

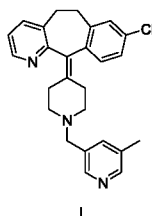
Liquid formulations of rupatadine fumarate

Field of the invention

The present application relates to cyclodextrin-free aqueous liquid formulations of rupatadine
5 fumarate.

Background of the invention

Rupatadine (I) is an authorized antihistaminic agent and has IUPAC name 8-Chloro-6,11-dihydro-11-[1-[(5-methyl-3-pyridinyl)methyl]-4-piperidinylidene]-5H-benzo[5,6]cyclohepta[1,2-b]pyridine,
10 CAS number 158876-82-5 for the free base and the following chemical formula:



Rupatadine is currently marketed in 10 mg (rupatadine) tablets as rupatadine fumarate (CAS 182349-12-8 for the fumarate salt) for the treatment of allergic rhinitis and urticaria in adults and teenagers.

15 Rupatadine free base was first disclosed in EP0577957.

Spanish patent application ES2087818 discloses the monofumarate salt of rupatadine (*i.e.* rupatadine fumarate) and aqueous liquid pharmaceutical compositions of rupatadine fumarate. In particular, this document discloses a syrup containing rupatadine fumarate at 4 g/L, sucrose, a flavouring agent, a sweetening agent and water; and a solution for injection which contains rupatadine fumarate at
20 20 g/L, benzyl alcohol, propyleneglycol and water.

EP0577957 discloses some liquid pharmaceutical compositions of rupatadine free base; compound **4** in EP0577957 is rupatadine free base. The formulations disclosed therein are identical to those disclosed in ES2087818 but rupatadine free base is used instead of rupatadine fumarate.

Despite the aqueous liquid pharmaceutical compositions disclosed in EP0577957 and
25 ES2087818, the inventors have found that the solubility in water of rupatadine fumarate is 2.9 g/L (see Reference example 1) and therefore these prior art formulations may have stability problems due to supersaturation of rupatadine free base or rupatadine fumarate and would not be suitable for use as a medicament.

CN101669901 and CN101669926 disclose liquid formulations of rupatadine free base using
30 cyclodextrins to dissolve rupatadine.

CN101669901 is directed to liquid formulations of rupatadine free base for ophthalmic delivery comprising rupatadine, a solvent and a cyclodextrin.

CN10169926 is directed to liquid formulations of rupatadine free base for nasal delivery comprising rupatadine, a solvent and a cyclodextrin. It is stated that rupatadine has low solubility in water
5 (1.39 mg/mL to 0.82 mg/mL at pH 3.0 to 7.0, table 9 in CN10169926) and the problem of its low solubility is solved using cyclodextrins (tables 10-12 of CN10169926) in order to obtain liquid formulations.

Due to the above, it is desirable to provide cyclodextrin-free aqueous liquid formulations of rupatadine fumarate.

10 **Brief description of the invention**

The present invention relates to a cyclodextrin-free aqueous liquid pharmaceutical composition comprising:

- rupatadine fumarate,
 - one or more cosolvents and
 - 15 - one or more pH regulating agents
- wherein the composition has a pH between 4 and 6.5.

Another embodiment of the invention is a process to prepare a composition according to claim 1 which comprises:

- 20 a) dissolving rupatadine fumarate in the one or more cosolvents to yield a first solution, and
- b) adding water and the one or more pH regulating agents to the first solution.

Another embodiment of the invention is a process to prepare a composition according to claim 1
25 when the pH regulating agent is a buffer which comprises:

- a) dissolving rupatadine fumarate in the one or more cosolvents to yield a first solution,
- b) dissolving the one or more pH regulating agents in water to yield a second solution, and
- 30 c) mixing the first and second solutions obtained in steps a) and b).

Another embodiment of the invention is a process to prepare a composition according to claim 1 when the pH regulating agent is a base or an acid which comprises:

- a) dissolving rupatadine fumarate in the one or more cosolvents,

- b) adding water to the previous solution, and
- c) adding the acid or the base .

Another embodiment of the present invention is a cyclodextrin-free aqueous liquid composition
5 comprising:

- rupatadine fumarate,
- one or more cosolvents and
- one or more pH regulating agents

wherein the composition has a pH between 4 and 6.5 for use in the treatment of allergic
10 conditions.

Another embodiment of the present invention is the use of a cyclodextrin-free aqueous liquid composition comprising:

- rupatadine fumarate,
- 15 - one or more cosolvents and
- one or more pH regulating agents

wherein the composition has a pH between 4 and 6.5 for the treatment of allergic conditions.

Another embodiment is a method of treating an allergic condition which comprises administering
20 to a subject in need thereof, preferably a human being, a cyclodextrin-free aqueous liquid composition comprising:

- rupatadine fumarate,
- one or more cosolvents and
- one or more pH regulating agents

25 wherein the composition has a pH between 4 and 6.5.

Definitions

As used herein, a cosolvent is a pharmaceutically acceptable organic solvent which is soluble in water (which dissolves at least one part of the solvent in two parts of water) and improves (*i.e.* increases)
30 the solubility of the solute (rupatadine fumarate in this context) in water. Examples of cosolvents include monohydric alcohols (e.g. ethanol, isopropanol...), polyhydric alcohols or polyols (e.g. propylene glycol, glycerine,...), ethers (e.g. macrogols such as macrogol 300 or macrogol 400, ...), substituted amides (e.g. dimethylacetamide, pyrrolidone,...) and the like.

As used herein "cosolvent(s)" is equivalent to "one or more cosolvents".

As used herein "pH regulating agent(s)" is equivalent to "one or more pH regulating agents".

As used herein "buffer(s)" is equivalent to "one or more buffers".

As used herein the term sweetener designates any natural or artificial substance capable of imparting sweet taste to aqueous solutions or dispersions.

5 As used herein a sugar is a carbohydrate of formula $(\text{CH}_2\text{O})_n$ wherein n is comprised between 5 and 12 (i.e. a monosaccharide or a disaccharide). Sugars (such as sucrose, fructose, glucose and the like) are capable of imparting a sweet taste to aqueous solutions or dispersions.

As used herein, a pH regulating agent is an agent that can change (decrease or increase) the pH of a solution or stabilize the pH of a solution at a given pH, e.g. an acid, a base or buffer. Therefore the
10 pH regulating agent can change or stabilize the pH of a solution of rupatadine fumarate.

A pharmaceutically acceptable organic solvent is an organic solvent which is authorised to be used in pharmaceutical preparations by the regulatory authorities. The pharmaceutically acceptable solvents are well known by the skilled person in the art; see e.g. Handbook of pharmaceutical excipients, APhA Publications 5th edition 2005, edited by Raymond C. Rowe, Paul J. Sheskey, Siân C. Owen, ISBN-
15 10: 1582120587.

The term "pharmaceutically acceptable salt" refers to those salts which are, according to medical judgement, suitable for use in contact with the tissues of humans and other mammals without undue toxicity, irritation, allergic response and the like. Pharmaceutically acceptable salts are well known in the art.

20 An acid is a substance that releases hydrogen ions and decreases the pH of a solution. A strong acid is an acid that when dissolved in water is completely ionized into hydrogen ions and the corresponding anion. A weak acid is a substance that when dissolved in water is only partially ionized into hydrogen ions and anions. Examples of strong acids include: HCl, H_2SO_4 , HNO_3 , *p*-toluenesulphonic acid and the like. Examples of weak acids include CH_3COOH , H_3PO_4 , citric acid, oxalic acid and the like.

25 A base is a substance that can accept hydrogen ions and increases the pH of a solution. A strong base is a base which when dissolved in water accepts the same amount (in mol) of hydrogen ions as of base dissolved. A weak base is a base that when dissolved in water accepts only a fraction (in mol) of the base dissolved. Examples of strong bases are: NaOH, KOH, LiOH and the like. Examples of weak bases are NH_3 , pyridine, methylamine, triethylamine, NaHCO_3 and the like.

30 The pK_a is a measurement of the strength of an acid. The lower the pK_a , the stronger the acidity. The higher the pK_a , the weaker the acid. The pK_b is a related measurement and is a measurement of the strength of a base; the lower the pK_b , the stronger the base and the higher the pK_b , the weaker the base.

A conjugate base of an acid is the anion of an acid when the acid has released a hydrogen ion, e.g. the conjugate base of H_3PO_4 , is H_2PO_4^- . The conjugate acid of a base is the cation formed when the hydrogen ion is accepted, e.g. the conjugate acid of NH_3 , is NH_4^+ .

In the present invention the term buffer is used to designate either a) a mixture of a weak acid and its conjugate base, b) a mixture of a weak base and its conjugate acid, c) a mixture of a weak base and a conjugate acid of a different base or d) a mixture of a weak acid and a conjugate base of a different acid. The term buffer solution is meant to designate a solution in water of a buffer. When small amounts of acids or bases are added to buffer solutions, the pH is maintained nearly constant. A buffer solution of an acid and its conjugate base in the same molar amount results in a pH equal to the pKa of the acid. As used herein, buffers are indicated as X/Y, which means the buffer is a mixture of components X and Y; for example the buffer Na_2HPO_4 /citric acid means it is a mixture of Na_2HPO_4 and citric acid.

As used herein a surfactant is an amphiphilic compound that lowers the surface tension of a liquid, the interfacial tension between two liquids or that between a liquid and a solid.

An acidic solution is a solution with acid pH, i.e. a pH lower than 7. A basic solution is a solution with basic pH, i.e. a pH higher than 7.

In the context of the present invention when rupatadine is mentioned it is intended to be considered as free base, when rupatadine fumarate is mentioned it is referred to said salt. In the present invention the concentrations of rupatadine fumarate solutions are expressed by reference to the corresponding amount of rupatadine free base (and are indicated as g (rupatadine)/L). Thus, to convert the concentrations of rupatadine fumarate expressed as g (rupatadine)/L to concentrations expressed as g (rupatadine fumarate)/L the values need to be multiplied by a factor of 1.28.

As used herein, the terms pharmaceutical composition, composition and formulation are used interchangeably.

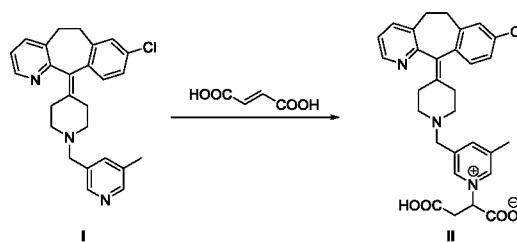
Unless otherwise indicated, all the experimental data and procedures described herein are obtained or performed at room temperature and atmospheric pressure.

Unless otherwise indicated, all concentrations indicated as % correspond to % w/v. Thus, a solution containing 1% of a solute means it contains 1 g(solute)/100 mL.

As used herein, when ranges are given it is intended to cover all the intermediate values as well as the end values. Thus, for example, when it is stated that "the pH is between 4.5 and 5.5", the pH can have any value between 4.5 and 5.5, including the end values 4.5 and 5.5.

Detailed description of the invention

The inventors have found that rupatadine fumarate in acidic solutions forms an adduct (Compound II) of rupatadine and fumaric acid.



Considering this, aqueous acidic pharmaceutical compositions of rupatadine fumarate are not suitable when formulating a medicament for the administration of rupatadine fumarate because Compound II will develop upon storage as an impurity at excessive levels. On the other hand, the solubility of rupatadine fumarate is pH dependent and the solubility is high at acidic pH and decreases when the pH raises (see Reference example 1); therefore aqueous pharmaceutical compositions comprising high levels of rupatadine fumarate at basic pH are also not possible because rupatadine fumarate is not sufficiently soluble.

According to the liquid pharmaceutical compositions of rupatadine and rupatadine fumarate disclosed in the art, those problems were not evident to the person skilled in the art.

The inventors have found that the above problems can be solved when formulating a cyclodextrin-free aqueous liquid pharmaceutical composition of rupatadine fumarate comprising:

- rupatadine fumarate,
- one or more cosolvents and
- one or more pH regulating agents

wherein the composition has a pH between 4 and 6.5.

In one embodiment the aqueous liquid pharmaceutical compositions of the present invention are solutions.

In an embodiment the total amount of cosolvent(s) is from 5 to 50 % of the formulation. In another embodiment the total amount of cosolvent(s) is from 5 to 25 % of the formulation.

In an embodiment, the composition comprises one or more cosolvents selected from the group consisting of monohydric alcohols, polyhydric alcohols or polyols, ethers and substituted amides.

In another embodiment, the one or more cosolvents are selected from the group consisting of ethanol, isopropanol, propylene glycol, glycerine, macrogol 300, macrogol 400, dimethylacetamide and pyrrolidone.

In an embodiment, the one or more cosolvents are selected from the group consisting of ethanol, propylene glycol, macrogol 300 and macrogol 400. In another embodiment, the one or more cosolvents are selected from the group consisting of propylene glycol, macrogol 300 and macrogol 400.

In another embodiment, the composition comprises only one cosolvent. In another embodiment the composition comprises only one cosolvent selected from the group consisting of ethanol, propylene

glycol, macrogol 300 and macrogol 400. In another embodiment the composition comprises only one cosolvent selected from the group consisting of propylene glycol and macrogol 400. In another embodiment the composition comprises only one cosolvent which is propylene glycol. In another embodiment the composition comprises only one cosolvent which is a macrogol, preferably macrogol 300
5 or macrogol 400. In another embodiment, the composition comprises only one cosolvent which is macrogol 300. In another embodiment, the composition comprises only one cosolvent which is macrogol 400.

It has also been found that the compositions of the present invention are particularly stable (in terms of formation of Compound II upon storage) when the cosolvent is not a surfactant, particularly when
10 it is not a polysorbate.

In an embodiment, the cosolvent(s) do not comprise a surfactant.

In another embodiment the cosolvent(s) do not comprise a surfactant and the total amount of cosolvent(s) is from 5 to 50 % of the formulation. In another embodiment the cosolvent(s) do not comprise a surfactant and the total amount of cosolvent(s) is from 5 to 25 % of the formulation.

15 The pH regulating agent(s) in the pharmaceutical compositions of the invention can be buffers, acids, bases, or mixtures thereof.

In one embodiment, the one or more pH regulating agents are selected from the group consisting of buffers and bases.

In another embodiment the one or more pH regulating agents are selected from the group
20 consisting of buffers. The buffer(s) are used to adjust the pH of the composition in the range of 4-6.5 and, to this effect, they preferably have a pKa in the range of 4-6.5. In another embodiment the buffer(s) show a pKa in the range of 4-6. In another embodiment the buffer(s) show a pKa in the range of 5-6.5. In a further embodiment the buffer(s) show a pKa in the range of 5-6. In a further embodiment the buffer(s) show a pKa in the range of 4.5-5.5. In another embodiment the buffer(s) show a pKa in the range of 4.5-6.
25 Examples of suitable buffers are: phosphate buffers (such as K_2HPO_4/KH_2PO_4 , Na_2HPO_4/NaH_2PO_4 , Na_2HPO_4/KH_2PO_4 and the like), Na_2HPO_4 /citric acid, citrate buffers, acetate buffers (such as acetic acid/sodium acetate, acetic acid/ammonium acetate and the like), and ammonium acetate/sodium edetate. These and further buffers can be found in the buffer solutions section of the European Pharmacopoeia (4.1.3), which is incorporated herein by reference. In an embodiment, the composition
30 comprises only one buffer. In an embodiment, the composition comprises only one buffer which is Na_2HPO_4 /citric acid, Na_2HPO_4/KH_2PO_4 or Na_2HPO_4/NaH_2PO_4 . In an embodiment the composition comprises only one buffer which is Na_2HPO_4 /citric acid or Na_2HPO_4/KH_2PO_4 . In another embodiment the composition comprises only one buffer which is Na_2HPO_4/NaH_2PO_4 . In another embodiment the

composition comprises only one buffer which is Na_2HPO_4 /citric acid. In another embodiment the composition comprises only one buffer which is Na_2HPO_4 / KH_2PO_4 .

Phosphate buffers are buffers formed with pharmaceutically acceptable salts of HPO_4^{2-} and H_2PO_4^- . Examples include K_2HPO_4 / KH_2PO_4 , Na_2HPO_4 / NaH_2PO_4 , Na_2HPO_4 / KH_2PO_4 and the like. Said
5 buffers can be obtained using the specific combination of phosphate salts or any phosphate species (including phosphoric acid) and adjusting the pH with acids or bases.

Citrate buffers are buffers formed using citric acid and/or pharmaceutically acceptable salts of citric acid. Said buffers can be obtained adding the specific citrate species or adding citric acid or citrate salts and adjusting the pH with acids or bases.

10 Acetate buffers are buffers formed using acetic acid and/or pharmaceutically acceptable salts of acetic acid such as sodium acetate or ammonium acetate and the like. Said buffers can be obtained adding the specific acetate species or adding acetic acid or acetate salts and adjusting the pH with acids or bases.

In an embodiment the one or more pH regulating agents are selected from the group consisting
15 of bases. Suitable bases are: NaOH , KOH and the like. In an embodiment, the composition comprises only one base. In an embodiment the composition comprises only one base which is NaOH .

In another embodiment the one or more pH regulating agents are selected from the group consisting of phosphate buffers, Na_2HPO_4 /citric acid, citrate buffers, acetate buffers, ammonium acetate/sodium edetate and NaOH .

20 In another embodiment the pH regulating agent is an acid. Suitable acids are HCl , H_3PO_4 and the like.

In an embodiment the total amount of the pH regulating agent(s) is from 1 % to 10 %. In an embodiment the total amount of the pH regulating agent(s) is from 1 % to 5 %. In a further embodiment the total amount of the pH regulating agent(s) is from 1 % to 3 %.

25 In an embodiment the pH of the formulation is between 4 and 6. In another embodiment the pH of the formulation is between 4.5 and 6. In another embodiment the pH of the formulation is between 5 and 6.5. In another embodiment the pH of the formulation is between 5 and 6. In another embodiment the pH of the formulation is between 4.5 and 5.5.

The pharmaceutical compositions of the invention can be used for oral administration.

30 The pharmaceutical compositions of the invention can be used for nasal administration.

When a pharmaceutical composition of the present invention is intended for nasal administration it is required to be isotonic or slightly hypertonic with the nasal mucosa.

The pharmaceutical compositions of the invention can further comprise one or more of usual pharmaceutically acceptable excipients. Said excipients are well known in the art and comprise sweeteners, preservatives, colorants, flavouring agents, thickening agents and the like.

Suitable excipients and its role can be found on Handbook of pharmaceutical excipients, APhA Publications 5th edition 2005, edited by Raymond C. Rowe, Paul J. Sheskey, Siân C. Owen, ISBN-10: 1582120587. Specially suitable excipients for use in the compositions of the invention are detailed below.

Rupatadine fumarate has a bitter taste and if the liquid pharmaceutical compositions according to the invention are intended for oral use it is desirable that said formulations further comprise a sweetener to mask this bitter taste.

10 Suitable sweeteners are preferably selected from the group consisting of sugars (such as sucrose, fructose, glucose and the like), artificial sweeteners (such as saccharin or its pharmaceutically acceptable salts (such as saccharin sodium), cyclamate or its pharmaceutically acceptable salts (such as cyclamate sodium), aspartame, acesulphame or its pharmaceutically acceptable salts (such as acesulphame potassium), sucralose, neohesperidin dihydrochalcone, naringin dihydrochalcone and the
15 like), and mixtures thereof.

In an embodiment the sweetener is a sugar, an artificial sweetener or mixtures thereof. In an embodiment the sweetener is sucrose, saccharin or its pharmaceutically acceptable salts (such as saccharin sodium), or mixtures thereof.

It has also been found that the compositions of the present invention comprising a sweetener are
20 particularly stable (in terms of formation of Compound II upon storage) when the sweetener is a sugar or an artificial sweetener, particularly when the sweetener is sucrose, saccharin or its pharmaceutically acceptable salts (such as saccharin sodium) or mixtures thereof. In an embodiment, the composition comprises a sweetener selected from a sugar, an artificial sweetener, and mixtures thereof. In another embodiment, the composition comprises a sweetener selected from sucrose, saccharin or its
25 pharmaceutically acceptable salts, and mixtures thereof.

In another embodiment, the compositions of the invention do not comprise a sweetener.

In another embodiment, the invention relates to compositions which further comprise one or more of the following excipients:

- one or more colorants.
- 30 - one or more flavouring agents.
- one or more preservative agents.

Suitable preservatives are methyl parahydroxybenzoate, benzyl alcohol, propyl parahydroxybenzoate, 2,4-dichlorobenzylic alcohol, benzalkonium chloride and the like.

Suitable colorants are red colorant E-123, caramel colour E-150, quinoline yellow E-104 and the like.

Suitable flavouring agents are strawberry flavour, cherry flavour, banana flavour, mint flavour, orange, lemon, vainillin, peppermint, grape and the like.

5 Suitable thickening agents are xantham gum, carmellose sodium, hypromellose and the like.

In an embodiment the pharmaceutical composition of rupatadine fumarate of the present invention comprises rupatadine fumarate at a concentration of from 0.5 to 1.5 g(rupatadine)/L. In another embodiment the pharmaceutical composition of rupatadine fumarate comprises rupatadine fumarate at a concentration of 1 g(rupatadine)/L.

10 Another embodiment of the present the invention is a cyclodextrin-free stable aqueous liquid pharmaceutical composition comprising:

- rupatadine fumarate,
- one or more cosolvents and
- one or more pH regulating agents

15 wherein the composition has a pH between 4 and 6.5 and wherein the total amount of cosolvent(s) is from 5 to 50 % of the formulation.

Another embodiment of the invention is a cyclodextrin-free stable aqueous liquid pharmaceutical composition comprising:

- 20 - rupatadine fumarate,
- one or more cosolvents and
 - one or more pH regulating agents

wherein the composition has a pH between 5 and 6.

Another embodiment of the invention is a cyclodextrin-free stable aqueous liquid pharmaceutical composition comprising:

- 25 - rupatadine fumarate,
- one or more cosolvents and
 - one or more pH regulating agents

wherein the composition has a pH between 5 and 6 and wherein the total amount of cosolvent(s) is from 5 to 50 % of the formulation.

30 Another embodiment of the invention is a cyclodextrin-free stable aqueous liquid pharmaceutical composition comprising:

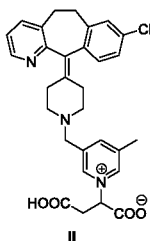
- rupatadine fumarate,
- one or more cosolvents and
- one or more pH regulating agents

wherein the composition has a pH between 5 and 6 and wherein the one or more cosolvents are selected from the group consisting of propylene glycol, macrogol 300 and macrogol 400.

Another embodiment of the present invention is the use of the cyclodextrin-free aqueous liquid formulations of the present invention for the treatment of allergic conditions. In one embodiment the allergic condition is allergic rhinitis or urticaria. In another embodiment the composition of the present invention is used for the treatment of allergic conditions in paediatric population. In another embodiment the allergic condition treated in the paediatric population is allergic rhinitis or urticaria.

Another embodiment is a method of treating an allergic condition which comprises administering to a subject in need thereof the abovementioned cyclodextrin-free aqueous liquid formulation of the present invention. In another embodiment the allergic condition is urticaria. In another embodiment the allergic condition is allergic rhinitis.

Another embodiment of the present invention is the use of Compound II



as purity marker of a rupatadine fumarate composition. The amount of Compound II in a rupatadine fumarate composition can be determined using an HPLC method such as the one described in *Method 2*.

Another embodiment of the present invention is a method of assessing the purity of a composition comprising rupatadine fumarate wherein the concentration of Compound II in said composition is determined using Compound II as a standard in an HPLC method, such as the one described in *Method 2*.

Methods

The following methods are used to determine the pH, the % of Compound II present and the clarity of the formulations described herein.

Method 1: Method of measuring the pH

The pH is measured according to the European Pharmacopoeia 2.2.3 at room temperature (20-25°C) and atmospheric pressure using a potentiometric pH meter (such as a Crison micro pH 2001) apparatus calibrated using a pH 7.00 and 4.01 buffer solutions.

Method 2: Method of measuring the % Compound II

The HPLC method used to determine the % Compound II present in a formulation is based on the European Pharmacopoeia 2.2.29 using the following conditions:

- room temperature and atmospheric pressure
- 5 - column: C18 10 μ m (3.9 mm x 30 cm)
- eluent: Methanol - Phosphate buffer solution pH 4.2 (75:25)
- eluent flow: 1.3 mL/min
- detection: UV-Visible spectrophotometer at 265 nm
- retention time of Rupatadine: aprox. 8.9 min
- 10 - relative retention time of Compound II: aprox. 0.43

Reference standard solutions of rupatadine and Compound II (which can be prepared as described in Reference Example 3) are used in the identification of the components. The test sample is compared to the equivalent placebo (same formulation without rupatadine fumarate) to check overlapping peaks with other excipients in the formulation.

- 15 The % Compound II is calculated as $100 \times (\text{area of Compound II peak}) / (\text{area of rupatadine peak})$.

Method 3: Method of measuring the clarity of a solution

The clarity of a solution was measured according to the European Pharmacopoeia 2.2.1 as follows at room temperature and atmospheric pressure.

- 20 Reference suspensions I-IV (suspension I is the clearest and IV the least clear) were prepared according to the European Pharmacopoeia 2.2.1. The samples of rupatadine fumarate solution to be tested were visually compared to the reference suspensions and their clarity was visually rated in relation to reference suspensions I to IV, i.e. a sample with clarity < I means that it is clearer than the clearest reference.

25

Method 4: Accelerated stability

The formulations were stored in a climatic chamber at 40°C / 75% Relative Humidity (RH) in closed amber glass vials during a 3 month period. At the end of the 3-m period, the % of Compound II present and the clarity of the solution were measured according to *Method 2* and *Method 3* respectively.

- 30 Accelerated stability studies allow predicting the stability of a composition in a short term. Typically it is considered that a composition has a desirable stability when after 1 month in the conditions mentioned above it does not have more than 0.45 % Compound II determined using *Method 2*, and preferably when after 1 month in the conditions mentioned above it does not have more than 0.30 %

Compound II determined using *Method 2*. Stable compositions typically do not have, after 3 months in the conditions mentioned above, more than 0.85 % Compound II determined using *Method 2*.

The solutions are also tested under *Method 3* to determine its clarity, which is an indication of the presence of precipitated material. Preferably stable solutions are clearer than the clearest reference when
5 evaluated using *Method 3*.

Reference examples

Reference example 1: Solubility of rupatadine fumarate in water at different pH

The solubility of rupatadine fumarate was determined by adding 25 g/L of rupatadine fumarate to
10 water and stirring during 16 - 24 h. The resulting solution was filtered and the amount of rupatadine determined using the *Method 2*.

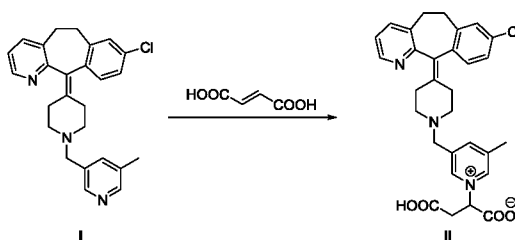
The solubility of rupatadine fumarate in water using the procedure described above is 2.9 g/L.

Using the same procedure, but using buffer solutions of known pH instead of water, the solubility of rupatadine fumarate at different pH was determined (the pH of the solution was measured prior to the
15 addition of rupatadine fumarate).

pH	Solubility (g(rupatadine fumarate)/L)
1.4	19.60
2.0	7.70
2.4	5.59
3.1	4.86
4.1	4.05
5.5	4.06
6.0	0.96
6.4	0.17
7.0	0.035
11.0	<0.005

Reference example 2: Rate of formation of Compound II in aqueous solutions of rupatadine fumarate

It has been found that rupatadine reacts with fumaric acid in acidic conditions to yield an adduct (Compound II):



Different aqueous solutions comprising rupatadine fumarate at a concentration of 1 g(rupatadine fumarate)/L at different pH (3.41, 4.38 and 5.00), obtained adding the required amount of solutions of $\text{HCl}_{(\text{aq})}$ or $\text{NaOH}_{(\text{aq})}$ to solutions containing only water and rupatadine fumarate, were stored at different

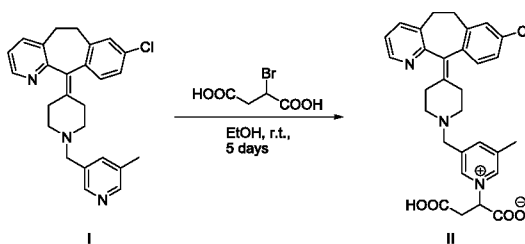
5 temperature conditions (room temperature and $40^\circ\text{C}/75\%\text{HR}$) during two months and analyzed at the beginning, at one month and at the end of the period using Method 2, see table below.

pH	% Compound II initial	% Compound II 1 month		% Compound II 2 months	
		$25 \pm 2^\circ\text{C}$	$40 \pm 2^\circ\text{C}$	$25 \pm 2^\circ\text{C}$	$40 \pm 2^\circ\text{C}$
3.41	0.035	0.174	0.737	0.276	1.396
4.38	0.036	0.090	0.357	0.142	0.646
5.00	0.040	0.039	0.112	0.051	0.182

These results show that the rate of formation of Compound II is pH- dependent. The lower the

10 pH, the higher the rate of formation of Compound II.

Reference example 3: Preparation of Compound II



35 g (0.084 mol) of rupatadine (I) were dissolved in 260 mL of ethanol in a 1000 mL flask. To that

15 solution 16.1 g (0.087 mol) of bromosuccinic acid were added and the mixture was allowed to react overnight at room temperature. The mixture was concentrated to half the volume and allowed to react at room temperature during 5 days.

The solvent was removed *in vacuo* and the solid washed with ethanol and with an ethanol:water:ammonia mixture. Next, it was purified by flash chromatography using a 9:1:1

20 ethanol:ammonia:water mixture.

Finally 4.51 g (0.0085 mol, 9.7 % yield) of the desired product (Compound II) were obtained.

¹H-NMR (300 MHz, CD₃OD): 8.71 (wide signal, 2H), 8.31 (m, 2H), 7.63 (d, *J*=7.31 Hz, 1H), 7.18 (m, 4H), 5.48 (dd, *J*=3.29 Hz, *J*=11.70 Hz, 1H), 3.69 (s, 2H), 3.41 (m, 3H), 3.11 (dd, *J*=11.7 Hz, *J*=17.2 Hz, 1H), 2.8 (m, 4H), 2.54 (s, 3H), 2.45 (m, 2H), 2.26 (m, 4H).

¹³C-NMR (75.43 MHz, CD₃OD): 176.35, 172.20, 158.73, 147.00, 144.65, 143.31, 143.26, 141.15, 140.03, 139.69, 139.47, 138.65, 138.62, 135.85, 134.06, 133.72, 131.91, 130.33, 127.01, 124.08, 75.81, 59.36, 55.47, 55.42, 42.30, 32.75, 32.03, 31.81, 31.77, 18.38.

IR (KBr): 3412, 1587, 1474, 1437, 1379, 1176, 1086, 992, 874, 829, 663 cm⁻¹.

EA: Calculated (C₃₀H₃₀ClN₃O₄·NH₃·H₂O): C 63.54; H 6.22; N 9.88

Found: C 63.47; H 6.41; N 9.61

10

The following examples illustrate the scope of the invention and are not intended to limit the scope of the invention in any way.

Examples

15 **Example 1: Preparation of a nasal liquid formulation of rupatadine fumarate (1.00 g(rupatadine)/L)**

The quantitative composition of this formulation is disclosed in the table below.

Rupatadine fumarate was dissolved in macrogol 400. This is the “active solution”.

Anhydrous citric acid and anhydrous disodium phosphate were dissolved in purified water and stirred until complete dissolution. This is the “vehicle solution”.

20 The “active solution” and the “vehicle solution” were mixed and homogenized. The preservative was added to the final solution. Finally, purified water was added to the resulting mixture to the desired volume.

Component		Amount (mg)
Rupatadine fumarate		1.28
Macrogol 400		50.00
Anhydrous citric acid		4.66
Anhydrous Na ₂ HPO ₄		7.31
Benzalkonium chloride		0.20
Purified water qs		1.00 mL
pH	t ₀	5.17
% Compound II	3 months 40°C/75% RH	0.64
Clarity	3 months 40°C/75% RH	< I

Example 2 to Example 7 Preparation of oral liquid formulations of rupatadine fumarate

25 **(1.00 g(rupatadine)/L) with NaOH as pH regulating agent**

Liquid formulations of rupatadine fumarate, as detailed in Table 1, were prepared using the following preparation methodology:

Rupatadine fumarate was dissolved in the cosolvent and the preservative, if present, was added to said solution. This is the “active solution”.

The pH regulating agent (NaOH 0.1 N) and the sweetening agents, if present, were dissolved in purified water and stirred until complete dissolution. This is the “vehicle solution”.

- 5 The “active solution” and the “vehicle solution” were mixed and homogenized. The remaining excipients (colorants, flavouring agents and the like), if present, were added to the previous mixture. Then the pH was adjusted to the desired pH when needed by addition of NaOH 0.1 N. Finally, purified water was added to the resulting mixture to the desired volume.

10

Component		Example 2	Example 3	Example 4	Example 5	Example 6	Example 7
Rupatadine fumarate		0.128 g	0.128 g	0.128 g	0.128 g	0.100 g	0.100 g
Propylene glycol		20.00 g	20.00 g	20.00 g	20.00 g	20.00 g	20.00 g
Saccharin sodium		0.100 g	----	----	----	----	----
NaOH 0.1 N qs		pH 5	pH 5	pH 5	pH 5	pH 5.5	pH 5
Methyl parahydroxybenzoate		----	0.180 g	----	----	----	----
Propyl parahydroxybenzoate		----	0.020 g	----	----	----	----
2,4-dichlorobenzyl alcohol		----	----	0.05 g	----	----	----
Xanthan gum		----	----	----	0.100 g	----	----
Purified water qs		100.00 mL	100.00 mL	100.00 mL	100.00 mL	100.00 mL	100.00 mL
pH	t ₀	5.02	5.01	5.00	5.00	5.60	5.00
% Compound II	3 months 40°C/75% RH	0.33	0.38	0.35	0.4	0.19 [‡]	0.38 [‡]
Clarity	3 months 40°C/75% RH	< I	< I	< I	NA	NA	NA

15

Table 1

NA: Not available. [‡] at 3.5 months.

Different sweeteners, colorants, flavouring agents and/or preservatives can be added to the previously described compositions.

20

Example 8 to Example 19 Preparation of oral liquid formulations of rupatadine fumarate
(1.00 g(rupatadine)/L) with a buffer as pH regulating agent

Liquid formulations of rupatadine fumarate, as detailed in Table 2 and Table 3, were prepared using the following preparation methodology:

- 5 Rupatadine fumarate was dissolved in the cosolvent and the preservative, if present, was added to said solution. This is the "active solution".

The pH regulating agent (the buffer), and the sweetening agents, if present, were dissolved in purified water and stirred until complete dissolution. This is the "vehicle solution".

- 10 The "active solution" and the "vehicle solution" were mixed and homogenized. The remaining excipients (colorants, flavouring agents and the like), if present, were added to the previous mixture. Finally, purified water was added to the resulting mixture to the desired volume.

Component		Example 8	Example 9	Example 10	Example 11	Example 12	Example 13
Rupatadine fumarate		0.128 g	0.128 g	0.128 g	0.128 g	0.128 g	0.128 g
Propylene glycol		20.00 g	20.00 g	20.00 g	20.00 g	20.00 g	20.00 g
Saccharin sodium		----	----	----	----	0.400 g	----
Sucrose		----	----	----	----	----	50.00 g
Anhydrous citric acid		0.4656 g	0.931 g	----	----	0.931 g	0.931g
Anhydrous Na ₂ HPO ₄		0.731 g	1.460 g	----	----	1.463 g	1.463 g
Anhydrous KH ₂ PO ₄		----	----	0.897 g	1.345 g	----	----
Anhydrous Na ₂ HPO ₄		----	----	11.35 mg	17.035 mg	----	----
Purified water qs		100.00 mL	100.00 mL	100.00 mL	100.00 mL	100.00 mL	100.00 mL
pH	t ₀	5.23	5.17	4.74	4.74	5.12	5.09
% Compound II	3 months 40°C/75% RH	0.36	0.53	NA	NA	0.52	0.83
Clarity	3 months 40°C/75% RH	< I	< I	NA	NA	< I [‡]	< I [‡]

15

Table 2

NA: Not available. ‡ at 3.5 months

- 20 Different sweeteners, colorants, flavouring agents and/or preservatives can be added to the previously described compositions.

Table 3

Component		Example 14	Example 15	Example 16	Example 17	Example 18	Example 19
Rupatadine fumarate		0.128 g	0.128 g	0.128 g	0.128 g	0.128 g	0.128 g
Propylene glycol		20.00 g	20.00 g	20.00 g	20.00 g	20.00 g	20.00 g
Saccharin sodium		----	----	----	----	0.05 g	0.100 g
Sucrose		----	----	----	----	30.00 g	50.00 g
Anhydrous citric acid		0.931 g	0.931 g	0.931 g	0.931 g	0.466 g	0.4656 g
Anhydrous Na ₂ HPO ₄		1.463 g	1.463 g	1.463 g	1.463 g	0.731 g	0.731 g
Methyl parahydroxybenzoate		----	----	----	----	0.100 g	0.1000g
Hypromellose		0.400 g	----	----	----	----	----
Sodium carmellose		----	0.700 g	----	----	----	----
Quinoline yellow E-104		----	----	----	0.0001 g	0.0001 g	0.0001 g
Banana flavour		----	----	----	----	0.25 g	----
Natural lemon flavour 68%V		----	----	0.400 g	----	----	0.400 g
Purified water qs		100.00 mL	100.00 mL	100.00 mL	100.00 mL	100.00 mL	100.00 mL
pH	t ₀	5.16	5.16	5.16	5.15	5.18	5.19
% Compound II	3 months 40°C/75% RH	0.50	0.47	0.56	0.53	0.60	0.68
Clarity	3 months 40°C/75% RH	< I ⁺	< I ⁺	< I ⁺	< I ⁺	< I	< I ⁺

NA: Not available. ⁺ at 3.5 months

Different sweeteners, colorants, flavouring agents and/or preservatives can be added to the previously described compositions.

5

Example 20: Stability of the formulations

As can be shown in the previous tables, the formulations of Example 1 to Example 9 and Example 12 to Example 19 showed good stability properties in the accelerated stability studies as described in *Method 4*.

10

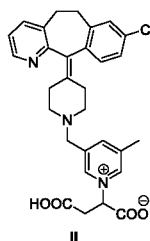
Claims

- 1.- A cyclodextrin-free aqueous liquid pharmaceutical composition comprising:
- rupatadine fumarate,
 - one or more cosolvents and
 - 5 - one or more pH regulating agents
- wherein the composition has a pH between 4 and 6.5.
- 2.- The pharmaceutical composition according to claim 1 which is a solution.
- 10 3.- The pharmaceutical composition according to any of the preceding claims wherein the total amount of cosolvent(s) is from 5 to 50 % of the formulation.
- 4.- The pharmaceutical composition according to any of the preceding claims wherein the cosolvent(s) do not comprise a surfactant.
- 15 5.- The pharmaceutical composition according to any of the preceding claims wherein the composition comprises one or more cosolvents selected from the group consisting of ethanol, isopropanol, propylene glycol, glycerine, macrogol 300, macrogol 400, dimethylacetamide and pyrrolidone.
- 20 6.- The pharmaceutical composition according to claim 5 wherein the composition comprises one or more cosolvents selected from the group consisting of ethanol, propylene glycol, macrogol 300 and macrogol 400.
- 25 7.- The pharmaceutical composition according to claim 6 wherein the composition comprises only one cosolvent.
- 8.- The pharmaceutical composition according to claim 7 wherein the cosolvent is selected from the group consisting of propylene glycol and macrogol 400.
- 30 9.- The pharmaceutical composition according to any of the preceding claims wherein the one or more pH regulating agents are selected from the group consisting of buffers and bases.

- 10.- The pharmaceutical composition according to claim 9 wherein the one or more pH regulating agents are selected from the group consisting of buffers.
- 11.- The pharmaceutical composition according to claim 10 wherein the one or more pH regulating
5 agents are selected from the group consisting of phosphate buffers, Na_2HPO_4 /citric acid, citrate buffers, acetate buffers, and ammonium acetate/sodium edetate.
- 12.- The pharmaceutical composition according to claim 11 wherein the composition comprises only one buffer selected from the group consisting of Na_2HPO_4 /citric acid and $\text{Na}_2\text{HPO}_4/\text{KH}_2\text{PO}_4$.
10
- 13.- The pharmaceutical composition according to claim 9 wherein the one or more pH regulating agents are selected from the group consisting of bases.
- 14.- The pharmaceutical composition according to claim 13 wherein the composition comprises only
15 one pH regulating agent which is NaOH.
- 15.- The pharmaceutical composition according to claims 1 to 14 wherein the pH is between 4.5 and 6.
- 20 16.- The pharmaceutical composition according to claim 15 wherein the pH is between 5 and 6.
- 17.- The pharmaceutical composition according to claim 15 wherein the pH is between 4.5 and 5.5.
- 18.- The pharmaceutical composition according to claims 1 to 17 which comprises a sweetener
25 selected from a sugar, an artificial sweetener, and mixtures thereof.
- 19.- The pharmaceutical composition according to claim 18 wherein the sweetener is selected from sucrose, saccharin or its pharmaceutically acceptable salts, and mixtures thereof.
- 30 20.- The pharmaceutical composition according to claims 1 to 17 which does not comprise a sweetener.
- 21.- The pharmaceutical composition according to any of the preceding claims which comprises rupatadine fumarate at a concentration of 0.5 to 1.5 g(rupatadine)/L.

- 22.- The pharmaceutical composition according to any of the preceding claims which comprises rupatadine fumarate at a concentration of 1 g(rupatadine)/L.
- 23.- The pharmaceutical composition according to any of the preceding claims which further
5 comprises one or more of the following excipients:
- one or more colorants,
 - one or more flavouring agents,
 - one or more preservative agents.
- 10 24.- A process to prepare the pharmaceutical composition according to any one of claims 1 to 23 comprising
- a) dissolving rupatadine fumarate in the one or more cosolvents to yield a first solution,
 - b) adding water and the one or more pH regulating agents to the first solution.
- 15 25.- A process to prepare the pharmaceutical composition according to any one of claims 1 to 23 when the pH regulating agent is a buffer comprising
- a) dissolving rupatadine fumarate in the one or more cosolvents to yield a first solution,
 - 20 b) dissolving the one or more pH regulating agents in water to yield a second solution, and
 - c) mixing the first and second solutions obtained in steps a) and b).
- 26.- A process to prepare the pharmaceutical composition according to any of claims 1 to 23 when
25 the pH regulating agent is a base or an acid comprising:
- a) dissolving rupatadine fumarate in the one or more cosolvents,
 - b) adding water to the previous solution, and
 - c) adding the acid or the base .
- 30 27.- The pharmaceutical composition according to claims 1 to 23 for use in the treatment of allergic conditions.
- 28.- The pharmaceutical composition according to claim 27 wherein the allergic condition is allergic rhinitis or urticaria.

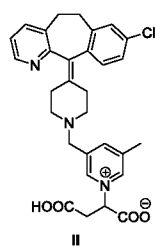
- 29.- The pharmaceutical composition according to claim 28 wherein the allergic condition is allergic rhinitis.
- 5 30.- The pharmaceutical composition according to claim 28 wherein the allergic condition is urticaria.
- 31.- The pharmaceutical composition according to claims 27 to 30 for use in the treatment of paediatric population.
- 10 32.- A method of treating an allergic condition which comprises administering to a subject in need thereof the pharmaceutical composition of claims 1 to 23.
- 33.- The method of claim 32 wherein the allergic condition is urticaria.
- 15 34.- The method of claim 32 wherein the allergic condition is allergic rhinitis.
- 35.- The use of the pharmaceutical composition according to claims 1 to 23 for the treatment of allergic conditions.
- 20 36.- The use according to claim 35 wherein the allergic condition is allergic rhinitis or urticaria.
- 37.- The use according to claims 35 or 36 for the treatment of paediatric population.
- 38.- The use of Compound II



25

as purity marker of a rupatadine fumarate composition.

- 39.- A method of assessing the purity of a composition comprising rupatadine fumarate wherein the concentration of Compound II



in said composition is determined using Compound II as a standard in an HPLC method.