IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	
Masayo HIGASHIYAMA	:	Docket No. 2004_1016A
Serial No. 10/500,354	:	Group Art Unit 1614
Filed on June 30, 2004	:	Examiner: Rae, Charlesworth E

For: AQUEOUS LIQUID PREPARATIONS AND LIGHT-STABILIZED AQUEOUS LIQUID PREPARATIONS

DECLARATION UNDER 37 CFR §1.132

Honorable Commissioner of
Patents,
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sirs:

I, Masayo HIGASHIYAMA, citizen of Japan and residing in Kobe-shi, Hyogo-ken, Japan, sincerely declare;

That my education and employment history is as follows:

1. I graduated from Nagoya City University, Japan, Graduate School of Pharmaceutical Sciences, in March 1995,
2. I received a Doctor's degree in Engineering from Kyushu Institute of Technology, Japan, in September 2007, and
3. since April 1995 up to this time, I have been an employee of Senju Pharmaceutical Co., Ltd., and engaged in the pharmaceutical research of ophthalmic formulation;

That I am a member of the Pharmaceutical Society of Japan since November 1993, and the Controlled Release Society since January 2002;

That I am a co-author of the following papers:

1. Yasueda S, Higashiyama M, Yamaguchi M, Isowaki A, Ohtori A; Corneal critical barrier against the penetration of dexamethasone and lomefloxacin hydrochloride: evaluation by the activation energy for drug partition and diffusion in cornea, *Drug Dev Ind Pharm.*, 2007, 33(8), 805-11,
2. Higashiyama M, Inada K, Ohtori A, Kakehi K; NMR

analysis of ion pair formation between timolol and sorbic acid in ophthalmic preparations, *J Pharm Biomed Anal.*, 2007, 43(4), 1335-42,

3. Higashiyama M, Tajika T, Inada K, Ohtori A; Improvement of the ocular bioavailability of carteolol by ion pair, *J Ocul Pharmacol Ther.*, 2006, 22(5), 333-9,

4. Yasueda S, Higashiyama M, Shirasaki Y, Inada K, Ohtori A; An HPLC method to evaluate purity of a steroidal drug, loteprednol etabonate, *J Pharm Biomed Anal.*, 2004, 36(2), 309-16; and

5. Higashiyama M, Inada K, Ohtori A, Tojo K; Improvement of the ocular bioavailability of timolol by sorbic acid, *Int J Pharm.*, 2004, 272(1-2), 91-8;

That I am the sole inventor of the above-identified U.S. patent application SN 10/500,354; and

That I conducted the following experiments 1-4 to demonstrate the unexpected superior effect of the present invention that (+)-(S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino]butyric acid and a pharmacologically acceptable acid addition salt thereof, particularly bepotastine besilate, can be light-stabilized in water by adding water-soluble metal chloride, the results of which follow hereunder.

Experiments

Experiment 1 Effect of water-soluble metal chloride on light-stability of bepotastine besilate

Test method

The aqueous liquid preparations (Formulations 1-6) shown in the following [Table 1], which contained bepotastine besilate, were prepared according to conventional methods and filled in glass ampoules by 5 mL each. Using a xenon long-life fade meter (FAL-25AX-Ec manufactured by SUGA TEST INSTRUMENTS Co., Ltd.), a light corresponding to not less than 200 $W \cdot h/m^2$ in a total near-ultraviolet radiation energy was irradiated (irradiation time: 23-34 hr), and the appearance of each formulated liquid

preparation was observed. The amount of light exposure was measured by a quinine chemical actinometry system described in the Drug Approval and Licensing Procedures in Japan 2001.

Table 1

Formulation	1	2	3	4	5	6
bepotastine besilate	1.5 g	1.5 g	1.5 g	1.5 g	1.5 g	1.5 g
sodium chloride	-	0.1 g	0.2 g	0.3 g	-	-
potassium chloride	-	-	-	-	0.79 g	-
calcium chloride $2H_2O$	-	-	-	-	-	1.18 g
sodium hydroxide	suitable amount	suitable amount	suitable amount	suitable amount	suitable amount	suitable amount
total amount	100 mL	100 mL	100 mL	100 mL	100 mL	100 mL
pH	7.0	7.0	6.7	6.9	6.7	6.8

Test results

The appearance after light irradiation was black green in Formulation 1, and a precipitate was observed. It was slightly dark green - pale yellow in Formulation 2, and a precipitate was slightly observed. The appearance of Formulations 3-6 did not change from that immediately after preparation and were pale yellow and clear. The results indicate that addition of a water-soluble metal chloride in not less than 0.2 w/v% improves stability of bepotastine besilate under light irradiation conditions.

Experiment 2 Effect of boric acid and glycerin on light-stability of bepotastine besilate

Test method

The aqueous liquid preparations (Formulations 7-9) shown in the following [Table 2], which contained bepotastine besilate, were prepared according to conventional methods and processed in the same manner as in Experiment 1, and the appearance of each formulated liquid preparation was observed.

Table 2

Formulation	7	8	9
bepotastine besilate	1.5 g	1.5 g	1.5 g
sodium dihydrogen phosphate dihydrate	0.1 g	-	-
boric acid	-	1.0 g	0.5 g
sodium chloride	0.6 g	-	-
glycerin	-	0.5 g	2.0 g
benzalkonium chloride	0.005 g	0.005 g	0.005 g
sodium hydroxide	suitable amount	suitable amount	suitable amount
total amount	100 mL	100 mL	100 mL
pH	6.8	6.8	6.8

Test results

The appearance after light irradiation did not change from that immediately after preparation and was pale yellow and clear for Formulation 7 comprising sodium chloride, but black green for Formulations 8 and 9 comprising boric acid and glycerin and a precipitate was observed. The results indicate that addition of boric acid and glycerin fails to improve stability of bepotastine besilate under light irradiation conditions.

Experiment 3 Effect of pH and bepotastine besilate concentration on light-stability of bepotastine besilate

Test method

The aqueous liquid preparations (Formulations 10-12) shown in the following [Table 3], which contained bepotastine besilate, were prepared according to conventional methods and processed in the same manner as in Experiment 1, and the appearance of each formulated liquid preparation was observed.

Table 3

Formulation	10	11	12
bepotastine besilate	1.5 g	1.5 g	0.1 g
sodium dihydrogen phosphate dihydrate	0.1 g	0.1 g	0.1 g
sodium chloride	0.6 g	0.6 g	0.82 g
benzalkonium chloride	0.005 g	0.005 g	0.005 g
sodium hydroxide	suitable amount	suitable amount	suitable amount
total amount	100 mL	100 mL	100 mL
pH	4.0	8.5	6.8

Test results

The appearance after light irradiation did not change from that immediately after preparation and was pale yellow and clear for Formulation 10 (pH 4) and Formulation 11 (pH 8.5) comprising sodium chloride. In addition, the appearance did not change from that immediately after preparation and was colorless and clear for Formulation 12 having a bepotastine besilate concentration of 0.1 w/v%. These results and the results of Formulation 7 (pH 6.8) in Experiment 2 indicate that addition of sodium chloride, which is a water-soluble metal chloride, improves light stability of bepotastine besilate at pH 4-8.5. In addition, they indicate that the light-stability of bepotastine besilate is improved in the concentration range of 0.1 w/v% - 1.5 w/v%.

Experiment 4 Effect of bepotastine besilate concentration and pH on light-stability of bepotastine besilate in aqueous preparation comprising glycerin

Test method

The aqueous liquid preparations (Formulations 13-17) shown in the following [Table 4], which contained bepotastine besilate, were prepared according to conventional methods and processed in the same manner as in Experiment 1, and the appearance of each formulated liquid preparation was observed.

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