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(54) **Antiallergic composition for ophthalmic or nasal use.**

(57) There is disclosed an antiallergic composition for ophthalmic or nasal use, comprising cetirizine or a salt thereof as an active ingredient. The antiallergic composition may further contain a cyclodextrin compound, as well as a surfactant and/or a water soluble polymer.

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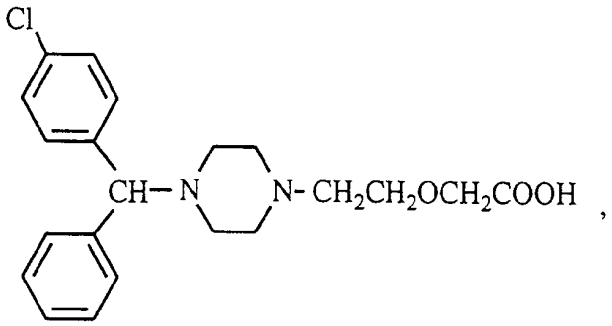
FIELD OF THE INVENTION

The present invention relates to an antiallergic composition for ophthalmic or nasal use, and more particularly, it relates to a cetirizine-containing antiallergic composi tion which is useful for the treatment of allergic diseases in the fields of ophthalmology and otorhinology.

BACKGROUND OF THE INVENTION

Cetirizine is an antiallergic compound of the formula:



the chemical name of which is [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]-ethoxy]acetic acid.

Cetirizine is well known to have an antiallergic effect, for example, by oral administration, and it is particularly useful as an antiallergic agent with significant specificity to histamine (see, e.g., JP-B 63-11353).

In the ophthalmic or nasal allergic diseases, taking the former as an example, systemic symptoms are frequently associated with ophthalmic symptoms, in which case the oral administration of an antiallergic agent is effective for their treatment. There are, however, some cases where no systemic abnormality can be detected even if marked changes are found in the eyes, and in particular, lesions found only in the eyes are not always accompanied by systemic abnormality. In such cases, topical therapy is preferred to systemic therapy because of its safety and effectiveness. This relationship between the systemic and topical symptoms holds true even in the field of otorhinology.

As an ophthalmic solution containing cetirizine, there is disclosed an anti allergic and antihistaminic composition (see, e.g., JP-A 4-9339). This composition comprises an antiallergic agent and an antihistaminic agent capable of exhibiting effective antihistaminic action when used in combination with the antiallergic agent. Cetirizine is exemplified as such an antihistaminic agent that is one of the essential ingredients of the composition.

However, no report has hitherto been made of an effect attained by the ophthalmic application of an antiallergic composition containing cetirizine as only one active ingredient.

Cetiridine has, although it is readily soluble in water, a disadvantage that a solution of cetirizine at low concentrations (below 1 w/v%) may cause the deposition of insoluble matter with the lapse of time, thereby decreasing the stability as an aqueous solution. This seems because cetirizine is one of the diphenylmethane derivatives capable of forming molecular aggregates (see, e.g., Masayuki Nakagaki (ed.), "Bussei-Butsuri (Material Science)," Nankodo, Tokyo, 1986, pp. 238-239). On the other hand, a solution of cetirizine at high concentrations where no insoluble matter will be deposited has strong irritating properties when applied in ophthalmic or nasal use, and it cannot be used as an ophthalmic or nasal solution. For this reason, there have not yet been developed an antiallergic composition for practical use containing cetirizine as the main active ingredi ent, which can be applied as an ophthalmic or nasal solution.

In general, it is difficult in most cases to prepare an ophthalmic or nasal solution with satisfactory safety and stability from a drug having irritating properties or capable of forming molecular aggregates, although it depends on the kind of the drug used.

Cyclodextrin compounds are well known to have a property of taking various drugs into their central portion to form clathrate compounds of these drugs because they are cyclic sugars. Therefore, cyclodextrin compounds have hitherto been used for the purpose of making a solution of various slightly-soluble drugs or improving the stability of drugs. However, when a cyclodextrin compound is blended with a certain drug, it becomes difficult in most cases to exhibit the efficacy of the drug, and this problem is particularly serious for external preparations.

SUMMARY OF THE INVENTION

Under these circumstances, the present inventors have intensively studied to develop a cetirizine-containing ophthalmic or nasal solution with satisfactory safety and stability, which can overcome the above-described disadvantages of cetirizine and which has no irritating properties to eyes and nasal mucosae. As the result, they have found that the addition of a cyclodextrin compound to an aqueous solution of cetirizine can reduce the deposition of insoluble matter even at low concentrations where molecular aggregates of cetirizine will be found in conventional cases. They have also found that an aqueous solution of cetirizine blended with a cyclodextrin compound can suppress the irritation of cetirizine to eyes or nasal mucosae even at high concentrations where such an irritation will be found in conventional cases, and that such an aqueous solution can maintain a sufficient inhibitory effect on allergic diseases of ocular or nasal portions. Further, they have found that the addition of a surfactant and/or a water-soluble polymer to an aqueous solution of cetirizine blended with a cyclodextrin compound can prevent the association of cetirizine in the aqueous solution for a long period of time. Thus, they have completed the present invention.

That is, the present invention provides an antiallergic composition for oph thalmic or nasal use, characterized in that it comprises cetirizine or a salt thereof as an active ingredient. It may further contain a cyclodextrin compound, as well as a surfactant and/or a water-soluble polymer.

The antiallergic composition of the present invention has almost no irritation to eyes and nasal mucosae, and it can be effectively used as a prophylactic and therapeutic agent for allergic diseases in the fields of ophthalmology and otorhinology, such as allergic conjunctivitis (e.g., conjunctival pollinosis), vernal conjunctivitis, uveitis and allergic rhinitis.

DETAILED DESCRIPTION OF THE INVENTION

The antiallergic composition of the present invention contains cetirizine or a salt thereof as an active ingredient. Examples of the salt of cetirizine are inorganic acid salts such as hydrochloride, sulfate, nitrate and phosphate; and organic acid salts such as acetate, citrate, tartrate and maleate.

The antiallergic composition of the present invention may further contain a cyclodextrin compound, as well as a surfactant and/or a water-soluble polymer.

Typical examples of the cyclodextrin compound are α-cyclodextrin, β-cycledextrin, γ-cyclodextrin, hydroxypropyl β-cyclodextrin, dimethyl β-cyclodextrin, maltosyl β-cyclodextrin and β-cyclodextrin sulfate. Particularly preferred are α-cyclodextrin, β-cyclodextrin and γ-cyclodextrin. These cyclodextrin compounds may be used alone or in combination.

The amount of cyclodextrin compound to be used may vary with its solubility and the concentration of cetirizine. It is, however, desirable that the amount of cycle dextrin compound is 0.5 to 3.0 times, preferably 1.0 to 2.0 times, as much as the mole of cetirizine.

The surfactants are preferably of the non-ionic type. Typical examples of the non-ionic surfactant are polysorbate 80, polyoxyethylene hydrogenated castor oil 50 and polyoxyethylene hydrogenated castor oil 60. These surfactants may be used alone or in combination.

The water-soluble polymer includes cellulose derivatives, vinyl polymers and polyols. Examples of the cellulose derivative are alkylcelluloses such as methylcellulose and carboxymethylcellulose; and hydroxyalkylcelluloses such as hydroxypropylcellulose and hydroxyethylcellulose. Typical examples of the vinyl polymer are polyvinyl pyrrolidone and polyvinyl alcohol. Typical examples of the polyol are a series of macrogol 200 to 6000. These water-soluble polymers may be used alone or in combination.

The amount of surfactant or water-soluble polymer to be used may vary with its kind and the concentration of cetirizine. It is, however, desirable that the amount of surfactant is 0.01 to 1.0 time, preferably 0.05 to 0.5 times, as much as the weight of cetirizine, and the amount of water-soluble polymer is 0.01 to 10.0 times, preferably 0.02 to 5.0 times, as much as the weight of cetirizine.

The antiallergic composition of the present invention can be used within the pH range adopted for ordinary ophthalmic or nasal solutions, and it is usually adjusted to pH 4.0 to 9.0, preferably pH 5.0 to 8.0.

The antiallergic composition of the present invention may further contain any conventional additives in suitable amounts, which are used in ordinary ophthalmic or nasal solutions, e.g., preservatives such as p-hydroxybenzoates, benzalkonium chloride and chlorobutanol; chelating agents such as disodium edetate and sodium citrate; agents for making isotonic solutions, such as sodium chloride, sorbitol and glycerin; buffer agents such as phosphates, boric acid and citrates; and pH controlling agents such as hydrochloric acid, acetic acid and sodium hydroxide. The amount of additive to be used can be determined by those skilled in the art within the same range as adopted for ordinary ophthalmic or nasal solutions.

The antiallergic composition of the present invention may further contain any therapeutic ingredients

other than cetirizine in suitable amounts, so long as the excellent advantages attained by the present invention are not deteriorated.

The antiallergic composition of the present invention may have various dosage forms which are pharmaceutically acceptable in the field of ophthalmology or otorhinology, such as solutions, suspensions, emulsions, gels and ointments. It may also be prepared, for example, in aqueous solution form and then lyophilized in powder form, which is reconstructed into an aqueous solution with distilled water at the time of use.

The concentration of cetirizine in the antiallergic composition of the present invention may vary with the administration route and allergic symptoms. It is, however, usually in the range of about 0.01 to 4.0 w/v%, preferably about 0.05 to 2.0 w/v%. For example, when used as an ophthalmic solution for adult patients, the antiallergic composi tion of the present invention is preferably administrated about 3 to 6 times a day in a dose of one to several drops at each time. When used as a nasal solution, the antiallergic corn position of the present invention is preferably atomized and inhaled about 3 to 6 times a day in a dose of 1 to 2 sprays at each time into the nasal cavity with an atomizer.

The present invention will be further illustrated by way of the following test examples and working examples, which are not to be construed to limit thereof.

Test Example 1: Eye irritation test in rabbits

(Method)

Using male Japanese white rabbits without any abnormality in the anterior parts of their eyes (4 groups of 3 rabbits), Composition C, D, E or F prepared in solution form according to the formulation shown in Table 1 was instilled into the right eyes of the rabbits in the corresponding group and only the vehicle into their left eyes 8 times a day at 1-hour intervals in a dose of one drop at each time for 5 days. For evaluation, a macroscopic examination of the anterior parts of the eyes and a corneal fluorescein staining assay were performed before the first instillation on day 1, 30 minutes after the last instillation on each of days 1, 3 and 5 of treatment, and on day 6.

TABLE 1

Ingredient (w/v%)	Compositions									
	A	B	C	D	E	F	G	H	J	K
Active ingredient										
Cetirizine hydrochloride	0.25	0.4	0.5	1.0	1.0	1.0	1.0	1.0	1.0	2.0
Additional ingredients										
α-Cyclodextrin	-	-	-	-	2.1	-	-	-	-	-
β-Cyclodextrin	-	-	-	-	-	2.45	-	-	-	4.9
γ-Cyclodextrin	-	-	-	-	-	-	2.81	-	-	-
Polyvinyl pyrrolidone	-	-	-	-	-	-	-	2.05	-	-
Chlorobutanol	-	-	-	-	-	-	-	-	0.3	-
Vehicle										
Con. glycerin	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Boric acid	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Sodium hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
pH	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0

(Results)

In the groups of rabbits topically dosed with Solution C or D, redness was observed on the palpebral conjunctiva and nictitating membrane after the last instillation on day 1. Particularly, in the group of rabbits given Solution D, their symptoms were so severe that individual blood vessels to be clearly observed on the normal palpebral conjunctiva were not definitely discernible. In addition, bulbar conjunctival vasodilation and palpebral conjunctival edema were observed. The redness as mentioned above was still observed even 16 hours after the last administration on day 1 and up to the beginning of instillation on day 2. The observation on day 3 of treatment also found redness of the conjunctiva as in the observation after the last instillation on day 1 but with an increased severity in both groups, indicating that cetirizine has a strong irritating effect on the conjunctiva. In the corneal fluorescein stain assay performed at the completion of instillation treatment, dye spots were observed over the entire corneal area in both groups, indicating that cetirizine also irritates the corneal epithelium. Judging that the rabbit eyes could not tolerate further instillation, the treatment with Solution C or D was discontinued on day 3.

In the group of rabbits given Solution E containing a cyclodextrin compound, slight redness was observed on the palpebral and bulbar conjunctivae after the last instillation on day 1, while very small amounts of discharge were found in some rabbits of the group dosed with Solution F. However, neither the redness nor the eye discharge as found on day 1 was no longer observed on and after day 3. Even in the corneal fluorescein staining assay done at the end of treatment, no change was found from the condition before the treatment and all the findings were invariably within the normal range, clearly indicating that a reduction in ocular irritation can be attained by the addition of a cyclodextrin compound to a composition of cetirizine hydrochloride. The eyes treated with the vehicle showed no sign of irritation caused by the vehicle.

Test Example 2: Toxicity test by instillation into rabbit eyes

(Method)

Using male Japanese white rabbits in good health without any abnormality in the ophthalmological examination (2 groups of 5 rabbits), ophthalmic composition F or K prepared in solution form according to the formulation shown in Table 1 was instilled into both eyes of the rabbits in the corresponding group 8 times a day in a dose of one drop at each time for 28 days. The rabbits were examined for the general condition, food con sumption, body weight and ophthalmological items (macroscopic observation of the anterior part of eyes, observation of the corneal stained spots and fundus oculi, measurement of the intraocular tension) with the lapse of time for 28 days, after which they were subjected to urinalysis, hematological examination, blood chemical examination, autopsy, organ weight measurement, histopathological examination of the eyeball and electron microscopic examination of the cornea.

(Results)

With respect to the instillation of Solution F or K, no abnormality was found in the ophthalmological examination, general condition and other examinations.

Test Example 3: Effect on rat histamine-induced conjunctivitis

(Method)

Male Wistar rats of about 100 g in weight were injected subconjunctivally each with 50 μl of 0.1 w/v% histamine at the upper eyelid. Each of the following test ophthalmic compositions in solution form was instilled into both eyes of the rats in the corresponding group at a dose of 3 μl for each eye 40 and 20 minutes before the histamine injection. The rats were sacrificed one hour after the histamine injection. The palpebral conjunctival edema weight was measured, and the edema inhibition rate was calculated using the edema weight of the physiological saline group as the maximal response. As the test ophthalmic solutions, a solution prepared by dissolving cetirizine hydrochloride in the vehicle (2.0 w/v% conc. glycerin, 0.4 w/v% aqueous boric acid and sodium hydroxide (q.s.); pH 7.0) to have a specified final concentration (hereinafter referred to as CE ophthalmic solution), a solution prepared by dissolving equimolar amounts of cetirizine hydrochloride and either α- or β-cyclodextrin in the vehicle at a specified final concentration (hereinafter referred to as CE + α-CD ophthalmic solution and CE + β-CD ophthalmic solution, respectively) and a solution prepared by dissolving diphenhydramine hydrochloride in the vehicle (hereinafter referred to as DPH ophthalmic solution) were

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