

anionic mucomimetic polymers and gelling polysaccharides, such as those described in U.S. Pat. No. 4,861,760 (Mazuel et al.), U.S. Pat. No. 4,911,920 (Jani et al.), and in commonly assigned U.S. Ser. No. 08/108,824 (Lang et al.). The contents of these patents and patent applications relating to the polymers cited above are incorporated herein by reference.

As will be appreciated by those skilled in the art, the compositions may be formulated in various dosage forms suitable for topical ophthalmic delivery, including solutions, suspensions, emulsions, gels and erodible solid ocular inserts. The compositions are preferably aqueous, have a pH between 3.5 to 8.0 and an osmolality between 260 to 320 milliOsmoles per kilogram (mOsm/kg).

The present invention is also directed to methods of treating glaucoma and other ophthalmic diseases and abnormalities. The methods comprise topically applying to the affected eye(s) of the patient a therapeutically effective amount of a composition according to the present invention. The frequency and amount of dosage will be determined by the clinician based on various clinical factors. The methods will typically comprise topical application of one or two drops (approximately 30 microliters) of a liquid composition, or an equivalent amount of a solid or semi-solid dosage form, to the affected eye one to two times per day.

EXAMPLE

The following topically administrable ophthalmic formulations are representative of the compositions of the present invention.

INGREDIENT	FORMULATION (wt %)		
	A	B	C
Compound 2	0.01	—	0.01
Compound 3	—	0.01	—
Cremophor® EL	0.5	0.5	0.5
Sodium Acetate (Trihydrate)	0.07	0.07	—
Tromethamine	—	—	0.12
Boric Acid	—	—	0.3
Mannitol	4.6	4.6	4.6
Disodium EDTA	0.1	0.1	0.1
Benzalkonium Chloride	0.01	0.01	0.01
NaOH and/or HCl	q.s. to pH 5	q.s. to pH 5	q.s. to pH 7
Purified Water	q.s. to 100%	q.s. to 100%	q.s. to 100%

Preparation of Formulations A-C

To a clean glass vessel of appropriate size was added approximately 75% of the batch volume of water. To this was sequentially added sodium acetate, tromethamine, boric acid, mannitol, EDTA, benzalkonium chloride and Cremophor® EL so that there was complete dissolution of one ingredient prior to the addition of the next ingredient. Next the pH of the solution was adjusted using NaOH and/or HCl, and the water was added to bring the volume to 100%.

In a separate clean glass vessel, the appropriate quantity of prostaglandin was added, followed by the appropriate quantity of the vehicle whose preparation was described above. The vessel was then tightly capped and sonicated in an ultrasonic bath for one hour or alternatively stirred with a magnetic stir bar overnight, until the prostaglandin was completely dissolved. The resulting solution was then sterile filtered (0.2 micron filter) into sterile containers. These containers were then aseptically plugged, capped and labelled.

The stabilizing effect of polyethoxylated castor oils in the compositions of the present invention was evaluated according to the following procedure.

1. Pipet the required quantity of 1% w/v prostaglandin ethanolic stock solution into 1.5 mL high performance liquid chromatograph (HPLC) sample vials.
2. Dry the sample vials under a stream of helium.
3. Add 1 mL of the appropriate vehicle (or HPLC mobile phase for standards).
4. Sonicate the vials one hour to dissolve the prostaglandin.
5. Run initial HPLC assays.
6. Place the HPLC sample vials into 20 cc scintillation vials with several mLs of deionized water and cap tightly. (Note: This prevents loss due to evaporation.) Standards are stored with HPLC mobile phase in the scintillation vial.
7. Place the vials in the appropriate controlled temperature ovens and reassay periodically by HPLC. Standards are stored in a refrigerator.
8. HPLC Data Analysis: Divide Sample Peak Area by Standard Peak Area and multiply by 100 to obtain Percent of Standard for each sample at each time point.
9. Plot Percent of Standard versus time on a semilogarithmic graph. Fit a monoexponential equation to the data. The slope times 2.303 is the apparent first-order degradation rate constant for each plot (Note: The factor of 2.303 converts common logarithm to natural logarithm).

FIG. 1 demonstrates the effect of increasing polyethoxylated castor oil concentration in Formulation A. The chemical stability of a given concentration of prostaglandin is increased as the concentration of Cremophor® EL is increased.

FIG. 2 demonstrates the superior stabilizing effect of the polyethoxylated castor oils, Cremophor® EL and Alkamuls® EL-620, over Polysorbate 80 in a type A Formulation (pH=5.0).

FIG. 3 demonstrates the superior stabilizing effect of the polyethoxylated castor oils, Cremophor® EL and Alkamuls® EL-620, over Polysorbate 80 in a type C formulation (pH=7.4).

The data shown in FIGS. 1-3 were generated using a Phenomenex 250 X 4.6 mm HPLC column with Spherisorb® 10 ODS(2) packing. The mobile phase was 50/50 acetonitrile/0.1% phosphoric acid at pH 3 with NaOH, 5 mM tetrabutylammonium hydroxide, and 5 mM sodium dodecylsulfate. The flow rate was 2 mL/minute, the detection was 190-192 nm UV, and the injection quantity was 25 µL.

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is claimed is:

1. A method of enhancing the chemical stability of an aqueous composition comprising a therapeutically-effective amount of a prostaglandin, wherein the method comprises adding a chemically-stabilizing amount of a polyethoxylated castor oil to the composition.

2. The method of claim 1 wherein the polyethoxylated castor oil is present at a concentration between about 0.02 wt % and about 20.0 wt %.

3. The method of claim 2 wherein the polyethoxylated castor oil is present at a concentration between about 0.1 wt % and about 5.0 wt %.