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 1611

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 Suita-shi, Osaka, 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 experiment 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.

Experiment

Effect of water-soluble metal chloride on light-stability of bepotastine besilate in aqueous solution as compared to the effect of glucose or mannitol

Test method

The aqueous liquid preparations (Formulations 7, 18 and 19) 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 the 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	7	18	19
bepotastine besilate	1.5 g	1.5 g	1.5 g
sodium dihydrogen phosphate dihydrate	0.1 g	0.1 g	0.1 g
sodium chloride	0.6 g	-	-
glucose	-	3.3 g	-
mannitol	-	-	3.3 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
appearance after light irradiation	pale-yellow and clear	black green, containing precipitate	black green, containing precipitate

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 0.6 w/v% sodium chloride. Meanwhile, the appearance after light irradiation turned black green for Formulation 18 and Formulation 19, comprising 3.3 w/v% glucose and 3.3 w/v% mannitol, and a precipitate was observed. The results indicate that a water-soluble metal chloride in a light stabilizing effective amount improves light-stability of bepotastine besilate, and saccharides such as glucose and mannitol do not improve light-stability of bepotastine besilate.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at Osaka Japan on this 22 day of December, 2008

Masayo Higashiyama

Masayo HIGASHIYAMA