(51) International Patent Classification:  
C07D 211/46 (2006.01) A61K 31/4515 (2006.01)

(21) International Application Number:  
PCT/IB2010/003200

(22) International Filing Date:  
11 December 2010 (11.12.2010)

(25) Filing Language:  
English

(26) Publication Language:  
English

(71) Applicant (for all designated States except US): MICRO LABS LIMITED [IN/IN]; No. 27, Race Course Road, Bangalore 560 001 Karnataka (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): REDDY, Thirupalu, M. [IN/IN]; Micro Labs Limited, 27 Race Course Road, Bangalore 560 001, Karnataka (IN). N. Chittibabu [IN/IN]; Micro Labs Limited, 27 Race Course Road, Bangalore 560 001, Karnataka (IN). REDDY, Srinivasa, P. [IN/IN]; Micro Labs Limited, 27 Race Course Road, Bangalore 560 001, Karnataka (IN). REDDY, Phankumar, B. [IN/IN]; Micro Labs Limited, 27 Race Course Road, Bangalore 560 001, Karnataka (IN). CHELUVARAJU [IN/IN]; Micro Labs Limited, 27 Race Course Road, Bangalore 560 001, Karnataka (IN). RAO, Madhusudana, G. [IN/IN]; Micro Labs Limited, 27 Race Course Road, Bangalore 560 001, Karnataka (IN). SURVE, Pradeep, G. [IN/IN]; B 1/2, Krishna CHS, Opp. Illex, Subhash Rd. A, Vile Parle (E), Mumbai 400057 (IN). MANDPE, Pankaj, S. [IN/IN]; M-101, Old Ashok Nagar Bldg., No.4 Co-Op Hsg Socy. Ltd., Vazira naka, L.T. Rd., Borivali (W), Mumbai 400091 (IN).

(74) Agents: NAIRO, Manoj, Vasudevan et al.; M/s Lex Orbis (Intellectual Property Practice), 709/710, Tolstoy House, 15-17 Tolstoy Marg, New Delhi 110 001 (IN).


Declarations under Rule 4.17:
— of inventorship (Rule 4.17(iv))

Published:
— with international search report (Art. 21(3))
— with information concerning one or more priority claims considered void (Rule 26bis.2(d))

(54) Title: PROCESS OF PREPARING EBASTINE

(57) Abstract: The present invention relates to a novel process for the preparation of pure Ebastine and use of the same in formulation without micronising. The invention further relates to the process of preparation of 1-[4-[1, 1-dimethyl ethyl phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one (compound II), an intermediate or preparation of Ebastine and use of the same in the preparation of pure Ebastine with the maximum particle size more than 1000 µm and D90 from 250 µm -1000 µm.
THIS APPLICATION IS A CONTINUATION IN PART OF WO2009157006.

FIELD OF THE INVENTION:

This invention relates to a novel process for the preparation of pure Ebastine and use of the same in formulation without micronising the same. The invention thus relates to the process of preparation of 1-[4-(1, 1-dimethyl ethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one (compound II), an intermediate or preparation of Ebastine and use of the same in the preparation of Ebastine.

BACKGROUND OF THE INVENTION:

1-[4-(1,1-Dimethylethyl)-phenyl]-4-[4-(diphenylmethoxy)-1-piperidinyl]-1-butanone, commonly known as Ebastine. Ebastine is discovered and developed by Fordonal. The structure of Ebastine is given below:

![Ebastine Structure](image)

Ebastine is commercially available in dosage forms like tablets, orodispersible tablets.

The inadequate bioavailability of Ebastine due to its poor water solubility has been a concern to formulate Ebastine into solid dosage forms.

Ebastine is generally prepared from 1-[4-(1, 1-dimethyl ethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one and diphenyl methyl bromide. Several methods for the preparation of Ebastine and its compositions are known in literature.

United States patent No 4,550,116 discloses synthesis of Ebastine according to following schemes. The first scheme is as follows:
In the process for the preparation of Ebastine fumarate (IV) in above scheme, 1-[4-(1,1-dimethyl ethyl)phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one (II) was refluxed with diphenylmethyl bromide (III) in presence of sodium carbonate and methyl isobutyl ketone for 36 hours.

The above-disclosed scheme has several disadvantages, which are as follows:
The compound (II) is purified in the form of fumarate salt and further it reacts with compound (III). The compound (III) is highly unstable and moisture sensitive. More over the compound (III) is costly. Also the process requires refluxing the reaction mixture for more than 36 hours with addition of compound (III) at every 12 hours time interval.

United States patent No 4,550,116 also discloses second scheme which is as follows:

In second scheme a process for the preparing Ebastine fumarate (IV) was carried out, by refluxing a mixture of 4-diphenylmethoxy piperidine with 1-(4-tert-butylphenyl)-4-chlorobutan-1-one in presence of sodium carbonate and methyl isobutyl ketone as a solvent.
In above scheme the preparation of 1-ethoxycarbonyl-4-dipheylmethoxypiperidine is highly expensive and commercially not viable because of its low yields. EP614362B1 discloses solid pharmaceutical composition having improved dissolution properties, containing a compound corresponding to the formula (including Ebastine), and their salts; characterized in that the compound of formula is micronized.

EP1898882A2 discloses stable nanoparticulate Ebastine, or a salt thereof, composition comprising: (a) particles of Ebastine or a salt thereof having an effective average particle size of less than about 2000 nm; and (b) at least one surface stabilizer.

EP1716848B1 solid pharmaceutical composition comprising at least a first and a second excipient mixed with a crystalline active principle in particles with a maximum particle size of less than 500 μm, of formula (including Ebastine), or a pharmaceutically acceptable salt of said active principle, characterized in that the first excipient is a non-ionic tensioactive agent.

Thus there is a need for the simple, cost effective and less time consuming commercially viable process for preparing Ebastine which can be used without micronization for developing the bioequivalent formulation.

**OBJECTS OF THE INVENTION:**

An object of the present invention is to provide an inexpensive or cost effective process of preparing Ebastine.

Another object of the present invention is to provide a process of preparing Ebastine wherein the process requires less time.

Yet another object of the present invention is to provide a process of preparing Ebastine which has a minimum of processing steps.

Another object is to provide a process for preparation of Ebastine from the use of the compound II.

Further object of, the present invention is to provide a process of preparing pure Ebastine with particle size \( D_{[v, 0.9]} \) within the range of 250 μm to 1000 μm and maximum particle size more than 1000 μm.

In another aspect, there is provided a pharmaceutical composition comprising Ebastine in non-micronized form, wherein \( D_{[v, 0.9]} \) particle size of active ingredient is within the range of 250 μm to 1000 μm and the maximum particle size of active ingredient is more than 1000 μm.
SUMMARY OF THE INVENTION

According to one aspect of the present invention there is provided a process for preparation of pure Ebastine, said process comprising reaction of 1-[4-(1, 1-dimethyl ethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one compound (II) and diphenyl methanol in presence of dehydrating agent in organic solvent system to obtain Ebastine fumarate salt (compound IV).

According to further aspect of the present invention there is provided a process for preparation of 1-[4-(1, 1-dimethyl ethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one compound (II) which is further used in the preparation of Ebastine, said process comprising coupling reaction between compound (I) and 4-hydroxy piperidine in presence of a base in organic solvent system, distilling the solvent under vacuum, dissolving resulting residue in ethyl acetate and water, washing the aqueous is washed in acidic pH with organic solvent to obtain compound II from a mixture of ethyl acetate and n-Hexane directly without any further purification.

According to further object of the present invention the pure Ebastine as prepared from the above process is used for the pharmaceutical composition without micronising the same. According to another object of the present invention a pharmaceutical composition comprising Ebastine in non-micronized form prepared from above process, wherein the D_{90} value of particle size of active ingredient is within the range of 250 μm to 1000 μm and the maximum particle size of active ingredient is more than 1000 μm.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to an efficient and cost effective method of synthesis of pure Ebastine comprising the preparation of 1-[4-(1, 1-dimethyl ethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one by reacting 1-(4-tertbutylphenyl)-4-chlorobutan-1-one and 4-hydroxy piperidine in organic solvent system in basic condition and further refluxing the 1-[4-(1, 1-dimethyl ethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one thus obtained with diphenyl methanol in presence of dehydrating agent by removing the generated water as an azeotrope to get the Ebastine, which is then converted to Fumarate salt. The Ebastine fumarate salt is then treated with base and pure Ebastine crystallized from alcohol.

According to one embodiment, the present invention provides a process of preparing the Ebastine, which has following synthetic scheme:
According to the present invention the coupling reaction between compound (I) and 4-hydroxy piperidine is carried out in presence of a base in organic solvent system, wherein organic solvent is selected from water miscible solvent such as acetonitrile, dioxane, N,N-dimethyl formamide, acetone etc and water immiscible solvent such as toluene, methyl isobutyl ketone, dichloromethane, xylene, chloroform, cyclohexane and mixtures thereof. Preferably the reaction is carried out in the presence of toluene. The base employed can be selected from organic and inorganic bases. The organic base can be selected from alkali metal carbonate or bicarbonate such as sodium carbonate, potassium carbonate, sodium bicarbonate or potassium bicarbonate and metal hydroxides such as lithium hydroxide, sodium hydroxide, or potassium hydroxide. The organic base can be selected from triethylamine, diisopropyl ethylamine or pyridine. The preferred base is sodium bicarbonate.

The reaction can be carried out from ambient temperature to reflux temperature of the solvent and it generally takes 6-12 hours to go to completion. Typically the reaction is carried out at refluxing temperature of the solvent for about 6-8hours. After the reaction has proceeded to a desired stage as judged by HPLC analysis, the solvent is distilled out under
vacuum and the resulting residue is dissolved in ethyl acetate and water. The organic layer pH is adjusted to acidic with mineral acids such as hydrochloric acid, sulphuric acid or acetic acid. The preferred pH is 2-3 and preferred acid is HCl. At acidic pH the aqueous layer is washed with organic solvent to remove impurities, the desired product is obtained from a mixture of ethyl acetate and n-Hexane directly without any further purification.

The present invention provides novel methods for preparing Ebastine. According to prior art literature Ebastine can be prepared by refluxing compound (II) with diphenyl methyl bromide or chloride in presence of sodium carbonate. According to present invention, the compound (II) and diphenyl methanol are reacted in presence of dehydrating agent in organic solvent system, wherein organic solvent can be selected from high boiling solvent such as toluene, xylene, methyl isobutyl ketone or dichloroethane. The preferred solvent is toluene. The dehydrating agent can be selected from p-toluene sulphonic acid monohydrate (PTSA), sulphuric acid, methane sulphonic acid, phosphorous pentoxide, titanium tetrachloride or dicyclohexylcarbodiimide (DCC) etc. The preferred dehydrating agent is p-toluene sulphonic acid monohydrate. The reaction can be carried out at refluxing temperature of the solvent to remove water as an azeotrope for about 6-16 hours. Preferably 6-8 hours. After the reaction has proceeded to a desired stage as judged by HPLC analysis. The desired compound (IV) is isolated in the form fumarate salt in organic solvent. The organic solvent can be selected from alcohols such as methanol, ethanol or isopropanol; nitriles such as acetonitrile or propionitrile; esters such as ethyl acetate, propyl acetate or butyl acetate; toluene, methyl isobutyl ketone and mixtures thereof. The preferred solvent is ethyl acetate.

In another embodiment of this invention, a pure Ebastine is obtained from Ebastine fumarate salt (IV) using base. The base is selected from alkali metal hydroxides, carbonates or bicarbonates, ammonia, tertiary amines and mixtures thereof. The preferred base is sodium hydroxide.

In another embodiment of this invention, a pure Ebastine is crystallized from resulting residue obtained from Ebastine fumarate salt (IV) in presence of organic solvent at -5 to +25°C. The organic solvent is selected from C1-C6 alcohols such as methanol, ethanol, and propanol; hexane, cyclohexane; diisopropyl ether and mixtures thereof. The preferred solvent is methanol. Thus obtained Ebastine purity is above 96.6% by HPLC.

The above process is used to make non micronized Ebastine compositions directly. The pharmaceutical compositions are administered orally. The pharmaceutical composition may be a solid dosage form. The solid dosage form may be one or more of tablet, capsule, powder,
disc, caplet, granules, pellets, granules in capsule, minitablets, minitablets in capsule, pellets in capsule, sachet and the like.

The pharmaceutical composition may be a tablet, which may be multilayered tablet. The tablet may be orodispersible.

The pharmaceutical composition contains Ebastine as active ingredient prepared by above mentioned process. The pharmaceutical composition may contain between 1 and 25% by weight of the active ingredient, Ebastine. The active ingredient may be present in the form of powder, granules, pellets, beads, microtablets, minitablets and crystals.

Ebastine is used herein as non-micronized form. The $D_{10\text{th}}^{[0.9]}$ value of particle size of Ebastine is within the range of 250 $\mu$m to 1000 $\mu$m. The maximum particle size of Ebastine is more than 1000 $\mu$m.

The pharmaceutical composition comprises one or more pharmaceutically acceptable inert excipients. The pharmaceutically acceptable inert excipients may be one or more of diluents, binders, surfactants, disintegrants, lubricants, glidants, solvents, sweeteners and flavoring agents and the like.

Suitable diluents may be one or more of microcrystalline cellulose, lactose, mannitol, calcium phosphate, calcium sulfate, kaolin, dry starch, powdered sugar, and the like.

Suitable binder may be one or more of, povidone, starch, stearic acid, gums, hydroxypropylmethyl cellulose and the like.

Suitable surfactants may be one or more of benzalkonium chloride, benzethonium chloride, cetpyridinium chloride, TPGS (d- alpha tocopheryl polyethylene glycol succinate), dioctyl sodium sulfosuccinate, poloxamers, polyoxylene caprylic/capric mono- and diglycerides, polyoxylene castor oil, hydrogenated castor oil, polyoxylene cetostearyl ether; polyoxylene stearate; polysorbate 20 and polysorbate 80, propylene glycol laureate, sodium lauryl sulfate, oleic acid, sodium oleate, triethanolamine oleate, glyceryl monooleate, sorbitan monolaurate, sorbitan monoooleate, sorbitan monopalmitate and sorbitan monostearate, lecithin, stearyl triethanolamine, lauryl aminopropionic acid and the like. The surfactant is used in a concentration of about 1 to about 30 weight % of the pharmaceutical composition.

Suitable disintegrant may be one or more of starch, croscarmellose sodium, crospovidone, sodium starch glycolate and the like.

Suitable lubricant may be one or more of magnesium stearate, zinc stearate, calcium stearate, stearic acid, sodium stearyl fumarate, hydrogenated vegetable oil, glycercyl behenate and the like.
Suitable glidant may be one or more of colloidal silicon dioxide, talc or cornstarch and the like.

Suitable solvents may be one or more of isopropyl alcohol, methylene chloride, water and the like.

Suitable sweeteners which may be one or more of aspartame, acesulfame potassium, cyclamate, glycyrrhizin, sucralose, saccharine, neohesperidine dihydrochalcone and the like.

Suitable flavors which may be one or more of mint flavor, orange flavor, lemon flavor, banana flavor, vanilla flavor, grapefruit flavor, cherry flavor, strawberry flavor, chocolate flavor, coffee flavor and the like.

The solid dosage form may optionally be film coated. The film coating may comprise one or more of film formers, solvents, plasticizers and the like.

Suitable film formers may be one or more of hydroxypropyl methyl cellulose, methyl hydroxyethyl cellulose, ethyl cellulose, hydroxypropyl cellulose, povidone, sodium carboxymethyl cellulose, polyethylene glycol, acrylates and the like.

Suitable solvents may be one or more of water, ethanol, methanol, isopropanol, chloroform, acetone, methyl ethyl ketone, methylene chloride and the like.

Suitable plasticizers may be one or more of propylene glycol, castor oil, glycerin, polyethylene glycol, polysorbates, and the like.

The pharmaceutical composition may be prepared by processes those known to ordinary skill in the art and include but not limited to dry granulation, wet granulation and direct compression. In a preferred embodiment, the process is wet granulation. The wet granulation may be aqueous or non-aqueous granulation.

When wet granulation is used to prepare tablet composition, the process comprises the steps of,

i. Dissolving Ebastine in a suitable solvent optionally with pharmaceutically acceptable inert excipients to form a solution,

ii. Adding pharmaceutically acceptable inert excipients to form a mixture,

iii. Granulating the mixture in step (ii) with solution formed in step (i) to form granules,

iv. Compressing the granules formed in step (iii) using suitable tooling’s.

The particle size data of 3 batches are given in Figures 1-3:

The present invention can be illustrated in one of its embodiments by the following non-limiting examples.
EXAMPLE-1:

Preparation of 1-[4-(1,1-dimethylethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one:

A mixture of 4-hydroxy piperidine (50g), 1-(4-tert-butylphenyl)-4-chlorobutan-1-one (119g) and sodium bicarbonate (84g) in toluene was refluxed for 6-8hrs. The progress of the reaction was monitored by HPLC. Distilled out the solvent completely under vacuum; the resulting residue was dissolved in ethyl acetate and water. Ethyl acetate layer was separated and washed with water. pH of the ethyl acetate layer was adjusted to 2-3 with 3N HCl solution, aqueous layer was washed with ethyl acetate and made the aqueous solution alkaline with aqueous sodium hydroxide and extracted with ethyl acetate. The organic layer was dried with sodium sulphate and solvent was removed completely under vacuum. The title compound was isolated from a mixture of 1:5 ethyl acetate and n-hexane.

Yield: 105g, Melting Point: 63-65°C.

EXAMPLE-2:

Preparation of 1-[4-(1,1-dimethylethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one:

A mixture of 4-hydroxy piperidine (10g), 1-(4-tert-butylphenyl)-4-chlorobutan-1-one (24g) and triethyl amine (20g) in methyl isobutyl ketone (100ml) was refluxed for 6-8 hrs. The progress of the reaction was monitored by HPLC. The reaction mass was cooled to room temperature and washed with water. The organic layer pH was adjusted to 2-3 with 3N HCl solution; the aqueous layer was washed with methyl isobutyl ketone and the aqueous solution was made alkaline with aqueous sodium hydroxide and extracted with ethyl acetate. The organic layer was dried over sodium sulphate and solvent was removed completely under vacuum. The title compound was isolated from a mixture of 1:5 ethyl acetate and n-hexane.

Yield: 18g, Melting Point: 63-65°C.

EXAMPLE-3:

Preparation of 1-[4-(1,1-dimethylethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one:

A mixture of 4-hydroxy piperidine (14g), 1-(4-tert-butylphenyl)-4-chlorobutan-1-one (33g) and sodium carbonate (30g) in acetonitrile (100ml) was refluxed for 10-14 hrs. The progress of the reaction was monitored by HPLC. The solvent was distilled out completely under vacuum and the resulting residue was dissolved in ethyl acetate (100ml) and water (100ml). Ethyl acetate layer was separated and washed with water. pH of the ethyl acetate layer was adjusted to 2-3 with 3N HCl solution, the aqueous layer was washed with ethyl
acetate and aqueous solution was made alkaline with aqueous sodium hydroxide and extracted with ethyl acetate. The organic layer was dried with sodium sulphate and solvent was removed completely under vacuum. The title compound was isolated from a mixture of 1:5 ethyl acetate and n-hexane.

Yield: 14g, Melting Point: 61-64°C

EXAMPLE-4:

Preparation of Ebastine:

A mixture of 1-[4-(1,1-dimethylethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one (150g) and p-toluene sulphonic acid monohydrate (105g) in toluene (500ml) was boiled to 100 – 110°C. A solution of diphenyl methanol (60g) in toluene (80ml) was added to a reaction mixture over 1 hour at refluxing temperature by continuously removing water as an azeotrope. Another solution of diphenyl methanol (60g) in toluene (80ml) was added to the reaction mixture over 1 hour at refluxing temperature by continuously removing water as an azeotrope, the mixture was boiled under reflux for 1.5 hrs. Another solution of diphenyl methanol of the same quantity was added under similar conditions. The reaction mixture was refluxed for 4-5 hrs. The progress of the reaction was monitored by HPLC. The solvent was distilled out completely under vacuum, the resulting residue was dissolved in ethyl acetate (750ml) and 10% sodium hydroxide solution (600ml) at 45 – 50°C. The organic layer was separated and washed with water, and 3N HCl solution and with 10% sodium bicarbonate solution. The ethyl acetate layer was then dried with sodium sulphate and refluxed with fumaric acid (85g, 0.73mol). The resulting Ebastine fumarate was filtered, washed with ethyl acetate and dried at 80 – 85°C.

The Ebastine fumarate salt (240g) was suspended in ethyl acetate (900ml) and 10% sodium hydroxide solution (800ml), stirred for 0.5 hours at room temperature to get a clear solution. The organic layer was separated and washed with water till neutral pH. Solvent was distilled out completely under vacuum and crystallized the resulting residue was crystallized from methanol. The obtained pure Ebastine solid was filtered and dried at 60 – 65°C.

Yield: 150g; Melting point: About 86°C. Purity by HPLC: 99.9%

EXAMPLE-5:

Preparation of Ebastine:

A mixture of 1-[4-(1,1-dimethylethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one (150g), p-toluene sulphonic acid monohydrate (105g) and diphenyl methanol (180g) in toluene (600ml) was refluxed for 12-15 hours by continuously removing water as an azeotrope. The progress of the reaction was monitored by HPLC. Solvent was distilled out
completely under vacuum and the resulting residue was dissolved in ethyl acetate (750ml) and 10% sodium hydroxide solution (600ml) at 45 – 50°C. The organic layer was separated and washed with water, 3N HCl solution and with 10% sodium bicarbonate solution. The ethyl acetate layer was dried with sodium sulphate and refluxed with fumaric acid (85g, 0.73mol). The resulting Ebastine fumarate was filtered, washed with ethyl acetate and dried at 80 – 85°C.

The Ebastine fumarate salt (200g) was then suspended in ethyl acetate (800ml) and 10% sodium hydroxide solution (700ml) and stirred for 0.5 hours at room temperature to get a clear solution. The organic layer was separated and washed with water. Solvent was distilled out completely under vacuum and resulting residue was crystallize from methanol. The obtained pure Ebastine solid was filtered and dried at 60 – 65°C.

Yield: 118g (51%); Melting point: About 86°C. Purity by HPLC: 99.85%

**EXAMPLE-6:**

**Preparation of Ebastine:**

A mixture of 1-[4-(1,1-dimethylethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one (25g, 0.08mol), sulphuric acid (24.2g, 0.25mol) and diphenyl methanol (30g, 0.16mol) in toluene (100ml) was refluxed for 8-10 hours by continuously removing water as an azeotrope. The progress of the reaction was monitored by HPLC. The reaction mixture was cooled to room temperature and washed with water. The organic layer was dried with sodium sulphate and solvent was removed completely under vacuum. The resulting residue was refluxed with ethyl acetate and fumaric acid (14.3g). The obtained Ebastine fumarate salt was filtered, washed with ethyl acetate and dried at 80-85°C.

The Ebastine fumarate salt (25g) thus obtained was suspended in ethyl acetate (150ml) and 10% sodium hydroxide solution (100ml), stirred for 0.5 hours at room temperature to get a clear solution. The organic layer was separated and washed with water. The solvent was distilled out completely under vacuum and the resulting residue was crystallized from methanol. The obtained pure Ebastine solid was filtered and dried at 60 – 65°C.

Yield: 12g ; Melting point: About 86°C. Purity by HPLC: 99.7%

**EXAMPLE-7:**

**Preparation of Ebastine:**

A mixture of 1-[4-(1,1-dimethylethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one (100g) and p-toluene sulphonic acid monohydrate (69.0g) in methyl isobutyl ketone (500ml) was boiled to 100–110°C. Diphenyl methanol (120g) was added to the reaction mixture over 3 hours at refluxing temperature by continuously removing water as an
The progress of the reaction mixture was monitored by HPLC. The reaction mixture was cooled to 50-55°C, 10% sodium hydroxide solution (500ml) and stir for 30 minutes at same temperature. The organic layer was separated and washed with water, 3N HCl solution and with 10% sodium bicarbonate solution. The ethyl acetate layer was dried with sodium sulphate and refluxed with fumaric acid (56g). The resulting Ebastine fumarate was filtered, washed with ethyl acetate and dried at 80 – 85°C.

The Ebastine fumarate salt (140g) was suspended in ethyl acetate (500ml) and 10% sodium hydroxide solution (350ml) and stirred for 0.5 hours at room temperature to get a clear solution. The organic layer was separated and washed with water till pH comes too neutral. The solvent was distilled out completely under vacuum and the resulting residue was crystallized from methanol. The obtained pure Ebastine solid was filtered and dried at 60 – 65°C.

Yield: 75 g; Melting point: About 86°C. Purity by HPLC: 99.9%

**Example – 8**

Table-1: Pharmaceutical composition

<table>
<thead>
<tr>
<th>SN</th>
<th>Ingredients</th>
<th>Qty (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Intra-granular</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Ebastine</td>
<td>10,000</td>
</tr>
<tr>
<td>2</td>
<td>Sodium Lauryl Sulphate</td>
<td>1,500</td>
</tr>
<tr>
<td>3</td>
<td>Isopropyl Alcohol</td>
<td>q.s.</td>
</tr>
<tr>
<td>4</td>
<td>Methylene Chloride</td>
<td>q.s.</td>
</tr>
<tr>
<td>5</td>
<td>Mannitol</td>
<td>124,500</td>
</tr>
<tr>
<td>6</td>
<td>Crospovidone</td>
<td>20,000</td>
</tr>
<tr>
<td></td>
<td><strong>Extra Granular</strong></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Aspartame</td>
<td>1,000</td>
</tr>
<tr>
<td>8</td>
<td>Peppermint Premium Powder</td>
<td>2,000</td>
</tr>
<tr>
<td>9</td>
<td>Crospovidone</td>
<td>30,000</td>
</tr>
<tr>
<td>10</td>
<td>Colloidal Silicon Dioxide</td>
<td>5,000</td>
</tr>
<tr>
<td></td>
<td><strong>Lubrication</strong></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Sodium Streayl Fumarate</td>
<td>6,000</td>
</tr>
</tbody>
</table>

The manufacturing process in brief is given below:

Ebastine API prepared from any of the above process was dissolved in Isopropyl Alcohol and Methylene Chloride mixture to form a solution. Sodium Lauryl Sulphate was
dispersed into solution to form dispersion. Mannitol and crospovidone were sifted to form a mixture. The mixture formed was granulated with the dispersion formed to form a wet mass. The wet mass formed was dried and sized to form granules. Aspartame, Peppermint Premium Powder, Crospovidone and Colloidal Silicon Dioxide were sifted and mixed with granules to form a blend.

The blend formed was compressed using suitable toolings with Sodium Stearyl Fumarate as a lubricant.

**Figure 1**

<table>
<thead>
<tr>
<th>Size (um)</th>
<th>Volume in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.1</td>
</tr>
<tr>
<td>0.02</td>
<td>0.2</td>
</tr>
<tr>
<td>0.03</td>
<td>0.3</td>
</tr>
<tr>
<td>0.04</td>
<td>0.4</td>
</tr>
<tr>
<td>0.05</td>
<td>0.5</td>
</tr>
<tr>
<td>0.06</td>
<td>0.6</td>
</tr>
<tr>
<td>0.07</td>
<td>0.7</td>
</tr>
<tr>
<td>0.08</td>
<td>0.8</td>
</tr>
<tr>
<td>0.09</td>
<td>0.9</td>
</tr>
<tr>
<td>0.10</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Ebasline - Average, Wednesday, September 22, 2010 2:10:28 PM

---

13
Figure 2

Particle Size Distribution

<table>
<thead>
<tr>
<th>Size [μm]</th>
<th>Volume [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>0.02</td>
<td>0.00</td>
</tr>
<tr>
<td>0.02</td>
<td>0.00</td>
</tr>
<tr>
<td>0.03</td>
<td>0.00</td>
</tr>
<tr>
<td>0.03</td>
<td>0.00</td>
</tr>
<tr>
<td>0.04</td>
<td>0.00</td>
</tr>
<tr>
<td>0.04</td>
<td>0.00</td>
</tr>
<tr>
<td>0.05</td>
<td>0.00</td>
</tr>
<tr>
<td>0.05</td>
<td>0.00</td>
</tr>
<tr>
<td>0.06</td>
<td>0.00</td>
</tr>
<tr>
<td>0.06</td>
<td>0.00</td>
</tr>
<tr>
<td>0.07</td>
<td>0.00</td>
</tr>
<tr>
<td>0.07</td>
<td>0.00</td>
</tr>
<tr>
<td>0.08</td>
<td>0.00</td>
</tr>
<tr>
<td>0.08</td>
<td>0.00</td>
</tr>
<tr>
<td>0.09</td>
<td>0.00</td>
</tr>
<tr>
<td>0.09</td>
<td>0.00</td>
</tr>
<tr>
<td>0.10</td>
<td>0.00</td>
</tr>
<tr>
<td>0.10</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Ebasline - Average, Wednesday, September 22, 2010 2:57:11 PM
Figure 3

Particle Size Distribution

| d(0.1): 15.746 μm | d(0.5): 86.998 μm | d(0.9): 425.548 μm |

- Ebastine - Average, Wednesday, September 22, 2010 3:37:53 PM

<table>
<thead>
<tr>
<th>Size (μm)</th>
<th>Volume %</th>
<th>Size (μm)</th>
<th>Volume %</th>
<th>Size (μm)</th>
<th>Volume %</th>
<th>Size (μm)</th>
<th>Volume %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>0.02</td>
<td>0.015</td>
<td>0.05</td>
<td>0.09</td>
<td>0.02</td>
<td>0.015</td>
<td>0.05</td>
</tr>
<tr>
<td>0.02</td>
<td>0.02</td>
<td>0.029</td>
<td>0.04</td>
<td>0.09</td>
<td>0.03</td>
<td>0.029</td>
<td>0.04</td>
</tr>
<tr>
<td>0.03</td>
<td>0.03</td>
<td>0.036</td>
<td>0.04</td>
<td>0.09</td>
<td>0.03</td>
<td>0.036</td>
<td>0.04</td>
</tr>
<tr>
<td>0.04</td>
<td>0.04</td>
<td>0.044</td>
<td>0.04</td>
<td>0.09</td>
<td>0.03</td>
<td>0.044</td>
<td>0.04</td>
</tr>
<tr>
<td>0.06</td>
<td>0.06</td>
<td>0.069</td>
<td>0.04</td>
<td>0.09</td>
<td>0.03</td>
<td>0.069</td>
<td>0.04</td>
</tr>
<tr>
<td>0.08</td>
<td>0.08</td>
<td>0.088</td>
<td>0.04</td>
<td>0.09</td>
<td>0.03</td>
<td>0.088</td>
<td>0.04</td>
</tr>
<tr>
<td>0.10</td>
<td>0.10</td>
<td>1.060</td>
<td>0.25</td>
<td>0.09</td>
<td>0.03</td>
<td>1.060</td>
<td>0.25</td>
</tr>
</tbody>
</table>
We claim:

1. A process for preparation of pure Ebastine, said process comprising reaction of 1-[4-(1, 1-dimethyl ethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one (compound II) and diphenyl methanol in presence of dehydrating agent in organic solvent system to obtain Ebastine fumarate salt (compound IV) in organic solvent.

2. The process as claimed in claim 1 wherein the organic solvent is selected from high boiling solvent such as toluene, xylene, methyl isobutyl ketone and dichloroethane, preferably toluene.

3. The process as claimed in any one of claims 1 wherein the dehydrating agent is selected from p-toluenesulphonic acid monohydrate (PTSA), sulphuric acid, methane sulphonic acid, phosphorous pentoxide, titanium tetrachloride and dicyclohexylcarbodiimide (DCC), preferably p-toluenesulphonic acid monohydrate.

4. The process as claimed in claim 1 wherein the reaction is carried out at refluxing temperature of the solvent to remove water as an azeotrope.

5. The process as claimed in claim 4 wherein the reaction is carried out for 6-8 hours.

6. The process as claimed in claim 1 wherein the organic solvent for obtaining Ebastine fumarate salt (compound IV) is selected from alcohols, nitriles, esters, hydrocarbons, ketonic solvents and mixtures thereof.

7. The process as claimed in claim 6 wherein the alcohol is selected from methanol, ethanol and isopropanol.

8. The process as claimed in claim 6 wherein the nitrile is selected from acetonitrile or propionitrile.

9. The process as claimed in claim 6 wherein the ester is selected from ethyl acetate, propyl acetate, butyl acetate; preferably ethyl acetate.

10. The process as claimed in claim 1 further comprising the preparation of pure Ebastine from Ebastine fumarate salt (IV) using base in organic solvent.

11. The process as claimed in claim 10 wherein the base is selected from alkali metal hydroxides, carbonates, bicarbonates, ammonia, tertiary amines and mixtures thereof, preferably sodium hydroxide.

12. The process as claimed in claim 10 wherein the organic solvent is selected from C<sub>1</sub>-C<sub>6</sub> alcohols, hexane, cyclohexane, diisopropyl ether and mixtures thereof.

13. The process as claimed in claim 12 wherein the C<sub>1</sub>-C<sub>6</sub> alcohols is selected from methanol, ethanol, and propanol; preferably methanol.
14. The process as claimed in claim 1 wherein 1-[4-(1, 1-dimethyl ethyl) phenyl]-4-(4-hydroxy piperidin-1-yl) butan-1-one compound (II) preparation comprising of coupling reaction between compound (I) and 4-hydroxy piperidine in presence of a base in organic solvent system, and obtain directly from a mixture of ethyl acetate and n-hexane directly without any further purification.

15. The process as claimed in claim 1 wherein the obtained Ebastine particles are with maximum particle size of more than 1000 μm.

16. The process as claimed in claim 1 wherein the obtained Ebastine has particle size D90 between 250 μm to 1000 μm.

17. Non-micronized Ebastine particles with particle size D [V, 0.9] value within the range of 250 μm to 1000 μm.

18. Non-micronized Ebastine particles with maximum particle size of more than 1000 μm.

19. A pharmaceutical composition comprising non-micronized Ebastine particles with particle size D [V, 0.9] value within the range of 250 μm to 1000 μm.

20. The pharmaceutical composition according to claim 19, wherein the composition is in the form of solid dosage form.

21. The pharmaceutical composition according to claim 20, wherein the composition is in the form of tablet.

22. The pharmaceutical composition according to claim 21, which further comprises pharmaceutically acceptable inert excipients.

23. The pharmaceutical composition according to claim 22, wherein the pharmaceutically acceptable inert excipients are selected from one or more of diluents, binders, surfactants, disintegrants, lubricants, glidants, solvents, sweeteners and flavoring agents.

24. A process for preparing tablet as claimed in claim 21 comprising the steps of,

i. Dissolving non micronized Ebastine in a suitable solvent optionally with pharmaceutically acceptable inert excipients to form a solution,

ii. Adding pharmaceutically acceptable inert excipients to form a mixture,

iii. Granulating the mixture in step (ii) with solution formed in step (i) to form granules,

iv. Compressing the granules formed in step (iii) using suitable toolings.

25. The process for preparing a composition according to claim 24, wherein the suitable solvent is one or more of isopropyl alcohol, methylene chloride and water.
### Classification of Subject Matter

**IPC:** C07D 211/46 (2006.01), A61K 31/4515 (2006.01)

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

### Fields Searched

Minimum documentation searched (classification system followed by classification symbols)

**IPC:** C07D, A61K

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, X-FULL

### Documents Considered to be Relevant

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>ES 2231043 A1 (LABORATORIOS CINFA, S.A.) 01 May 2005 (01.05.2005) The whole document</td>
<td>19-25</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

* 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 but published on or after the international filing date
- **L** document which may throw doubts on priority claim(s) 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 prior to the international filing date but later than the priority date claimed

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

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

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

**&** document member of the same patent family

---

**Date of the actual completion of the international search:**
09 May 2011 (09.05.2011)

**Date of mailing of the international search report:**
17 May 2011 (17.05.2011)

**Name and mailing address of the ISA/AT**
Austrian Patent Office
Dresdner Straße 87, A-1200 Vienna
Facsimile No. +43 / 1 / 534 24-535

**Authorized officer**
WIEDERMANN J.
Telephone No. +43 / 1 / 534 24-187

---

Form PCT/ISA/210 (second sheet) (July 2009)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO A1 2009157006</td>
<td>WO A1 2009157006</td>
<td>2009-12-30</td>
</tr>
</tbody>
</table>