurity-B, impurity-C, impurity-E, impurity-F, impurity-G, impurity-H and impurity-I

[33] The system suitability values and mass numbers of fesoterodine fumarate and its impurities were summarized in Table 2.

[Table 2]

Compound (n=1)	Rt	Rs	N	T	(m/z)
Impurity-E	1.08		4054	1.91	426.5
Impurity- A	1.50	5.25	4548	1.39	342.4
Impurity- G	1.64	1.58	7054	1.57	510.6
Fesoterodine	6.00	24.51	7568	0.68	412.5
Impurity- C	6.93	4.87	68887	1.06	432.5
Impurity- F	8.76	15.50	80176	1.10	410.5
Impurity- I	11.60	16.29	47705	1.27	396.5
Impurity- B	13.64	8.53	39821	1.20	482.6
Impurity- H	16.03	7.91	28698	1.07	416.5

**n=l: determination, Rt: retention time, Rs: USP resolution, N: number of theoretical plates (USP tangent method), T: USP tailing factor, m/z: mass number.*

[34] High level of degradation in test solution was observed using 3% hydrogen peroxide at initial point, 0.1M sodium hydroxide at initial point and 1M HC1 at 60°C for 6 hours. Impurities observed in stress condition using PDA detector,. Major degradants was impurity-A .Other unknown were also specific in this method .The peak test results obtained from PDA & LC-MS/MS confirm that the fesoterodine peak is homogeneous and pure in all analyzed stress samples.

[35] The percentage recovery of fesoterodine of its impurities in bulk drug samples was done at 0.15 %. The percentage recovery of Impurity-A, impurity-B, impurity-C, impurity-E, impurity-F, impurity-G, impurity-H and impurity-I in bulk drugs samples was ranged from 90.00 to 110.00.

[36] In deliberate varied chromatographic conditions (pH and column), the robustness of the method is confirmed.

[37] **Experimental**

[38] The LC system, used for method development and forced degradation studies and method validation was Waters-Alliance (manufactured by Waters India Ltd) LC system with a photo diode detector. The out put signal was monitored and processed using Empower software system (designed by Waters India) on IBM computer (Digital Equipment Co).

[39] The chromatographic column used was a Waters Aquity BEH C18 100mmx2.1 mm column with 1.7 μιη particles. The mobile phase consists buffer (1.4 g of Disodium hydrogen phosphate in 1000 mL of water pH-8.0 with ortho phosphoric acid), and solvent is acetonitrile. The flow rate of the mobile phase was kept at 0.3 ml/min. Beginning with the gradient ratio of mobile phase buffer and solvent 50:50(v/v), system was continued at the same ratio for 2 minutes. The ratio was changed linearly 30:70(v/v) within 7 minutes and again system was continued at the same ratio for 9 minutes. After 1.5 minutes the initial gradient of 50:50 is for 2.5 minutes to be conditioned for every analysis. The column temperature was maintained at 45°C and the wavelength was monitored at a wavelength of 220 nm. The injection volume was 3 μL for related substances determination. Acetonitrile was used as diluent during the standard and test samples preparation.

[40] **Preparation of reference solution-1**

[41] 7.0 mg of impurity- A were accurately weighed and transferred to the lOOmL volumetric flask(BOROSIL-Class-A) , separately; 50ml of diluent was added in to the flask and shaken for five minutes in an ultrasonic bath and made up to mark with diluent.

[42] **Preparation of reference solution-2**

[43] 7.5 mg of each impurity-B, impurity-C, impurity-E, impurity-F, impurity-G, impurity-H and impurity-I and 5.0 mg of fesoterodine fumarate were accurately weighed and transferred to the 50mL volumetric flask(BOROSIL-Class-A) , separately; 50ml of diluent was added in to the flask and shaken for five minutes in an ultrasonic bath and made up to mark with diluent. Pipette out 5.0mL from solution and transferred in to a 50mL volumetric flask (BOROSIL-Class-A), and made up to mark with diluent.

[44] A working solution of 1000μg/ml was prepared for related substances determination analysis.

[45]

[46]

Claims

[Claim 1] An UPLC method for analyzing Fesoterodine, wherein the mobile phase comprises two or more liquids, including a first eluent A and a second eluent B, and the relative concentration of the liquids is varied to a predetermined gradient.

[Claim 2] An UPLC method according to claim 1, wherein the first eluent A is buffer.

[Claim 3] An UPLC method according to claim 1, wherein the first eluent B is acetonitrile.

[Claim 4] An UPLC method according to claim 1, wherein gradient of A eluent and B eluent in the ratio of 50:50(v/v) initial and progressively increased to 30:70(v/v) in 16 minutes.

[Claim 5] An UPLC method according to claim 2, wherein buffer is 1.4 g of Disodium hydrogen phosphate in 1000 mL of water and the pH about 8.0

[Claim 6] An UPLC method for fesoterodine fumarate containing less than about 5% area by UPLC, preferably less than about 3% area by UPLC, more preferably less than 1% area by UPLC, of total impurities.

[Claim 7] An UPLC method determining the amount of impurities in Fesoterodine sample comprises the steps of:

(a) combining a Fesoterodine fumarate sample with buffer and acetonitrile in the ratio of 50:50 (v/v) to obtain a solution;

(b) injecting the sample solution into a 100mmx2.1 mm column with 1.7 μιη Acquity BEH C18 column;

(c) gradient eluting the sample with a mixture of A Eluent and B Eluent in the ratio of 50:50 (v/v) initial and progressively increased to 30:70(v/v) in 16 minutes;

(d) Preparing Eluent A by dissolving 1.4 g of Disodium hydrogen phosphate in 1000 mL of water and the pH adjusted was about 8.0 with diluted ortho phosphoric acid and filter through 0.22 micron filter paper;

(e) Measuring of the amounts of fesoterodine and each impurity at 220nm wavelength with a UV detector having an appropriate recording device.

Applicant: Alembic Pharmaceuticals Limited **Sheet 1**

Spiked solution (Fesoterodine fumarate+ 0.15% of each Known impurity spiked solution) @ 220 nm.

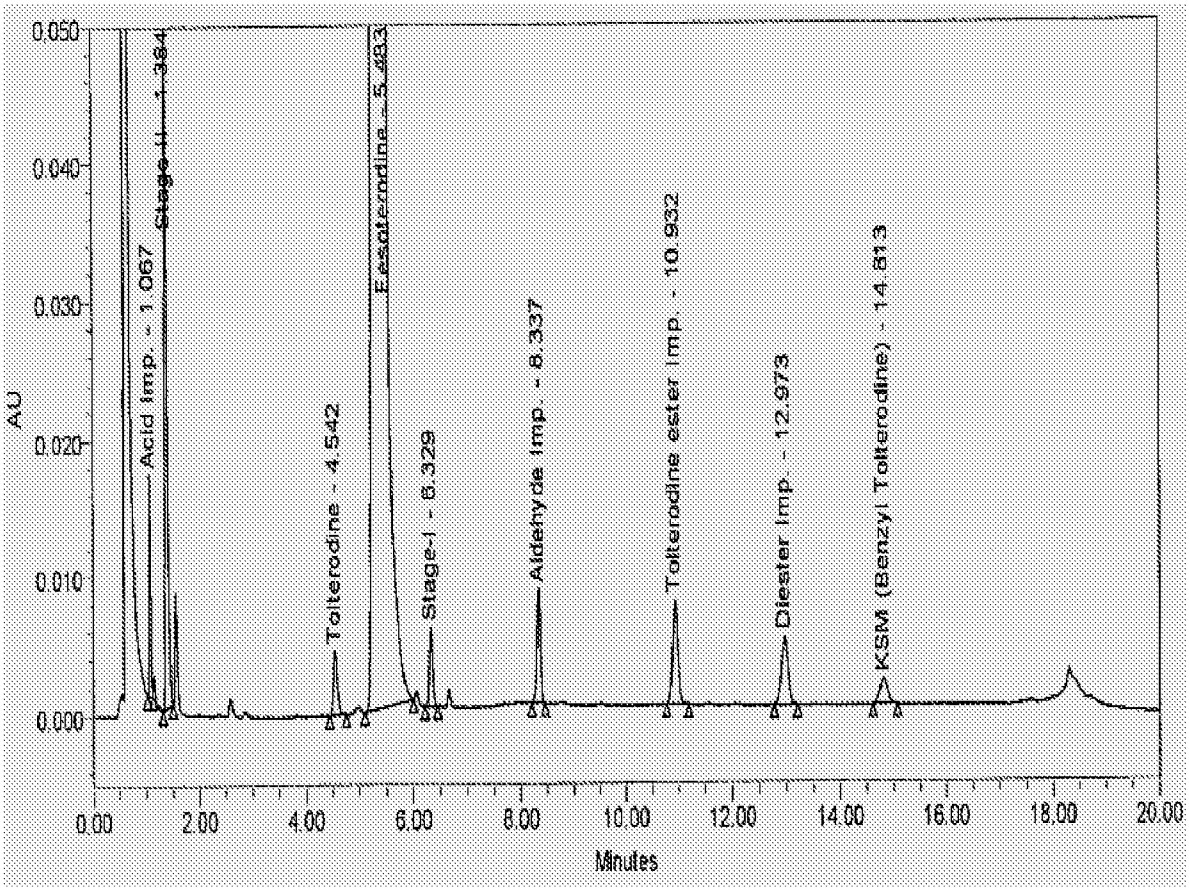


Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2012/054100

A. CLASSIFICATION OF SUBJECT MATTER

G01N30/34 (2006.01)i

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)

IPC: G01N30/-

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 practicable, search terms used)

EPODOC; WPI; CNPAT; CNKI; GOOGLE SCHOLAR: uplc, hplc, fesoterodin+, fumarat+, elu+, buffer?, acetonitril??, gradient, performance w liquid w chromatography

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO2010010464A2 (ACTAVIS GROUP PTC EHF) 28 Jan. 2010 (28.01.2010) Page 9 paragraphs 4,8 of the description	1-3,6
A	CN101949898A (SHANGHAI ANPEL SCI. INSLR. CO. LTD., et al.) 19 Jan. 2011 (19.01.2011) Claim 1	1-7

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

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Date of the actual completion of the international search	Date of mailing of the international search report
18 Dec. 2012 (18.12.2012)	**10 Jan. 2013 (10.01.2013)**
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer JIANG, Xufeng Telephone No. (86-10)82245472

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