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(54) **METHOD AND COMPOSITION FOR TREATING RHINITIS**

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(57) **ABSTRACT**

A pharmaceutical composition for the treatment of rhinitis by nasal or ocular administration comprises zwitterionic cetirizine, polar lipid liposome, a pharmaceutical acceptable aqueous carrier and, optionally, a pharmaceutically acceptable buffer capable of providing a pH of from pH 4.0 to pH 8.0, with the proviso that, if the polar lipid comprises phospholipid, the amount of phospholipid in the composition from is from 10 mg per mL to 120 mg per mL. Also disclosed are methods for its preparation and methods for treating rhinitis by its nasal or ocular administration.

METHOD AND COMPOSITION FOR TREATING RHINITIS

FIELD OF THE INVENTION

[0001] The present invention relates to a method for treating rhinitis, and to a corresponding pharmaceutical composition.

BACKGROUND OF THE INVENTION

[0002] Allergic and non-allergic rhinitis are common disorders affecting about 30% of the population. Rhinitis does have considerable impact on quality of life. In fact, rhinitis is regarded to affect the quality of life, even more so than, e.g., asthma.

[0003] Hay fever and perennial allergic rhinitis are characterised by sneezing, rhinorrhea, nasal congestion, pruritus, conjunctivitis and pharyngitis. In perennial rhinitis, chronic nasal obstruction is often prominent and may extend to eustachian tube obstruction. Oral or local antihistamines are first line treatment, and nasal steroids second line treatment for rhinitis. For most patients, topical corticosteroids and long acting antihistamine agents provide significant relief of symptoms. Antihistamines may also affect non-immunologically (non-IgE) mediated hypersensitivity reactions such as non-allergic rhinitis, exercise induced asthma, cold urticaria, and non-specific bronchial hyperreactivity.

[0004] Cetirizine dihydrochloride, [2-{4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl-}ethoxy]acetic acid is an orally and locally active, potent, long acting peripheral histamine H_1 receptor antagonist. Cetirizine is one of the most widely used second generation antihistamines for the treatment of rhino-conjunctivitis and urticaria. It is effective, well tolerated, and safe when used orally in a dose of 10 mg daily. Sedation and dry mouth do however occur as side effects in orally treated patients. Cetirizine is also approved in children for the treatment of rhinitis.

[0005] The main clinical affects of antihistamines include reduced sneezing and rhinorrhea, while nasal blockage is less responsive. Local administration of antihistamines (azelastine and levocabastine) has advantages, such as rapid onset of action and fewer side effects. At present cetirizine dihydrochloride is not an approved medicine for local administration, although it has been administered in that manner in clinical trials.

[0006] Some effect was seen on symptoms when cetirizine (presumably as di-hydrochloride) was given as a nasal spray in patients with perennial allergic rhinitis. Concentrations of 0.625, 1.25, and 2.5 mg/mL of cetirizine were sprayed three times a day for two weeks (Clement P, Roovers M H, Francillon C, Dodion P. *Dose-ranging, placebo-controlled study of cetirizine nasal spray in adults with perennial allergic rhinitis.* Allergy September 1994; 49(8):668-72). The most common side effects were related to nasal events, though no difference in incidence between the placebo and the cetirizine-treated groups were seen. However, the authors speculate that local irritation had an adverse effect on treatment efficacy. In another trial (Francillon C, Pécoud A. *Effect of nasal spray of cetirizine in a nasal provocation test with allergen.* J Allergy Clin Immunol 1993:91, Suppl 2:258 (abstract)), cetirizine nasal spray was found to reduce symptoms and increase nasal peak flow after an allergen challenge. In exercise-induced asthma, a good protective effect was seen when cetirizine mist was administered to the lung with a nebulizer (Ghosh S K, De Vos C, McIlroy I, Patel K R. *Effect of cetirizine on exercise induced asthma.* Thorax April 1991; 46(4):242-4).

[0007] Due to the irritation of the nasal mucosa by cetirizine it is necessary to decrease its immediate exposure of the drug in nasal administration. It has been reported that this can be achieved by providing cetirizine in form of a composition containing cyclodextrin (EP 0 605 203 B1).

[0008] The lipophilicity behaviour of the cationic (anion: chloride), zwitterionic, and anionic forms of cetirizine in buffered aqueous phosphatidylcholine liposome systems containing from about 1 to 33.5 mg/mL of phospholipid has been studied (Plemper van Balen G et al. *Lipophilicity behaviour of the zwitterionic antihistamine cetirizine in phosphatidylcholine liposomes/water systems.* Pharm. Res. 2001; 18:694-701. The aim with the study was to gain insight into the mechanism of interaction of the various electrical species of cetirizine with membranes. In respect of the cationic species, both hydrophobic and electrostatic interactions were found to be involved. The authors consider the zitterionic form of cetirizine, which dominates in the pH range of from about pH 4 to about pH 7, and even from about pH 3 to about pH 8, to be prevented from entry into the liposomal membrane by rendering the formation of lipophilic folded conformers of cetirizine more difficult.

OBJECTS OF THE INVENTION

[0009] It is an object of the present invention to provide a pharmaceutical composition for nasal administration of cetirizine that protects the nasal mucosa from irritation by the active agent.

[0010] It is another object of the present invention to provide a pharmaceutical composition for ocular administration of cetirizine that protects the ocular mucosa from irritation by the active agent.

[0011] Still another object of the present invention is to provide a process for the manufacture of this composition.

[0012] An additional object of the invention is to provide a method for the treatment of rhinitis by nasal administration of cetirizine which lacks at least some of the drawbacks of known methods.

[0013] Further object of the invention will become apparent from the study of the following summary of the invention, the description of preferred embodiments thereof, and the appended claims.

SUMMARY OF THE INVENTION

[0014] The present invention is based on the finding that the presence of liposomes in an aqueous cetirizine solution of a pH at which its zwitterionic form predominates, such as a pH from about pH 4 or pH 5 to about pH 7 and even pH 8, reduces or even eliminates irritation of the nasal mucosa or the ocular mucosa caused by the drug.

[0015] According to the present invention is disclosed a pharmaceutical composition for the treatment of rhinitis by nasal or ocular administration comprising zwitterionic cetirizine, polar lipid liposome, a pharmaceutical acceptable aqueous carrier and, optionally, a pharmaceutically accept-

able buffer capable of providing a pH of from pH 4 to pH 8, preferably from pH 5.0 to pH 7.0, with the proviso that, if the polar lipid comprises phospholipid, the amount of phospholipid in the composition from is from 10 or 17 mg to 120 mg per mL, more preferred from 35 mg to 70 mg per mL.

[0016] Any pharmaceutically acceptable salt of cetirizine as well as the zwitterionic form thereof can be used in the invention. Particularly preferred is the use of nitrate salts of cetirizine, most preferred of cetirizine dinitrate.

[0017] It is preferred for the composition of the invention to comprise cetirizine or a salt of cetirizine in an amount of from 1 mg/mL to 23 mg/mL calculated on the zwitterionic form, preferably in an amount of from 5.5 mg/mL to 22 mg/mL.

[0018] The composition of the invention can be administered as a nasal spray, nasal drops, and eye drops. It is also possible to administer it as a fine mist to the lungs by nebulization. Irrespective of administration route the irritating properties of cetirizine are reduced by the composition of the invention.

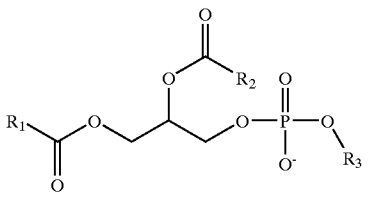
[0019] Liposomes are well known in the art. A liposome is a structure consisting of one or more concentric spheres of lipid bilayers separated by water or aqueous buffer compartments.

[0020] Numerous patents and scientific papers on liposomes have been published and the technical field of applying various lipid derivatives in combination with amphiphatic compounds such as phospholipids are well known to those skilled in the art. Liposomes can be prepared by various methods using solvents, reduced pressure, two-phase systems, freeze drying, sonication etc. described, for instance, in *Liposome Drug Delivery Systems,* Betageri G V et al., Technomic Publishing AG, Basel, Switzerland, 1993, which is incorporated herein by reference.

[0021] Liposomes may be based on phospholipids, in particular phosphatidylcholine (PC), phosphatidylglycerol (PG), phosphatidylinositol (PI), phosphatidic acid (PA), phosphatidylserine (PS), or mixtures thereof.

[0022] The phospholipids of the invention comprise polar and non-polar groups linked to a backbone entity carrying hydroxyl groups, such as glycerol. According to a preferred embodiment of the invention the phospholipid is of natural origin, preferably membrane phospholipid. According to another preferred embodiment of the invention the phospholipid is of synthetic or semi-synthetic origin.

[0023] Phospholipids can be represented by the general formula I



(I)

[0024] wherein R_1 and R_2 independently represent a saturated or unsaturated, branched or straight chain alkyl or alkylene group having 7-23 carbon atoms, preferably 11-19 carbon atoms; and R_3 represents an amide or ester bonding group, such as —CH_2—CHOH—CH_2OH (phosphatidylglycerol), —CH_2—CH_2—CH_2—$N(CH_3)_3$ (phosphatidylcholine), —CH_2—CH_2—NH_2 (phosphatidylethanolamine), H (phosphatidic acid), —CH_2—$CH(NH_2)$—COOH (phosphatidylserine).

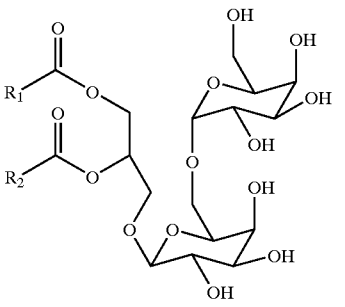
[0025] Particularly preferred phospholipids are those swelling in water, which are capable of spontaneous liposome formation. For a phospholipid to form a liposome in excess of water it is necessary that a lamellar liquid crystalline phase is formed, as with phosphatidylcholine (PC). Phosphatidylethanolamine (PE) on the other hand normally favours the reversed hexagonal phase.

[0026] If the phospholipid of the invention does not swell spontaneously in water, it is nevertheless possible to obtain liposomes from it by adding a more polar, swellable phospholipid, such as an anionic phospholipid, preferably phosphatidylglycerol.

[0027] The liposome formation can be performed at room temperature or any other temperature above 0° C. if the phase transition temperature of the acyl chains (chain melting; gel-to-liquid crystals) is below the freezing point of water, which is the case for natural phospholipids.

[0028] According to a first preferred aspect of the invention the polar lipid comprises or, more preferred, consists of glycolipid. In this application, the term glycolipid designates a compound containing one or more monosaccharide residues bound by a glycosidic linkage to a hydrophobic moiety such as an acylglycerol, a sphingoid or a ceramide (N-acylsphingoid).

[0029] According to a second preferred aspect of the invention glycolipid is a glycoglycerolipid. In this application the term glycoglycerolipid designates a glycolipid containing one or more glycerol residues. According to a particularly preferred aspect of the invention glycoglycerolipid comprises or consists of galactoglycerolipid, preferably digalactosyldiacylglycerol of the general formula (II)



[0030] R_1 and R_2 having the same meaning as in general formula (I).

[0031] According to a third preferred aspect of the invention glycolipid is a glycosphingolipid. In this application the term glycosphingolipid designates lipids containing at least one monosaccharide residue and either a sphingoid or a ceramide. Glycosphingolipid comprises neutral glycophingolipids such as mono- and oligoglycosylsphingoids as well

as mono- and oligoglycosylceramides. Most preferred are the respective mono forms. Glycosphingolipid additionally comprises acidic glycosphingolipids such as sialoglycosphingolipids, uronoglycosphingolipids, sulfoglycosphingolipids, phosphoglycosphingolipids, and phosphonoglycosphingolipids. The glycosphingolipid can be ceramide, monohexosylceramide, dihexosylceramide, sphingomyelin, lysosphingomyelin, sphingosine, or mixtures thereof. Preferably the glycosphingolipid is sphingomyelin or products derived from sphingomyelin. The sphingomyelin content is preferably established by chromatographic methods. Sphingomyelin can be extracted from milk, preferably bovine milk, brain, egg yolk or erythrocytes from animal blood, preferably sheep. Synthetic and semi-synthetic sphingolipids are comprised by the invention.

[0032] According to a fourth preferred aspect of the invention glycolipid is a glycophosphatidylinositol. In this application the term glycophosphatidylinositol designates glycolipid which contains saccharides glycosidically linked to the inositol moiety of phosphatidylinositols.

[0033] The composition of the invention may also comprise antioxidant. Antioxidants of the invention comprise alpha tocopherol, ascorbic acid, butylated hydroxyanisole, butylated hydroxytoluene, citric acid, fumaric acid, malic acid, monothioglycerol, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, potassium metabisulfite, sodium sulfite, tartaric acid, and vitamin E.

[0034] The buffer of the invention is a pharmaceutically acceptable buffer of any kind that does not interfere with the formation of liposomes, such as a phosphate, citrate, or acetate buffer, and which is capable of maintaining a pH of from about pH 4 to about pH 8 or from about pH 5.0 to about pH 7.0.

[0035] According to the invention a chelating agent may be used to reduce the metal ion catalysed oxidation of phospholipid and/or cetirizine. Examples of useful chelating agents are ethylenediaminetetraacetic acid (EDTA), ethylenediaminetriacetic acid and diethylenetriaminepentaacetic acid (DTPA). It is also possible to use other agents that protect the composition of the invention and, in particular, possible unsaturated fatty acid residues therein, from oxidation.

[0036] The composition of the invention can comprise one or more preservatives. Examples of common preservatives for liquid pharmaceutical compositions are benzalkonium chloride, benzoic acid, butylated hydroxyanisole, butylparaben, chlorbutanol, ethylparaben, methylparaben, phenoxyethanol, and phenylethyl alcohol.

[0037] To retain the composition of the invention at its application site it can also comprise viscosity-increasing agent such as, for instance, hydrophilic polymers like polyethyleneglycol, cellulose derivatives such as hydroxypropylmethyl cellulose.

[0038] Buffering agents, preservatives, viscosity-increasing agents, anti-oxidants, chelating agents and other optional additives will be selected keeping in mind that their detrimental effect on liposome stability should be kept at a minimum. For a given agent this can be ascertained by simple experiments, which are within the reach of a person skilled in the art.

[0039] According to the invention is also disclosed a process for preparing a composition of the aforementioned kind. Preferably the liposome of the invention is prepared by direct swelling of the compound in an aqueous medium without adding any other substances such as stabilizers etc. which are normally required.

[0040] In particular, according to the present invention, is disclosed a process for preparing a pharmaceutical composition for the treatment of rhinitis by nasal or ocular administration comprising zwitterionic cetirizine, polar lipid liposome, a pharmaceutical acceptable aqueous carrier and, optionally, a pharmaceutically acceptable buffer capable of providing a pH of from about pH 4 to about pH 8, preferably from about pH 5.0 to about pH 7.0, with the proviso that, if the polar lipid comprises phospholipid, the amount of phospholipid in the composition is from 10 or 17 mg to 120 mg per mL, more preferred from 35 mg to 70 mg per mL, comprising

[0041] (a) providing a polar lipid or a mixture of polar lipids that is swellable in aqueous media;

[0042] (b) providing an aqueous solution of cetirizine and buffer having a pH of from pH 4 to pH 8;

[0043] (c) adding the polar lipid to the aqueous solution while stirring, thereby forming a cetirizine liposome preparation;

[0044] (d) optionally adjusting the pH of the preparation to a desired value within the range of from pH 4 to pH 8 by adding an acid or a base;

[0045] (e) optionally adding water or saline to the preparation to obtain a desired final batch volume;

[0046] (f) homogenising the preparation to obtain said pharmaceutical composition.

[0047] A preferred aqueous medium is a buffered aqueous solution of cetirizine. Useful buffers are those capable of buffering at a pH within the range from pH 4 to pH 8, more preferred from about pH 5.0 to about pH 7.0, and comprise phosphate buffer, citrate buffer, acetate buffer. The person skilled in the art is aware of the inherent buffering effect of zwitterionic cetirizine.

[0048] The formation of the liposomes of the invention is facilitated by the spontaneous swelling the polar lipid in water forming a lamellar liquid crystalline phase having a maximum water content of about 35% by weight. Depending on the lipid or lipid mixture used and the other conditions a spontaneous formation of liposomes can be obtained when water is added to this lamellar phase. If spontaneous formation is not obtained, the formation of liposomes can be accomplished by mechanical dispersion of the lamellar liquid-crystalline phase in excess water.

[0049] A preferred dispersion method is vigorous mechanical mixing by, for instance, high speed homogenisation, such as by means of an Ultra Turrax® (Jankel & Kühnke, Germany) homogeniser, but shaking, vortexing and rolling can also be performed.

[0050] A homogeneous size distribution of the liposomes of the invention is desirable. It can be obtained by extrusion through a membrane filter, such as one made of polycarbonate, with a pore size of 100 nm. Membrane filters for use in the invention can be procured from Avestin Inc., Canada.

A reduced average liposome size and narrowed liposome size distribution is also obtained when the liposomal dispersion is subjected to high-pressure homogenisation with a suitable homogeniser (Rannie A P V, type 7.30 VH, Rannie A S, Denmark) at 500 bar for 4-6 cycles.

[0051] Surprisingly it was found that the presence of cetirizine in a liposome vehicle resulted in a reduction of liposome size. Smaller liposomes are generally more stable physically and, due to their higher surface/volume ratio, easier resorbed by the mucosa.

[0052] The preparation of the composition according to the invention does not normally require conventional treatment with organic solvents such as chloroform or dichloromethane. However, if two or more membrane lipids are used it may be necessary to treat them with organic solvent prior to the addition of the aqueous solvent.

[0053] According to the present invention is also disclosed a method for treating rhinitis comprising the nasal administration of a pharmacologically effective amount of the composition of the invention to a person suffering from rhinitis. For nasal administration any state-of-the-art devices suitable for producing sprays of aqueous liposomal dispersions can be used. It is also possible to administer the composition of the invention by nasal drops and even by inhalation of cetirizine liposome mist from a nebulizer. A corresponding method of treatment according to the invention by ocular administration is also dislosed. Preferably the composition of ocular administration is in the form of eye drops.

[0054] According to the present invention is furthermore disclosed a method for the manufacture of a pharmaceutical composition for the treatment of rhinitis by nasal or ocular administration comprising cetirizine and a pharmacologically acceptable liposomal carrier comprising polar lipid dispersed in an aqueous medium with the proviso that, if the polar lipid comprises phospholipid, the amount of phospholipid in the composition is from 10 mg or 17 mg per mL to 120 mg per mL, more preferred from 35 mg per mL to 70 mg per mL.

[0055] In the following the invention will be explained in more detail by reference to a number of preferred embodiments.

DESCRIPTION OF PREFERRED EMBODIMENTS

MANUFACTURE OF EXEMPLARY COMPOSITIONS OF THE INVENTION (EXAMPLES 1-4)

EXAMPLE 1

[0056]

TABLE 1

Batch formula of the composition of the invention	
Cetirizine dinitrate*	22.2 g
Phospholipid (from soybean**)	70.0 g
Disodium phosphate dihydrate; $Na_2HPO_4.2H_2O$	21.3 g
Potassium dihydrogenphosphate; KH_2PO_4	11.0 g
1 M Hydrochloric acid and/or 1 M sodium hydroxide	to pH 7.0
Water for injection	to 2.0 L

*White solid, crystallized from THF/acetonitrile/water 2:1:0.28. Obtained from commercially available cetirizine dihydrochloride via neutralisation of the free base with nitric acid.
**Lipoid S75, Lipoid GmbH, Germany

[0057] General procedure. For weights and volumes reference is made to Table 1. A buffer solution is prepared by dissolving the buffering agents disodium phosphate dihydrate ($Na_2HPO_4.2H_2O$) and potassium dihydrogen phosphate (KH_2PO_4) in 1600 ml water (80% of the total batch volume) in a 2000 mL volumetric flask. The weighed amount of active agent is added to the buffer solution and dissolved by stirring with a magnetic stirrer, followed by addition of 100 ml aqueous 1 M sodium hydroxide. The phospholipid is separately weighed and added to the cetirizine solution. Stirring is continued until a well dispersed suspension has been formed, the pH of which is adjusted to pH 7.0±0.1 with 1.0 M NaOH or 1.0 M HCl. The volume of the preparation is then brought to the final batch volume of 2000 mL. The preparation is transferred to a 5 L glass vessel provided with an Ultra Turrax® T25 homogeniser (Jankel & Kühnke, Germany). Homogenisation is carried out at 22000 rpm for 3×2 minutes interrupted by 10 min settling periods. 10 mL aliquots of the thus obtained composition of the invention are removed from the stirred dispersion and transferred to glass vials onto which spray heads (VP7 or VP7D; Valois S. A., France) are either crimped on or attached by screw fitting after filling. The stirred composition as well as the composition aliquots in the vials is protected from light.

[0058] Ultrasonication. Ultrasonication further reduces mean particle size. In this method the vials with the homogenised composition of the invention are placed in an ultrasonication bath and sonicated for 2×10 minutes, whereupon the samples have an almost clear appearance in comparison with the opaque composition afforded by Ultra-Turrax® homogenisation.

[0059] The aforementioned particle size reduction methods are compared in Table 2. Particle size distribution was determined by laser diffraction (Mastersizer 2000, Malvern Instrument, UK). A Fraunhofer theory based method was used to calculate the particle size of the high speed homogenised sample whereas a MIE (2.50/0.001) theory based method was used for calculation of the particle size of the sample additionally subjected to sonication.

TABLE 2

Particle size reduction (composition of the invention)	
Treatment	Average size (nm)
High speed homogenisation	940
High speed homogenisation + ultrasonication	162

EXAMPLE 2

[0060]

TABLE 3

Batch formula of the composition of the invention	
Cetirizine dinitrate	2.22 mg
Phospholipid (soybean; Lipoid S75; Lipoid GmbH, Germany)	7.00 mg
Citric acid, anhydrous	3.84 mg
Sodium hydroxide, solid	1.67 mg
Ascorbic acid	0.20 mg
EDTA sodium	0.20 mg
HCl, 1 M and/or NaOH, 1 M	To pH 5.0
Water for injection	To 200 mL

[0061] General procedure. For weights and volumes reference is made to Table 3. A buffer solution is prepared by dissolving anhydrous citric acid and solid sodium hydroxide in 160 mL water (80% of the total batch volume) in a 200 mL volumetric flask. The weighed amount of active agent is added and dissolved by stirring with a magnetic stirrer. The phospholipid is separately weighed and added to the cetirizine solution. Stirring is continued until a well dispersed suspension has been formed, the pH of which is adjusted to pH 5.0±0.1 with 1.0 M NaOH and/or 1.0 M HCl. The volume of the preparation is then brought to the final batch volume of 200 mL. The preparation is transferred to a high pressure homogeniser (Rannie A P V, type 7.30 VH, Rannie A S, Denmark) and homogenised at 500-800 bar for 5 cycles. Aliquots of the thus obtained composition of the invention are removed from the collecting vessel and transferred to glass vials.

[0062] In Table 4 the particle size reduction method is compared with high speed homogenisation (Ultra Turrax® T25 homogeniser (Jankel & Kühnke, Germany), as described in Example 1. The composition described in this example has been used in both homogenisation methods. Particle size distribution was determined by dynamic light scattering (Zetasizer 4, Malvern Instruments, UK) at an angle of 90° and at room temperature, using a ZET5104 sizing cell and auto:CONTIN analysis mode.

TABLE 4

Particle size reduction (composition of the invention)

Treatment	Cetirizine (mg/mL)	Z average mean (nm)
High speed homogenisation	11.1	282
High pressure homogenisation at 500 bar	11.1	77
High pressure homogenisation at 800 bar	11.1	50
High pressure homogenisation at 500 bar	0	130
High pressure homogenisation at 800 bar	0	121

[0063] The methods used for preparing these exemplary batch compositions were adapted for preparing the following additional compositions of the invention.

EXAMPLE 3

[0064]

TABLE 5

Composition of the invention	
Cetirizine dinitrate	5.6 mg
Phospholipid (soybean; Lipoid S75; Lipoid GmbH, Germany)	35.0 mg
Disodium phosphate dihydrate; $Na_2HPO_4.2H_2O$	10.7 mg
Potassium dihydrogen phosphate; KH_2PO_4	5.5 mg
1 M HCl and/or 1 M NaOH	To pH 7.0
Water for injection	To 1 mL

EXAMPLE 4

[0065]

TABLE 6

Composition of the invention	
Cetirizine dinitrate	22.2 mg
Phospholipid (soybean; Lipoid S75; Lipoid GmbH, Germany)	35.0 mg
Disodium phosphate dihydrate; $Na_2HPO_4.2H_2O$	10.7 mg
Potassium dihydroqen phosphate; KH_2PO_4	5.5 mg
1 M HCl and/or 1 M NaOH	To pH 7.0
Water for injection	To 1 mL

EXAMPLE 5

[0066]

TABLE 7

Composition of the invention	
Cetirizine dinitrate	11.2 mg
Phospholipid (soybean; Lipoid S75; Lipoid GrnbH, Germany)	70.0 mg
Disodium phosphate dihydrate; $Na_2HPO_4.2H_2O$	10.7 mg
Potassium dihydrogen phosphate; KH_2PO_4	5.5 mg
1 M HCl and/or 1 M NaOH	To pH 7.0
Water for injection	To 1 mL

EXAMPLE 6

[0067]

TABLE 8

Composition of the invention	
Cetirizine dinitrate	11.1 mg
Phospholipid (dioleoylphoshatidylcholine; DOPC, Larodan Fine Chemicals, Sweden)	35.0
Disodium phosphate dihydrate; $Na_2HPO_4.2H_2O$	10.7
Potassium dihydrogen phosphate; KH_2PO_4	5.5
1 M HCl and/or 1 M sodium hydroxide	To pH 7.0
Water for injection	To 1 mL

EXAMPLE 7

[0068]

TABLE 9

Composition of the invention	
Cetirizin dinitrate	11.1 mg
Phospholipid (dioleoylphosphatidylglycerol; DOPG, Avanti Polar Lipids, AL, USA)	35.0 mg
Disodium phosphate dihydrate; $Na_2HPO_4.2H_2O$	10.7 mg
Potassium dihydrogen phosphate; KH_2PO_4	5.5 mg
1 M HCl and/or 1 M sodium hydroxide	To pH 7.0
Water for injection	To 1 mL

EXAMPLE 8

[0069]

TABLE 10

Composition of the invention	
Cetirizine dinitrate	11.1 mg
Galactolipid (digalactosyldiacylglycerol; DGDG, Larodan Fine Chemicals, Sweden)	35.0 mg
Disodium phosphate dihydrate; $Na_2HPO_4.2H_2O$	10.7 mg
Potassium dihydrogen phosphate; KH_2PO_4	5.5 mg
1 M HCl and/or 1 M sodium hydroxide	To pH 7.0
Water for injection	To 1 mL

EXAMPLE 9

[0070] Nasal irritation test in a dog model. Cetirizine dinitrate (5.6, 11.1 and 22.2 mg/mL, respectively, in the composition of EXAMPLES 1-3; not homogenised) was administered twice daily for 14 days to four male beagle dogs per group (5-6 months old, weighing 10.1-14.2 kg). Clinical signs and body weights were monitored throughout the study. A necropsy was performed, and the nasal cavity was collected and processed (fixated, decalcified and stained with haematoxylin and eosin). Four sections from the nasal cavity were evaluated microscopically, covering squamous, ciliated respiratory, and olfactory epithelium. No treatment-related clinical signs were observed during the administration period. The mean body weight gain over the administration period was unremarkable. The macroscopic and microscopic examination of the nasal cavity and the nasal mucosa preparations did not reveal any signs of mucosal irritation or other change.

EXAMPLE 10

[0071] Ocular irritation test in a rabbit model. The potential irritating properties of the phospholipid composition of the invention (EXAMPLE 1-3) was also assessed in an eye irritation test in three white (albino), female New Zealand rabbits per treatment weighing between 2.8 to 3.4 kg. The concentrations investigated were 5.6, 11.1 and 22.2 mg/mL in the composition of EXAMPLE 1. 0.1 mL of the composition was placed in the left eye of each rabbit. The right eye served as untreated control. The eyes were examined prior to treatment and at 1, 24, 48, and 72 h after treatment. The ocular reaction to treatment was graded according to a subjective numerical scoring system. Signs of conjunctival irritation (redness) were observed in two rabbits in the group receiving the composition containing 22.2 mg/mL cetirizine dinitrate. In the first rabbit a score 2 (diffuse, crimson colour, individual vessels not easily discernable) on a scale graded 0-3 was noted one hour after treatment. In the second rabbit a score 1 (some hyperaemic blood vessels) on a four grade scale was noted at 24 h. In both cases the redness was not present at subsequent observations, and was thus considered reversible. No other signs of eye irritation were observed in any of the animals.

EXAMPLE 11

[0072] Nasal irritation test. A single dose (110 μL in each nostril) of cetirizine dinitrate (11.1 mg/mL) was administered to five healthy volunteers at four sessions in one of four formulations (I-IV) in each session. Formulations I, II, and III are formulations of the invention whereas reference formulation IV is not a formulation of the invention. The test was performed to investigate the reduction of irritation by liposome formulation as compared to plain buffer solution. Also the influence of particle size and the ratio phospholipid to cetirizine was studied.

TABLE 11

Cetirizine dinitrate formulations used in testing nasal irritation

Formulation	Composition	mg Phospholipid Features per mL Vehicle	Features
I	EXAMPLE 1	35	High speed homogenised
II	EXAMPLE 1	35	High speed homogenised + ultrasonicated
III	EXAMPLE 5	70	High speed homogenised + ultrasonicated
IV	Reference	nil; phosphate buffer	Plain buffered aqueous solution

[0073] Nasal symptom score were assessed at 1, 10, 30 minutes post administration. The nasal symptom score included the following variables: nasal congestion, rhinorrhea, itching/sneezing, burning/pain, and taste. These symptoms were qualified by the subjects according to a no—mild—moderate—severe symptom scale (0-3). The results are reported as total score, adding all five subjects scores (maximum score of 15).

[0074] The phospholipid formulations were better tolerated than the plain buffer solution. Smaller liposomes seem to be of advantage. The mild discomfort reported by all subjects at 1 minute had practically disappeared at 10 min for the two formulations (II and III) that had reduced particle size by sonication. In contrast, the initial mild discomfort reported for formulation I persisted at 10 minutes. Increasing the ratio of phospholipid to cetirizine did not further improve the performance of the formulation.

TABLE 12

Nasal irritation test in healthy volunteers.

Formulation	Congestion	Rhinorrhea	Itching/ sneezing	Burning/ Pain	Taste	TOTAL SCORE
		1 min Post Administration				
I	0	3	1	6.5	1	11.5
II	0	1	1	6.0	0	8
III	0	0	1	5.5	0	6.5
IV	0	6	2	14.5	2	24.5
		10 min Post Administration				
I	0	1	1	6	4	12
II	0	0	0	2	2	4
III	0	0	1	1	4.5	6.5
IV	0	1	1	8	3	13
		30 min Post Administration				
I	0	0	1	1	3	5
II	0	0	1	0	0	1
III	0	0	0	1	0	1
IV	0	0	0	1.5	1	2.5

EXAMPLE 12

[0075] Nasal irritation test. A single dose (110 μL in each nostril) of cetirizine dinitrate (11.1 mg/mL) was administered to four healthy volunteers at four sessions in one of four formulations (I-IV) in each session. The test was performed to investigate the irritative properties of formulations with different membrane lipids of natural and synthetic origin.

TABLE 13

Cetirizine dinitrate formulations used in testing nasal irritation

Formulation	Composition	Membrane lipid	
I	EXAMPLE 1	Lipoid S75	Natural
II	EXAMPLE 6	Dioleoylphoshatidylcholine (DOPC)	Synthetic
III	EXAMPLE 7	Dioleoylphoshatidylglycerol (DOPG)	Synthetic
IV	EXAMPLE 8	Digalactosyldiacylglycerol (DGDG)	Natural

[0076] Nasal symptom score were assessed at 1, 10, 30 minutes post administration. The nasal symptom score included the following variables: nasal congestion, rhinorrhea, itching/sneezing, burning/pain, and taste. These symptoms were qualified by the subjects according to a no—mild—moderate—severe symptom scale (0-3). The results are reported as total score, adding all four subjects scores (maximum score of 12).

[0077] The formulations containing DOPC and DOPG were very well tolerated with practically no reports of any kind at 1 minute. At 10 minutes there is still a tendency of better tolerability of these two formulations as compared to the membrane lipids of natural origin.

TABLE 14

Nasal irritation test in healthy volunteers.

Formulation	Congestion	Rhinorrhea	Itching/ sneezing	Burning/ Pain	Taste	TOTAL SCORE
		1 min Post Administration				
I	0	1	1	3	2	7
II	0	1	0	1	0	2
III	1	0	1	0	0	1
IV	0	1.5	2	2	4	9.5
		10 min Post Administration				
I	0	1	0	2	3	6
II	0	0	0	1	2	3
III	0	0.5	0.5	1	2	4
IV	0.5	0.5	0	1	4	6
		30 min Post Administration				
I	1	0	0	0	0	1
II	0	0	0	0	0	0
III	0	0	1	0	1	2
IV	0	0	0	0	0	0

1. Pharmaceutical composition for the treatment of rhinitis by nasal or ocular administration comprising zwitterionic cetirizine, polar lipid liposome, a pharmaceutical acceptable aqueous carrier and, optionally, a pharmaceutically acceptable buffer capable of providing a pH of from pH 4.0 to pH 8.0, with the proviso that, if the polar lipid comprises phospholipid, the amount of phospholipid in the composition is from 10 mg per mL to 120 mg per mL.

2. The composition of claim 1, wherein the amount of phospholipid is from 17 mg per mL to 120 mg per mL.

3. The composition of claim 1, wherein the amount of phospholipid is from 35 mg per mL to 70 mg per mL.

4. The composition of claim 1, wherein said pH is from 5.0 to 7.0.

5. The composition of claim 1, wherein the zwitterionic cetirizine has been obtained from a chloride or nitrate salt of cetirizine.

6. The composition of claim 5, wherein the salt is cetirizine dinitrate.

7. The composition of claim 1, wherein the buffer is selected from phosphate buffer, citrate buffer, acetate buffer.

8. The composition of claim 1 comprising cetirizine or a salt of cetirizine in an amount of from 1 mg/mL to 23 mg/mL calculated on the zwitterionic form.

9. The composition of claim 1, comprising cetirizine or a salt of cetirizine in an amount of from 5.5 mg/mL to 22 mg/mL.

10. The composition of claim 1 wherein the liposome is based on a phospholipid or on a mixture of phospholipids.

11. The composition of claim 10, wherein the phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, phosphatidic acid, and phosphatidylserine

12. The composition of claim 10, wherein at least one phospholipid is of natural origin.

13. The composition of claim 10, wherein at least one phospholipid is of synthetic or semi-synthetic origin.

14. The composition of claim 1, wherein the liposome is based on a glycolipid or a mixture of glycolipids.

15. The composition of claim 1, wherein the liposome consists of a glycolipid or a mixture of glycolipids.

16. The composition of claim 14, where the glycolipid is glycoglycerolipid.

17. The composition of claim 16, wherein the glycoglycerolipid comprises galactoglycerolipid.

18. The composition of claim 16, wherein glycoglycerolipid comprises digalactosyldiacylglycerol.

19. The composition of claim 18, wherein glycoglycerolipid substantially consists of digalactosyldiacylglycerol.

20. The composition of claim 14, wherein the glycolipid is a glycosphingolipid.

21. The composition of claim 14, wherein the glycolipid is a glycophosphatidylinositol.

22. The composition of claim 1 comprising at least one antioxidant, chelating agent, preservative, or viscosity-increasing agent.

23. A process for preparing a pharmaceutical composition for the treatment of rhinitis by nasal or ocular administration comprising zwitterionic cetirizine, polar lipid liposome, a pharmaceutical acceptable aqueous carrier and, optionally, a pharmaceutically acceptable buffer capable of providing a pH of from about pH 4 to about pH 8, with the proviso that, if the polar lipid comprises phospholipid, the amount of phospholipid in the composition is from 10 to 120 mg per mL, comprising

(a) providing a polar lipid or a mixture of polar lipids that is swellable in aqueous media;

(b) providing an aqueous solution of cetirizine and buffer having a pH of from pH 4 to pH 8;

(c) adding the polar lipid to the aqueous solution while stirring, thereby forming a cetirizine liposome preparation;

(d) optionally adjusting the pH of the preparation to a desired value within the range of from pH 4 to pH 8 by adding an acid or a base;

(e) optionally adding water or saline or a buffer having a pH of from pH 4 to pH 8 to the preparation to obtain a desired final batch volume;

(f) homogenising the preparation to obtain said pharmaceutical composition.

24. The process of claim 23, wherein the amount of phospholipid in the composition is from 17 to 120 mg per mL.

25. The process of claim 23, wherein the amount of phosphlipid in the composition is from 35 mg to 70 mg per mL.

26. The process of claim 23, wherein the pH is from from pH 5.0 to pH 7.0.

27. The process of claim 23, wherein said mixture of swellable polar lipids has be pre-treated with organic solvent.

28. The process of claim 23, wherein homogenisation comprises at least one of vigorous mechanical mixing, shaking, vortexing, or rolling.

29. The process of claim 22, additional comprising reduction of liposome size.

30. The process of claim 29, wherein the reduction of liposome size comprises extrusion through a membrane filter or high-pressure homogenization or both.

31. A method for the manufacture of a pharmaceutical composition for the treatment of rhinitis comprising combining cetirizine and a pharmacologically acceptable liposomal carrier comprising polar lipid dispersed in an aqueous medium, with the proviso that, if the polar lipid comprises phospholipid, the amount of phospholipid in the composition is from 10 mg to 120 mg per mL.

32. The method of claim 31, wherein the polar lipid is glycoglycerolipid.

33. The method of claim 32, wherein the glycoglycerolipid comprises galactoglycerolipid.

34. A method of treating rhinitis comprising nasal administration of a pharmacologically effective amount of the composition of claim 1.

35. A method of treating rhinitis comprising ocular administration of a pharmacologically effective amount of the composition claim 1.

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