United States Patent

Grunwaldt

[15] **3,679,804**

[45] **July 25, 1972**

[54] METHOD FOR TREATING GLAUCOMA WITH ALKYL GALLATES

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[73] Assignee: **Geigy Chemical Corporation,** Greenburgh, N.Y.

[22] Filed: **May 1, 1969**

[21] Appl. No.: **821,099**

[52] **U.S. Cl.** **424/308,** 424/330

[51] **Int. Cl.** **A61r 27/00**

[58] **Field of Search** 424/308, 330

[56] **References Cited**

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Primary Examiner—Sam Rosen

Attorney—Karl F. Jorda, Bruce M. Collins, Martin J. Spellman, Jr. and Nestor W. Shust

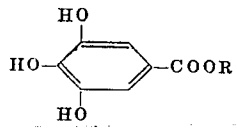
[57] **ABSTRACT**

Pharmaceutical compositions containing alkyl gallates are employed for treating glaucoma.

2 Claims, No Drawings

METHOD FOR TREATING GLAUCOMA WITH ALKYL GALLATES

The present invention pertains to compositions acceptable for topical administration to the cornea of warm-blooded animals, particularly mammals, and containing a compound of the formula



wherein R is alkyl of from one to nine carbon atoms. Such alkyl groups can be straight or branch chained and include such groups as methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, nonyl and the like.

It is known that glaucoma is a disease which is marked by increased pressure within the eyeball and at a later stage damage to the optic disk and, consequently, gradual loss of vision. A significant decrease in the rate of formation of the aqueous humour which results in a lowered equilibrium pressure in the eye can be brought about, for instance, by electrical stimulation of the preganglionic cervical sympathetic nerve. Pharmacologically, a decrease in the inflow of aqueous humour follows the topical administration of l-adrenaline and l-isoprenaline.

The present invention is based on the discovery that alkyl gallates effectively prevent the catabolism of norepinephrine and epinephrine and thereby enhance the pharmacological properties of these compounds. It is accordingly possible to treat glaucoma by topically administering a combination of norepinephrine or epinephrine and an alkyl gallate. In addition to norepinephrine and epinephrine, other amines, namely the so-called sympathomimetic amines which resemble norepinephrine and epinephrine chemically and pharmacologically may be used. Such amines are ephedrine, phenylephrine; preferred are epinephrine and norepinephrine.

The administration of an alkyl gallate in the practice of the present invention for treating glaucoma, in combination with a sympathomimetic amine such as epinephrine or norepinephrine is effected through the use of a pharmaceutical composition adapted for topical administration to the eye. These compositions include solutions and ointments. If necessary, solubilizing agents suitable for the treatment of eyes are added. Such solubilizing agents include propylene glycol, polyethylene glycol, polysorbate 80 and poloxalene. In addition to solubilizing the gallates through the addition of one of these agents, it is also possible to form a soluble complex with the borate ion. It is advantageous to add preservatives compatible with the ingredients and non-irritating to the eye. Such preservatives include merthiolate, phenyl mercuric acetate, benzalkonium chloride, and phenylethanol. It is also advantageous to use a buffered solution of a pH between 5 and 7, preferably about 6. Suitable buffers include borate, phosphate, and acetate buffer systems.

Generally, the alkyl gallate will be present in such compositions in an amount of from about 0.25 percent to about 2 percent, preferably from about 0.5 percent to about 1 percent while epinephrine or norepinephrine will be present in an amount of about 0.1 percent to about 1 percent, preferably about 0.25 percent to about 0.5 percent. Preparation and use of different dosages concentrations permits greater flexibility for treatment since factors such as the age of the individual and the severity of particular conditions can be taken into consideration. The actual dosage administered is adjusted to see and depends upon the response elicited, with observance of the usual precautions dictated by sound professional practice.

In view of the nature of the administration, solutions and ointments represent the preferred pharmaceutical forms for topical administration to eyes. Thus, simple sterile aqueous solutions can be administered through the use of drops. Ointments can be applied directly to the eye.

The following examples further illustrate the preparations of the present invention and processes for obtaining them.

EXAMPLE 1

A topical solution of 1 percent epinephrine and 1 percent of propyl gallate is prepared by dissolving an appropriate quantity in sterile water, maintaining aseptic technique throughout. The solution is sterilized by bacteriologic filtration and filled into steril glass dropper bottles. This solution is administered topically by dropping appropriate quantities into the eye in accordance with the need.

EXAMPLE 2

A sterile aqueous solution of 0.5 percent norepinephrine and 1 percent of butyl gallate is prepared according to Example 1 for topical use.

EXAMPLE 3

A sterile aqueous solution of 0.25 percent epinephrine and 1 percent of butyl gallate is prepared according to Example 1 for topical administration.

EXAMPLE 4

The following gallates, all of which are known or can be synthesized readily by techniques familiar to those skilled in the art, are converted to dosage forms analogous to those of Examples 1, 2, or 3:

methyl gallate
ethyl gallate
isopropyl gallate
octyl gallate
nonyl gallate

In the case of insolubility in water, a solubilizing agent such as polyoxyethylene ricinoleate is used.

EXAMPLE 5

A solution was prepared from the following compounds:

epinephrine	0.50%
butyl gallate	1.00%
pluronic F-68	15.00%
phenylethanol	0.25%
benzalkonium chloride	0.02%
acetic acid	0.05%
sodium acetate	2.00%
disodium EDTA	0.05%
sodium bisulfite	0.10%
water, distilled q.s.	100.00%

In preparing the solution, it is necessary that the pluronic F–68 be dissolved in water before addition of the butyl gallate.

EXAMPLE 6

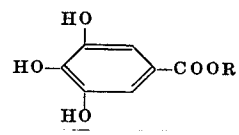
An ophthalmic ointment can be prepared as follows:

butyl gallate	1.00%
epinephrine bitartrate	1.00%
purified water	10.00%
hydrophilic petrolatum q.s.	100.00%

The epinephrine bitartrate would be dissolved in the water. A slurry of this solution and the butyl gallate is then incorporated into the hydrophilic petrolatum.

What is claimed is:

1. The method of potentiating the mydriatic property of a sympathomimetic amine selected from the group consisting of epinephrine and norepinephrine which comprises administering topically to the eye, in addition to about 0.1 percent to about 1 percent of said amine, from about 0.5 percent to about 2 percent of an alkyl gallate of the formula



wherein R is alkyl of from one to nine carbon atoms.

2. The method according to claim 1 wherein said alkyl gallate is butyl gallate.

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,679,804 Dated July 25, 1972

Inventor(s) Edgar Grunwaldt

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Cover page, after "[73] Assignee:" delete "Geigy Chemical Corporation, Greenburgh, N. Y." and substitute --- CIBA-GEIGY Corporation, Ardsley, N. Y. ---

Signed and sealed this 11th day of June 1974.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

C. MARSHALL DANN
Commissioner of Patents