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(54) Title: NASALLY ADMINISTRABLE, BIOAVAILABLE PHARMACEUTICAL COMPOSITION OF LORATADINE

(57) Abstract: The present invention relates to nasally administrable, bioavailable pharmaceutical compositions of loratadine for the treatment of allergic rhinitis and processes for their preparation. These formulations include a solid dispersion of loratadine with a carrier in an aqueous vehicle and provide the same bioavailability as an oral dosage form at reduced dose.



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**NASALLY ADMINISTRABLE, BIOAVAILABLE
PHARMACEUTICAL COMPOSITION OF LORATADINE**

Technical Field of the Invention

The present invention relates to nasally administrable, bioavailable pharmaceutical
5 compositions of loratadine for the treatment of allergic rhinitis and processes for their
preparation.

Background of the Invention

Loratadine is a long acting, non-sedating histamine-1-receptor (H-1 receptor)
antagonist. Loratadine is used in the treatment of the symptoms of allergic reactions, such
10 as, for example, the relief of nasal and non-nasal symptoms associated with seasonal or
perennial allergic rhinitis.

Nasal administration is suggested as an alternative route for compounds that have
poor intestinal absorption or high hepatic first pass metabolism. Nasal administration
often provides more rapid or complete absorption than the oral route. The reasons
15 attributed are: (1) the nose has a large surface area available for drug absorption due to the
coverage of the epithelial surface by numerous microvilli; (2) the sub-epithelial layer is
highly vascularised; and (3) venous blood from the nose passes directly into the systemic
circulation and, therefore, avoids the loss of drug by first pass metabolism in the liver.

It has been observed that the local application of anti-histamines on a mucosal
20 surface, such as nasal mucosa, is associated with adverse effects particularly on cilia
present on these surfaces. These adverse effects include inhibition of ciliary movement
and hypersensitivity reactions. The anti-histamines of the phenothiazines class are
strongly associated with hypersensitivity reactions. Thus, for these reasons, the local
application of anti-histamines for the treatment of diseases such as allergic rhinitis has not
25 been fully explored.

Summary of the Invention

In one general aspect there is provided a nasally administrable, bioavailable
pharmaceutical composition of a solid dispersion of loratadine in a carrier.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the pharmaceutical composition may have a bioavailability that is similar to an orally administered composition of loratadine. The pharmaceutical composition may have a bioavailability that is similar to an orally administered composition of loratadine, at a reduced dose. The pharmaceutical composition may have a bioavailability that is similar to an orally administered composition of loratadine, at 1/5th of the oral dose. Upon nasal administration the pharmaceutical composition may cause reduced side effects relative to an orally administered pharmaceutical composition of loratadine. For example, upon nasal administration the pharmaceutical composition may be free from nasal irritation. The pharmaceutical composition may be intended to treat allergic rhinitis.

The loratadine concentration may be from about 0.1 mg/mL to about 15 mg/mL weight by volume of the pharmaceutical composition; or, more particularly, from about 1mg/mL to about 10mg/mL weight by volume of the pharmaceutical composition.

The solid dispersion of loratadine with a carrier may be in a pharmaceutically acceptable aqueous vehicle. The carrier may be selected from one or more of cyclodextrin, polyethylene glycol, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropylcellulose, and carboxymethylcellulose. In particular, the carrier may be cyclodextrin. In the pharmaceutical composition, the ratio of loratadine to cyclodextrin may be from about 1:20 to about 1: 40 weight by weight. More particularly, the ratio of loratadine to cyclodextrin may be from about 1:25 to about 1: 35 weight by weight.

The cyclodextrin concentration may be from about 1% to about 50% weight by volume. More particularly, the cyclodextrin concentration may be from about 1% to about 40% weight by volume. Even more particularly, the cyclodextrin concentration may be from about 1% to about 30% weight by volume. The cyclodextrin is selected from one or more of α -cyclodextrin, β -cyclodextrin and γ -cyclodextrin. In particular, the cyclodextrin may be β -cyclodextrin and, more particularly, the β -cyclodextrin may be hydroxypropyl- β -cyclodextrin. The β -cyclodextrin may be sulphobutylether- β -cyclodextrin.

The pharmaceutically acceptable aqueous vehicle may be one or both of purified water and water for injection. The pharmaceutical composition may further include one or more of tonicity adjusting agents, pH modifiers, buffers viscosity enhancers, and

preservatives. The tonicity adjusting agent may be selected from one or more of sodium chloride, glucose, mannitol sorbitol, xylitol and glycerol. In particular, the tonicity adjusting agent may be sodium chloride.

5 The pH modifier may be selected from an acid or a base. If the pH modifier is an acid, the acid may be one or both of citric acid and hydrochloric acid. If the pH modifier is a base, the base may be one or both of sodium hydroxide and sodium citrate.

The buffer may be selected from one or more of phosphate, acetate and citrate buffer. The viscosity enhancer may be selected from one or more of xanthan gum, carboxymethyl cellulose, chitosan, hydroxypropyl cellulose, hydroxypropyl
10 methylcellulose, hydroxymethyl cellulose, hydroxyethylcellulose, carboxyvinyl polymer and combinations thereof.

The pH of the aqueous pharmaceutical composition may be from about 4 to about 8. In particular, the pH of the aqueous pharmaceutical composition may be from about 5 to about 8.

15 In another general aspect there is provided a process for preparing a nasally administrable bioavailable pharmaceutical composition of loratadine. The process includes preparing a solid dispersion of loratadine with a carrier in a pharmaceutically acceptable aqueous vehicle.

Embodiments of the process may include one or more of the following features or
20 those described above. For example, the carrier may be selected from one or more of cyclodextrin, polyethylene glycol, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropylcellulose, and carboxymethylcellulose. In particular, the carrier may be cyclodextrin.

Preparing a solid dispersion may include dissolving loratadine in a
25 pharmaceutically acceptable aqueous vehicle in the presence of one or more cyclodextrins to form a water-soluble loratadine-cyclodextrin complex. The ratio of loratadine to cyclodextrin may be from about 1:20 to about 1: 40 weight by weight. More particularly, the ratio of loratadine to cyclodextrin may be from about 1:25 to about 1: 35 weight by weight. The cyclodextrin concentration may be from about 1% to about 50% weight by
30 volume. In particular, the cyclodextrin concentration may be from about 1% to about 30%

weight by volume. The cyclodextrin may be selected from one or more of α -cyclodextrin, β -cyclodextrin and γ -cyclodextrin. In particular, the cyclodextrin may be β -cyclodextrin and, more particularly, the β -cyclodextrin may be hydroxypropyl- β -cyclodextrin. The β -cyclodextrin may be sulphobutylether- β -cyclodextrin.

5 The pharmaceutically acceptable aqueous vehicle may be one or both of purified water and water for injection. The vehicle may further include one or more of tonicity adjusting agents, pH modifiers, buffers viscosity enhancers and preservatives. The tonicity adjusting agent may be selected from one or more of sodium chloride, glucose, mannitol, sorbitol, xylitol and glycerol. The pH modifier may be selected from an acid or
10 a base. The pH of the pharmaceutical composition may be from about 4 to about 8. The buffer may be selected from one or both of phosphate, acetate and citrate buffer. The viscosity enhancer may be selected from one or more of xanthan gum, carboxymethyl cellulose, chitosan, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxymethyl cellulose, hydroxyethylcellulose, carboxyvinyl polymer and combinations
15 thereof.

In another general aspect there is provided a method of treating allergic rhinitis. The method includes nasally administering a bioavailable pharmaceutical composition of loratadine.

Embodiments of the method of treating allergic rhinitis may include one or more of
20 the following features or those described above. For example, the pharmaceutical composition may include a solid dispersion of loratadine with a carrier in a pharmaceutically acceptable aqueous vehicle.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be
25 apparent from the description and claims.

Description of the Invention

Loratadine is currently available in oral dosage forms, such as conventional tablets, orally disintegrating tablets and syrups. Loratadine is extensively metabolized in the liver prior to availability in systemic circulation. An alternative route is desirable that can
30 provide therapeutic plasma levels of loratadine, rapid onset of action, ease of

administration and reduced side effects in comparison to oral administration. These advantages should be offered by administration of loratadine by nasal route. However, no commercial dosage form of loratadine is believed to be available which can be administered by nasal route. We have surprisingly found a pharmaceutical composition of loratadine that can alleviate symptoms of allergic rhinitis when administered by nasal route. The nasal administration of these aqueous pharmaceutical compositions of loratadine requires only a fraction of the oral dose of loratadine to elicit a therapeutic response. The reduced amount of drug also considerably reduces the adverse effects.

The onset of action is fast due to rapid absorption from mucosal surface. It may also contribute to alleviating symptoms of allergic rhinitis by local effect. The nasally administrated loratadine pharmaceutical compositions described herein generally are stable and free from particulate matter, thereby being non-irritating to the nasal mucosa. The process for the preparation of these aqueous pharmaceutical compositions of loratadine is simple, less time consuming and hence economical.

Loratadine is practically insoluble in water and shows the highest solubility in a solution having a pH between pH 2 to 3. However, such a formulation of pH 2 to 3 would cause irritation to nasal mucosa. An aqueous formulation of loratadine having a pH of about 7 would be desirable.

We have developed an aqueous pharmaceutical composition comprising loratadine having a pH suitable for nasal administration. Particularly, these formulations have a pH of from about 4 to about 8, more particularly from about 5 to about 8. These formulations comprise a solid dispersion of loratadine with a carrier in a pharmaceutically acceptable aqueous vehicle. Generally, the solid dispersion may be prepared by dissolving loratadine and the carrier in a common solvent followed by removal of the solvent by evaporation. The dried solid dispersion can then be incorporated in a pharmaceutically acceptable vehicle. The carrier may be selected from cyclodextrin, polyethylene glycol, polyvinylpyrrolidone, and cellulose derivatives such as hydroxypropyl methylcellulose, hydroxypropylcellulose, carboxymethylcellulose and the like.

In one embodiment, there is provided an aqueous formulation of loratadine comprising a solid dispersion of loratadine with cyclodextrin which forms a water-soluble complex of loratadine with cyclodextrin. The concentration of loratadine in aqueous

compositions can be from about 0.1 mg/mL to about 15 mg/mL and particularly from about 1 mg/mL to about 10 mg/mL weight by volume of the composition.

Cyclodextrins (CD) are cyclic oligosaccharides typically containing 6(α -CD), 7(β -CD), or 8(γ -CD) glucopyranose units. The present compositions include derivatives of cyclodextrins such as alkyl and alkoxy substituted cyclodextrins. Particularly suitable derivatives include β -cyclodextrins such as dimethyl- β -cyclodextrins, trimethyl- β -cyclodextrins, sulphobutylether- β -cyclodextrins and hydroxypropyl- β -cyclodextrin. A particularly suitable cyclodextrin is hydroxypropyl- β -cyclodextrin.

The concentration of cyclodextrin can be from about 1% to about 50%, particularly from about 1% to about 40%, more particularly from about 1% to about 30% weight by volume of the composition. Generally, 15% weight by volume solution of a cyclodextrin such as hydroxypropyl- β -cyclodextrin is able to solubilize 0.5% weight by volume of loratadine. The solubility of loratadine has been found to be directly proportional to the concentration of cyclodextrin. For example, a 30% weight by volume solution of hydroxypropyl- β -cyclodextrin solubilizes about 1.0% weight by volume of loratadine. The amount of loratadine that can be solubilized depends upon the type and amount of cyclodextrin being used. Generally, the ratio of loratadine to cyclodextrin is from about 1:20 to about 1:40 weight by weight, particularly from about 1:25 to about 1:35 weight by weight.

The pharmaceutically acceptable aqueous vehicle can be purified water or water for injection. The vehicle can further include isotonicity adjusting agents such as sodium chloride, glucose, mannitol, sorbitol, xylitol and glycerol; pH modifiers including acids such as citric acid and hydrochloric acid, and bases such as sodium hydroxide and sodium citrate; buffers such as phosphate, acetate and citrate buffer. Additionally, viscosity enhancers can also be included. Suitable viscosity enhancers include xanthan gum and cellulosic ethers such as methyl cellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose and the like. Also the present compositions described herein can include preservatives such as benzalkonium chloride, benzyl alcohol, chlorhexidine gluconate and disodium EDTA. Generally, the concentration of the preservative can be from about 0.001% to about 2% depending upon the selected preservative.

A typical composition for nasal delivery will include from about 0.1 mg/mL to about 15 mg/mL of loratadine, in a 1% to about 50% weight by volume solution of a cyclodextrin prepared in a pharmaceutically acceptable aqueous vehicle such as water.

5 The aqueous pharmaceutical compositions of the invention can be prepared by any conventional technique known in the art. For example, in one process cyclodextrin is dissolved in a pharmaceutically acceptable aqueous vehicle and loratadine is added to the solution with stirring to give a clear solution. The process can be accelerated by heating.

10 The present formulation can be administered in the nasal cavity using a spray device such as those supplied by Valois and Pfeiffer. These devices may be single dose or multi-dose systems. Depending upon the choice of whether a preservative-free pump is used, such as the VP7/100 D CS 20 Ag supplied by Valois, the aqueous vehicle may or may not include preservatives. Generally, these aqueous compositions are to be administered in the form of spray but they can also be instilled into the nose with a dropper. A typical dosage range for a 5 mg/mL loratadine nasal spray composition
15 include from about 45 μ L to about 300 μ L per nostril, particularly from about 50 μ L to about 200 μ L per nostril, and more particularly from about 60 μ L to about 150 μ L per nostril.

The following examples are provided for the purpose of illustrating the invention and are not intended to limit the scope of the inventions in any way.

20 **EXAMPLE 1**

An aqueous pharmaceutical composition was prepared comprising loratadine (5mg/ml), hydroxypropyl- β -cyclodextrin (15% w/v) and water for injection as follows.

Each ml of the composition contains:

Loratadine	5mg
25 Hydroxypropyl- β -cyclodextrin	15% w/v
Water for injection q.s to	1 ml

Procedure:

1. The hydroxypropyl- β -cyclodextrin was dissolved in water for injection.
2. The solution was heated to 60-70°C and loratadine added to it with continuous stirring until a clear solution was obtained.
- 5 3. The volume was made up with water for injection.
4. The solution was filtered through a 0.2 μ nylon filter and filled into USP Type I clear glass vials (15-30ml).
5. The vials were sealed with metered dose nasal spray pumps.
6. Actuators were placed on the nasal spray pumps.
- 10 The stability of the aqueous composition prepared according to Example 1 was determined after storage at 40°C and 75% relative humidity (RH) for a period of 3 months. The results of the stability studies are summarized in Table 1.

Table 1. Stability data of loratadine nasal spray composition prepared as per Example 1 stored at 40°C and 75% relative humidity for three months

S. No.	Condition	Description	pH	Assay (mg/ml)	Particulate Matter
1	Initial	Clear colourless liquid	6.91	5.10	No particulate matter
2	40°C/75% RH for 1 month	Clear colourless liquid	6.85	5.17	No particulate matter
3	40°C/75% RH for 2 months	Clear colourless liquid	6.87	5.18	No particulate matter
4	40°C/75% RH for 3 months	Clear colourless liquid	6.84	5.15	No particulate matter

- 15 The data in Table 1 clearly indicates that the loratadine nasal spray composition prepared according to Example 1 is stable.

EXAMPLE 2

A sub-nasal toxicity study was conducted in Sprague Dawley rats to determine the toxicity profile of the aqueous loratadine nasal spray composition (5mg/ml) of Example 1 when applied daily for 90 days in the nasal cavity of rats. The loratadine nasal spray composition of Example 1 was administered to rats via the nasal route at dose levels ranging from 0 ml/animal to 0.4 ml/animal. Male and female animals from control and different dose groups survived through the dosing period of 90 days and recovery period of 28 days. No significant dose related signs of intoxication were observed in the animals during the dosing and recovery periods. The animals showed normal food intake and body weight gain throughout the study. Ophthalmologic examination conducted prior to and at the end of dosing did not reveal any abnormality attributable to the treatment. Haematological investigations in the control and test groups at the end of the dosing period and recovery showed no abnormalities. Clinical chemistry and urine analysis did not reveal any abnormality and organ weight data of the test animals was found to be comparable to the respective control animals. Histopathological examination of nasal cavity and other organs was found normal and showed no abnormalities.

EXAMPLE 3

An open label, non-comparative, two dose-level study was conducted to assess the efficacy and tolerability of loratadine nasal spray (5 mg/ml). Loratadine nasal spray was administered as two sprays per nostril either once a day or twice a day to a total of 44 patients. Twenty one patients received loratadine 4 mg (2 mg bid) and 23 patients received loratadine 2 mg (once a day) for two weeks. Nasal symptoms such as rhinorrhoea, nasal stiffness, nasal itching and sneezing were assessed. The results are presented below in Table 2.

Table 2. Efficacy and tolerability studies of Loratadine nasal spray

Parameter		Dose 4 mg/day	Dose 2 mg/day
Reduction in frequency of total nasal symptoms score from baseline		64.7%	72.6%
Reduction in severity of nasal symptoms		70.9%	68.3%
Reduction in total mean rhinoscopic symptoms (swelling, hyperemia, excess, secretion and obstruction)		71%	78%
Global assessment	Patients	52.4%	34.8%
	Physician	62%	47.8%

EXAMPLE 4

A single dose, randomized, two treatment, two way cross-over study was conducted to evaluate the pharmacokinetic parameters and to compare the bioavailability of loratadine nasal spray (test, 5 mg/ml) and loratadine 10 mg oral tablets (reference) in twelve healthy, human male volunteers.

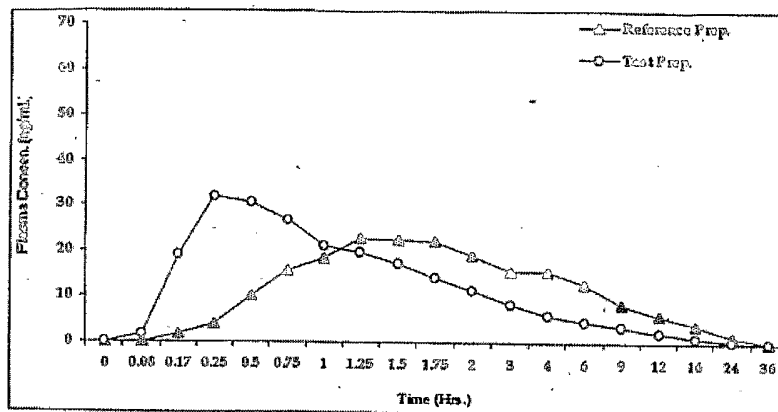
The reference dose was one tablet containing loratadine 10 mg and the test preparation dose was two nasal sprays, in each nostril, i.e., each spray delivered 100 μ L/spray or a total of 2 mg of loratadine. The various pharmacokinetic parameters were evaluated and are provided below in Table 3.

Table 3. Pharmacokinetic Parameters of Loratadine Nasal Spray versus Loratadine tablet

Parameter	Loratadine oral tablet 10 mg	Loratadine Nasal Spray 2 mg
$C_{\max}$ (ng/ml)	31.42 ± 16.16	35.94 ± 14.86
$T_{\max}$ (hr)	1.60 ± 0.84	0.36 ± 0.21
$AUC_{(0-36)}$ (ng.hr/ml)	194.93 ± 94.67	101.97 ± 56.40

Graph-1 shows the bioavailability of nasal spray in comparison to oral tablet.

GRAPH 1. MEAN PLASMA CONCENTRATION-TIME PROFILE OF TWELVE VOLUNTEERS SHOWING LORATADINE PLASMA LEVELS GIVEN BY ORAL TABLET AND NASAL SPRAY.



5 On the basis of comparison of the $AUC_{(0-36)}$ after single administration, the relative bioavailability of the nasal spray was found to be 52.31% of that of the reference.

Although the invention has been described in connection with specific embodiments, various modifications and variations of the described compositions and their methods of use as well as the concept of the invention will be apparent to those skilled in the art. Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. For example, the present formulation may include preservatives such as benzalkonium chloride, viscosity enhancers such as the water-soluble cellulosic ethers as disclosed in Examples 5, 6, 7 and 8 given below.

15 **EXAMPLE 5**

Loratadine	5 mg
Hydroxypropyl- β -cyclodextrin	15% w/v
Benzalkonium chloride	0.02%
Water for injection q.s to	1 ml

20 **EXAMPLE 6**

Loratadine	10 mg
Hydroxypropyl- β -cyclodextrin	30% w/v

Benzalkonium chloride	0.02%
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Water for injection q.s to	1 ml
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EXAMPLE 7

Loratadine	5 mg
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5 Hydroxypropyl- β -cyclodextrin	15% w/v
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Benzalkonium chloride	0.02%
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Hydroxypropylmethylcellulose	2-3%
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Water for injection q.s to	1 ml
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EXAMPLE 8

10 Loratadine	5 mg
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Hydroxypropyl- β -cyclodextrin	15% w/v
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Hydroxypropylmethylcellulose	2-3%
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Water for injection q.s to	1 ml
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WE CLAIM:

- 1 1. A nasally administrable, bioavailable pharmaceutical composition comprising a
2 solid dispersion of loratadine in a carrier.
- 1 2. The pharmaceutical composition according to claim 1 wherein the pharmaceutical
2 composition has a bioavailability that is similar to an orally administered
3 composition of loratadine.
- 1 3. The pharmaceutical composition according to claim 1 wherein the pharmaceutical
2 composition has a bioavailability that is similar to an orally administered
3 composition of loratadine, at a reduced dose.
- 1 4. The pharmaceutical composition according to claim 1 wherein the pharmaceutical
2 composition has a bioavailability that is similar to an orally administered
3 composition of loratadine, at 1/5th of the oral dose.
- 1 5. The pharmaceutical composition according to claim 1 wherein upon nasal
2 administration the pharmaceutical composition causes reduced side effects relative
3 to an orally administered pharmaceutical composition of loratadine.
- 1 6. The pharmaceutical composition according to claim 1 wherein upon nasal
2 administration the pharmaceutical composition is free from nasal irritation.
- 1 7. The pharmaceutical composition according to claim 1 wherein the loratadine
2 concentration comprises from about 0.1 mg/mL to about 15 mg/mL weight by
3 volume.
- 1 8. The pharmaceutical composition according to claim 7 wherein loratadine
2 concentration is from about 1mg/mL to about 10mg/mL weight by volume of the
3 pharmaceutical composition.
- 1 9. The pharmaceutical composition according to claim 1 wherein the solid dispersion
2 of loratadine with the carrier is in a pharmaceutically acceptable aqueous vehicle.
- 1 10. The pharmaceutical composition according to claim 9 wherein the carrier is
2 selected from one or more of cyclodextrin, polyethylene glycol,

- 3 polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropylcellulose,
4 and carboxymethylcellulose.
- 1 11. The pharmaceutical composition according to claim 10 wherein the carrier
2 comprises cyclodextrin.
- 1 12. The pharmaceutical composition according to claim 11 wherein the ratio of
2 loratadine to cyclodextrin comprises from about 1:20 to about 1: 40 weight by
3 weight.
- 1 13. The pharmaceutical composition according to claim 12 wherein the ratio of
2 loratadine to cyclodextrin comprises from about 1:25 to about 1: 35 weight by
3 weight.
- 1 14. The pharmaceutical composition according to claim 11 wherein the cyclodextrin
2 concentration is from about 1% to about 50% weight by volume.
- 1 15. The pharmaceutical composition according to claim 14 wherein the cyclodextrin
2 concentration is from about 1% to about 40% weight by volume.
- 1 16. The pharmaceutical composition according to claim 15 wherein the cyclodextrin
2 concentration is from about 1% to about 30% weight by volume.
- 1 17. The pharmaceutical composition according to claim 11 wherein the cyclodextrin is
2 selected from one or more of α -cyclodextrin, β -cyclodextrin and γ -cyclodextrin.
- 1 18. The pharmaceutical composition according to claim 17 wherein the cyclodextrin
2 comprises β -cyclodextrin.
- 1 19. The pharmaceutical composition according to claim 18 wherein the β -cyclodextrin
2 comprises hydroxypropyl- β -cyclodextrin.
- 1 20. The pharmaceutical composition according to claim 18 wherein the β -cyclodextrin
2 comprises sulphobutylether- β -cyclodextrin.
- 1 21. The pharmaceutical composition according to claim 9 wherein the
2 pharmaceutically acceptable aqueous vehicle comprises one or both of purified
3 water and water for injection.

- 1 22. The pharmaceutical composition according to claim 9 wherein the pharmaceutical
2 composition further comprises one or more of tonicity adjusting agents, pH
3 modifiers, buffers viscosity enhancers, and preservatives.
- 1 23. The pharmaceutical composition according to claim 22 wherein the tonicity
2 adjusting agent is selected from one or more of sodium chloride, glucose, mannitol
3 sorbitol, xylitol and glycerol.
- 1 24. The pharmaceutical composition according to claim 23 wherein the tonicity
2 adjusting agent comprises sodium chloride.
- 1 25. The pharmaceutical composition according to claim 22 wherein the pH modifier is
2 selected from an acid or a base.
- 1 26. The pharmaceutical composition according to claim 25 wherein the pH modifier is
2 an acid and the acid comprises one or both of citric acid and hydrochloric acid.
- 1 27. The pharmaceutical composition according to claim 25 wherein the pH modifier is
2 a base and the base comprises one or both of sodium hydroxide and sodium citrate.
- 1 28. The pharmaceutical composition according to claim 22 wherein the buffer is
2 selected from one or more of phosphate, acetate and citrate buffer.
- 1 29. The pharmaceutical composition according to claim 22 wherein the viscosity
2 enhancer is selected from one or more of xanthan gum, carboxymethyl cellulose,
3 chitosan, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxymethyl
4 cellulose, hydroxyethylcellulose, carboxyvinyl polymer and combinations thereof.
- 1 30. The pharmaceutical composition according to claim 1 wherein the pH of the
2 aqueous pharmaceutical composition is from about 4 to about 8.
- 1 31. The pharmaceutical composition according to claim 1 wherein the pH of the
2 aqueous pharmaceutical composition is from about 5 to about 8.
- 1 32. The pharmaceutical composition according to claim 1 wherein the pharmaceutical
2 composition is intended to treat allergic rhinitis.

- 1 33. A process for the preparation of a nasally administrable bioavailable
2 pharmaceutical composition of loratadine, the process comprising preparing a solid
3 dispersion of loratadine with a carrier in a pharmaceutically acceptable aqueous
4 vehicle.
- 1 34. The process according to claim 33 wherein the carrier is selected from one or more
2 of cyclodextrin, polyethylene glycol, polyvinylpyrrolidone, hydroxypropyl
3 methylcellulose, hydroxypropylcellulose, and carboxymethylcellulose.
- 1 35. The process according to claim 34 wherein the carrier comprises cyclodextrin.
- 1 36. The process according to claim 33 wherein preparing a solid dispersion comprises
2 dissolving loratadine in a pharmaceutically acceptable aqueous vehicle in the
3 presence of one or more cyclodextrins to form a water-soluble loratadine-
4 cyclodextrin complex.
- 1 37. The process according to claim 36 wherein the ratio of loratadine to cyclodextrin is
2 from about 1:20 to about 1: 40 weight by weight.
- 1 38. The process according to claim 36 wherein the ratio of loratadine to cyclodextrin is
2 from about 1:25 to about 1: 35 weight by weight.
- 1 39. The process according to claim 36 wherein the cyclodextrin concentration is from
2 about 1% to about 50% weight by volume.
- 1 40. The process according to claim 36 wherein the cyclodextrin concentration is from
2 about 1% to about 30% weight by volume.
- 1 41. The process according to claim 34 wherein the cyclodextrin is selected from one or
2 more of α -cyclodextrin, β -cyclodextrin and γ -cyclodextrin.
- 1 42. The process according to claim 33 wherein the pharmaceutically acceptable
2 aqueous vehicle comprises one or both of purified water and water for injection.
- 1 43. The process according to claim 33 wherein the vehicle further comprises one or
2 more of tonicity adjusting agents, pH modifiers, buffers viscosity enhancers and
3 preservatives.

- 1 44. The process according to claim 43 wherein the tonicity adjusting agent is selected
2 from one or more of sodium chloride, glucose, mannitol, sorbitol, xylitol and
3 glycerol.
- 1 45. The process according to claim 43 wherein the pH modifier is selected from an
2 acid or a base.
- 1 46. The process according to claim 43 wherein the buffer is selected from one or both
2 of phosphate, acetate and citrate buffer.
- 1 47. The process according to claim 43 wherein the viscosity enhancer is selected from
2 one or more of xanthan gum, carboxymethyl cellulose, chitosan, hydroxypropyl
3 cellulose, hydroxypropyl methylcellulose, hydroxymethyl cellulose,
4 hydroxyethylcellulose, carboxyvinyl polymer and combinations thereof.
- 1 48. The process according to claim 33 wherein the pH of the pharmaceutical
2 composition is from about 4 to about 8.
- 1 49. A method of treating allergic rhinitis, the method comprising nasally administering
2 a bioavailable pharmaceutical composition of loratadine.
- 1 50. The method according to claim 49 wherein the pharmaceutical composition
2 comprises a solid dispersion of loratadine with a carrier in a pharmaceutically
3 acceptable aqueous vehicle.