

<b>(51) International Patent Classification<sup>5</sup> :</b> <b>A61K 31/19, 9/00, 47/18</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 94/15597</b> <b>(43) International Publication Date:</b> 21 July 1994 (21.07.94)
<b>(21) International Application Number:</b> PCT/US94/00188 <b>(22) International Filing Date:</b> 6 January 1994 (06.01.94) <b>(30) Priority Data:</b> 08/003,107                      11 January 1993 (11.01.93)                      US <b>(71) Applicant:</b> ALLERGAN, INC. [US/US]; 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (US). <b>(72) Inventor:</b> WONG, Michelle, P.; 15662 Myrtle Avenue, Tustin, CA 92680 (US). <b>(74) Agents:</b> BARAN, Robert, J. et al.; Allergan, Inc., 2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92713-9534 (US).		<b>(81) Designated States:</b> AU, GA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> OPTHALMIC COMPOSITIONS COMPRISING BENZYLLAURYLDIMETHYLAMMONIUM CHLORIDE		
<b>(57) Abstract</b> <p>An ophthalmic solution generally includes an ophthalmologically acceptable drug formulation incompatible with benzalkonium chloride and lauralkonium chloride present in an anti-microbially effective amount. The incompatibility of the ophthalmologically acceptable drug manifests itself by forming insoluble ion pairs with the benzalkonium chloride. It has been found that lauralkonium chloride which is the C<sub>12</sub> homolog of benzalkonium chloride is effective as a preservative without apparent interaction with the acidic ophthalmologically acceptable drug and formulations maintain their antimicrobial efficiency over periods of up to one year or more.</p>		

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## OPHTHALMIC COMPOSITIONS COMPRISING BENZYL LAURYL DIMETHYLAMMONIUM CHLORIDE

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The present invention generally relates to improved ophthalmic formulations and solutions and more particularly to improved preservative systems for ophthalmologically acceptable drug formulations which have an incompatibility with benzalkonium chloride. More specifically, the present invention pertains to the preservative for an anti-inflammatory drug such as sodium flurbiprofen (Ocufer®).

Ophthalmologically acceptable drug formulations generally contain effective compounds and a number of ophthalmologically acceptable excipients. Such excipients generally include solutions, ointments, and suspensions, etc. More specifically, such excipients include stabilizing agents, surfactants, buffering systems, chelating systems, viscosity agents, and, importantly, a preservative.

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Ophthalmic formulations, understandably, must be sterile and if a multi-dose regime is intended, the formulation must be preserved with an effective antimicrobial agent.

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As discussed in U.S. Patent No. 5,110,493, organo-mercurials have been used extensively as the preservatives in ophthalmic solutions. As reported in this reference, these compounds pose difficulties due to potential mercury toxicity as well as poor chemical stability.

Therefore, benzalkonium chloride, which is a quaternary ammonium compound, has been widely used in ophthalmic solutions. It is also well-known, however, that benzalkonium chloride is considered incompatible with anionic drugs, forming insoluble compounds which cause the solution to turn cloudy.

This is because of the fact that many acidic drug entities carry a negative charge at physiological pH. In fact, all acidic drug entities will carry a negative charge at all pH above their pKa.

In the case of benzalkonium chloride, which is a positively charged preservative, ion pairs can be formed with negatively charged drug compounds, forming an insoluble ion pair which causes the drug to precipitate out of solution. Concomitant with the removal of the drug from solution is the removal of benzalkonium chloride, thereby rendering this quaternary germicide incapable of performing its function as an antimicrobial agent.

Benzalkonium chloride is a mixture of alkyldimethylbenzylammonium chloride of the general formula as shown below in which R represents a mixture of the alkyls from  $C_8H_{17}$  to  $C_{18}H_{37}$

As hereinbefore noted, it is well-known that benzalkonium chloride is generally incompatible with anionic detergents or anionic drug compounds.

See U.S. Patent No. 5,110,493, and The Merck Index, 11th Edition, Merck & Co., Inc., 1989.

5 The present invention specifically relates to the discovery that a particular member of a group of compounds, generally known as benzalkonium chloride, exhibits properties totally different from other members of the group and different from the gross properties of the mixture known as benzalkonium chloride.

10 This discovery by the applicant must be taken in the context that all compositions are made of the same substances, retaining their fixed chemical properties. The elements are capable of an infinity of permutations, and selection of that group or element of a group which proves serviceable to a given need requires a high degree of originality.  
15 This general premise relates to the invention at hand. The applicant has discovered that lauralkonium chloride, which is the  $C_{12}$  homolog of benzalkonium chloride, is compatible with acidic drug entities with apparently no insoluble ion pairs being formed therewith. This is contrary to the properties of the mixture of alkyldimethylbenzylammonium chloride,  
20 known as benzalkonium chloride, which includes a mixture of the alkyls from  $C_8H_{17}$  to  $C_{18}H_{37}$ .

### SUMMARY OF THE INVENTION

25 An ophthalmic solution, in accordance with the present invention, generally includes an ophthalmologically acceptable drug formulation incompatible with benzalkonium chloride and lauralkonium chloride present in an antimicrobially effective amount. More specifically, flurbiprofen is an example of an acidic drug that forms an insoluble ion-

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