US005631287A

United States Patent [19]

Schneider

[11] Patent Number: 5,631,287

[45] Date of Patent: May 20, 1997

[54] **STORAGE-STABLE PROSTAGLANDIN COMPOSITIONS**

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[73] Assignee: **Alcon Laboratories, Inc.**, Fort Worth, Tex.

[21] Appl. No.: **362,677**

[22] Filed: **Dec. 22, 1994**

[51] **Int. Cl.**[6] **A61K 31/557**

[52] **U.S. Cl.** **514/530**; 514/573; 560/118

[58] **Field of Search** 514/530, 573; 560/118, 121; 562/503

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,004,752	4/1991	Raduechel	514/530

FOREIGN PATENT DOCUMENTS

0132027A1	1/1985	European Pat. Off. .
0407148A3	1/1991	European Pat. Off. .
0645145A3	3/1995	European Pat. Off. .
0667160A2	8/1995	European Pat. Off. .
WO95/05163	2/1995	WIPO .

OTHER PUBLICATIONS

Foster et al., "Intraocular Penetration of Miconazole in Rabbits," *Arch. Ophthalmol.* 97/9, pp. 1703–1706 (1979) (abstract only).

Primary Examiner—Robert Gerstl

Attorney, Agent, or Firm—Patrick M. Ryan

[57] **ABSTRACT**

The use of polyethoxylated castor oils in prostaglandin compositions greatly enhances the prostaglandin's chemical stability.

12 Claims, 3 Drawing Sheets

FIG. 1

Stability of Compound No. 2. at 65°C in pH 5.0 Preserved Vehicle with Cremophor® EL.

- □ 5% Cremophor® EL / 0.01% Compound No. 2.
- ◇ 0.5% Cremophor® EL / 0.01% Compound No. 2.
- ○ 0.5% Cremophor® EL / 0.001% Compound No. 2.
- △ 0.05% Cremophor® EL / 0.001% Compound No. 2.

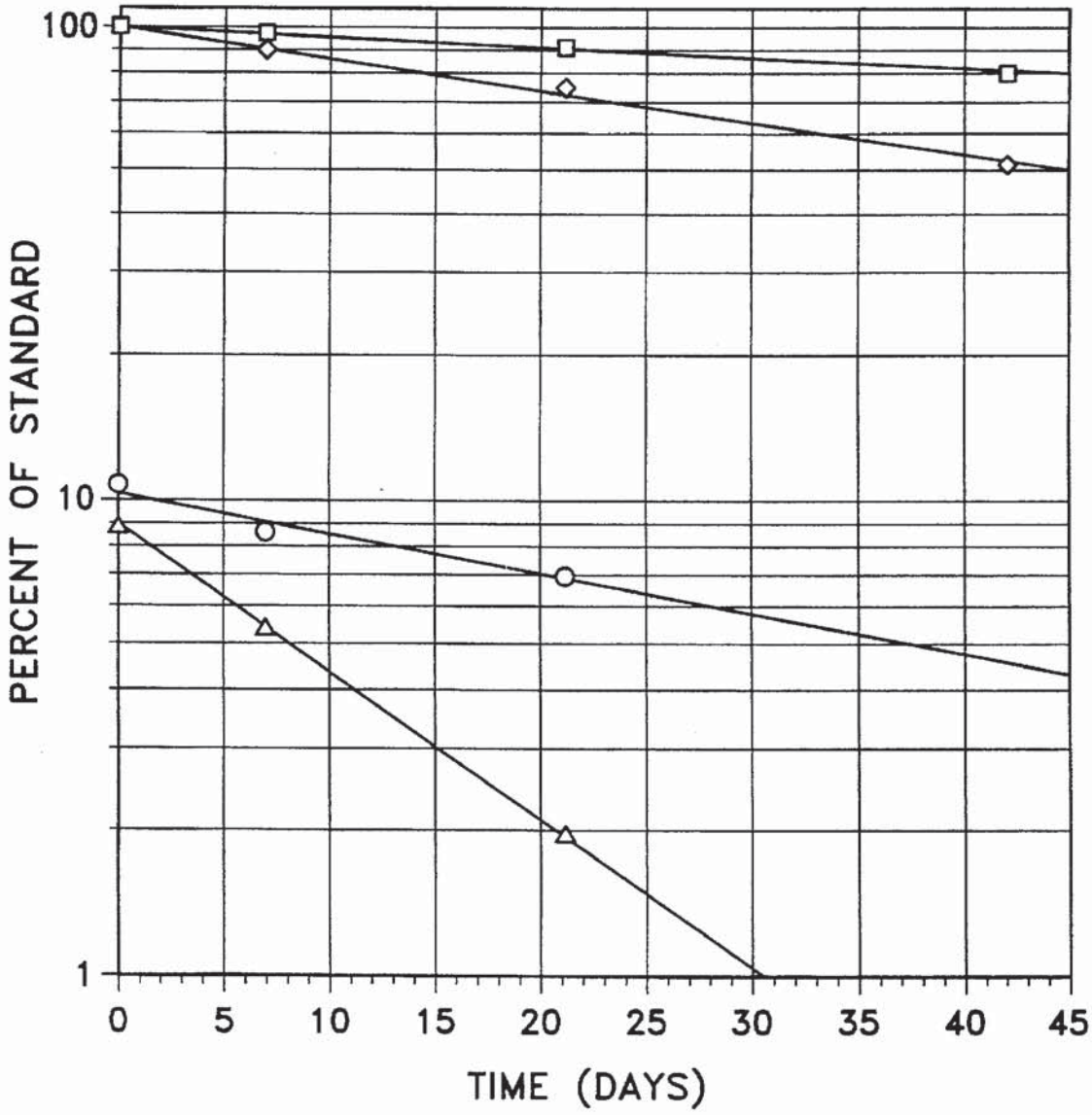


FIG. 2

Stability of 0.01% Compound No. 2. at 55°C in pH 5.0 Preserved Vehicle with the indicated Surfactant.

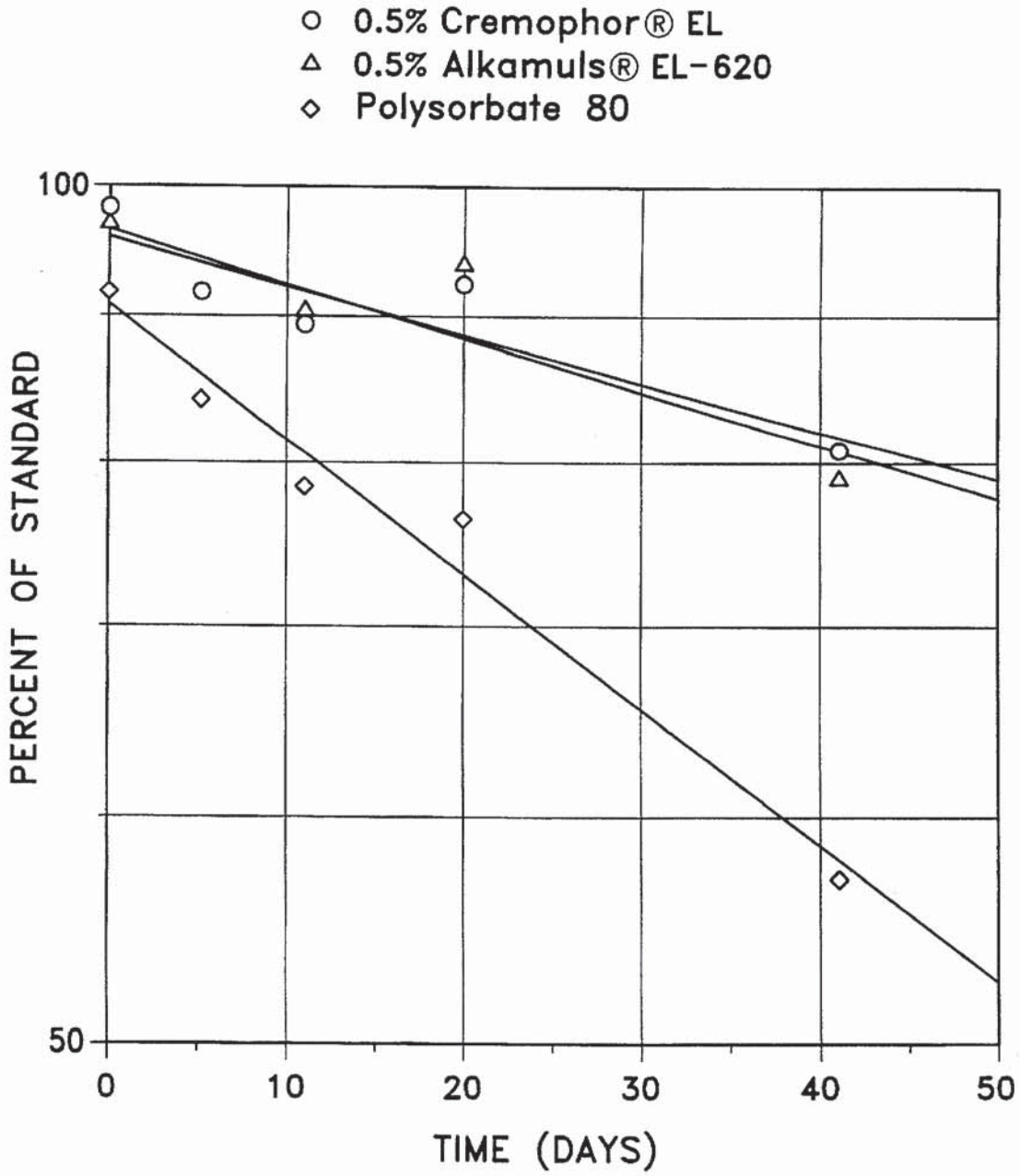
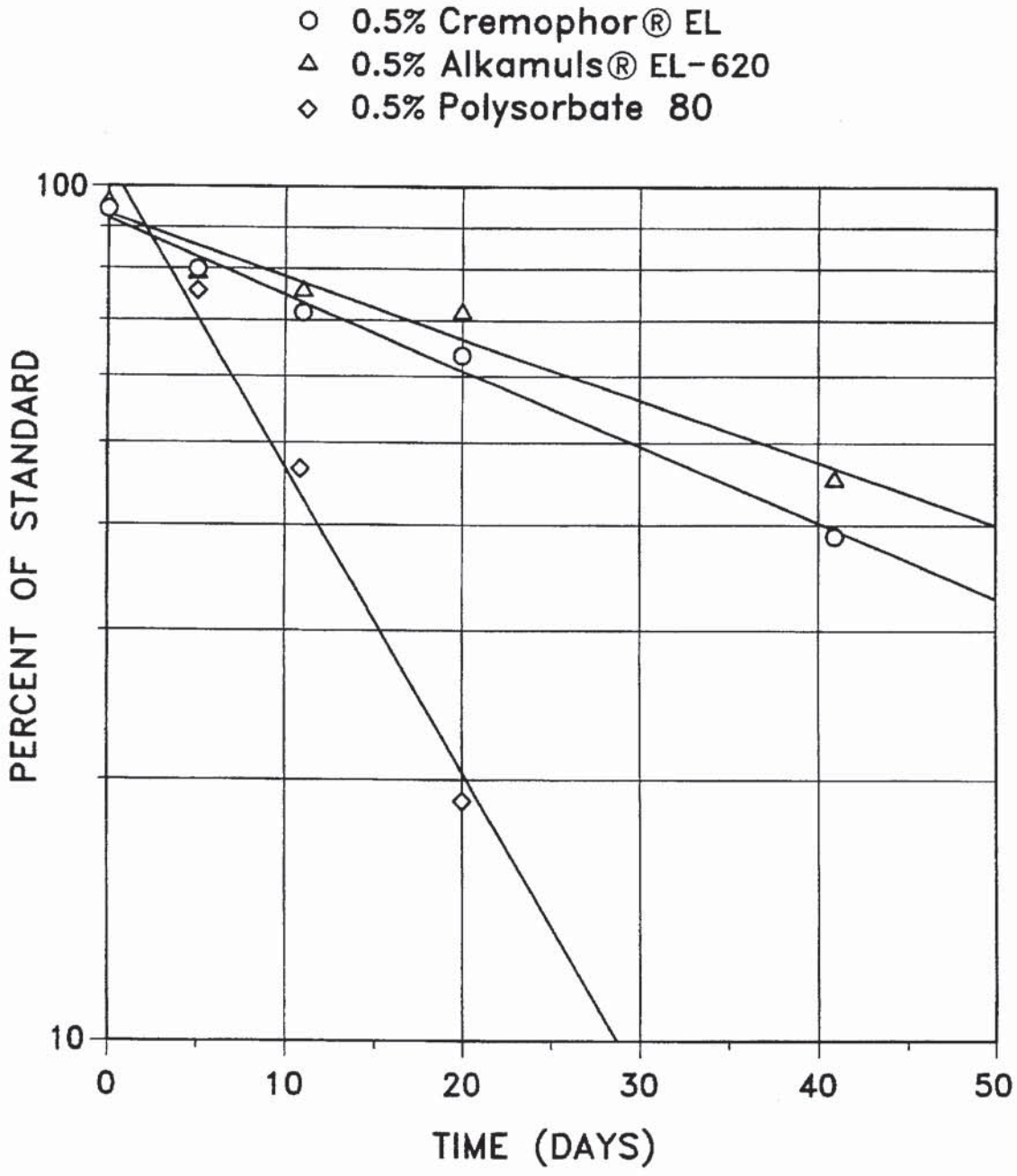


FIG. 3

Stability of 0.01% Compound No. 2. at 55°C in pH 7.4 Preserved Vehicle with the indicated Surfactant.



STORAGE-STABLE PROSTAGLANDIN COMPOSITIONS

BACKGROUND OF THE INVENTION

The present invention relates generally to prostaglandin compositions. In particular, the present invention relates to storage stable, pharmaceutical compositions containing prostaglandins and surfactants. As used herein, the term "prostaglandin" or "PG" shall refer to prostaglandins and derivatives and analogues thereof including pharmaceutically acceptable salts and esters, except as otherwise indicated by context.

Prostaglandins have notoriously low water solubility, and are generally unstable. Attempts have been made to solubilize and stabilize various prostaglandins by complexing them with different cyclodextrins. See, for example: EP 330 511 A2 (Ueno et al.) and EP 435 682 A2 (Wheeler). These attempts have met with varying success.

Surfactants and/or solubilizers have been used with other types of drugs having low water solubility. However, the addition of surfactants and/or solubilizers may enhance or adversely affect the chemical stability of drug compounds. See *Surfactant Systems, Their Chemistry, Pharmacy, and Biology*, (eds. Attwood et al.), Chapman and Hall, New York, 1983, Ch. 11, particularly pp. 698–714.

The use of non-ionic surfactants, such as polyethoxylated castor oils, as solubilizing agents is known. See, for example, U.S. Pat. No. 4,960,799 (Nagy).

The use of non-ionic surfactants such as polyethoxylated castor oils in stable emulsions is also known. U.S. Pat. No. 4,075,333 (Josse) discloses stable, intravenous emulsion formulations of vitamins. El-Sayed et al., *Int. J. Pharm.*, 13:303–12 (1983) discloses stable oil-in-water emulsions of an antineoplastic drug. U.S. Pat. No. 5,185,372 (Ushio et al.) discloses topically administrable ophthalmic formulations of vitamin A which are stable preparations in which a non-ionic surfactant is used to form an emulsion of vitamin A in an aqueous medium,

What is needed is a commercially viable, storage-stable prostaglandin composition.

SUMMARY OF THE INVENTION

The present invention is directed to the use of polyethoxylated castor oils in pharmaceutical compositions containing prostaglandins. It has now been unexpectedly discovered that the use of such polyethoxylated castor oils in such compositions enhances the chemical stability of prostaglandins in pharmaceutical compositions. The compositions of the present invention can be administered to the body in a variety of ways. When topically applied to the eye, the compositions of the present invention provide both initial and continual comfort.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the stabilizing effect at different concentrations of a polyethoxylated castor oil in a preserved prostaglandin formulation at pH 5.0.

FIG. **2** compares the stabilizing effect of different surfactants in a preserved prostaglandin formulation at pH 5.0.

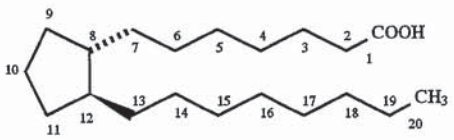
FIG. **3** compares the stabilizing effect of different surfactants in a preserved prostaglandin formulation at pH 7.4.

DETAILED DESCRIPTION OF THE INVENTION

some instances, the parent acids of some prostaglandin esters are also unstable. The pharmaceutical compositions of the present invention, however, are storage stable. These compositions contain a prostaglandin and a stability-enhancing amount of a polyethoxylated castor oil.

The polyethoxylated castor oils useful in the compositions of the present invention are commercially available, and include those classified as PEG-2 to PEG-200 castor oils, as well as those classified as PEG-5 to PEG-200 hydrogenated castor oils. Such polyethoxylated castor oils include those manufactured by Rhone-Poulenc (Cranbury, N.J.) under the Alkamuls® brand, and those manufactured by BASF (Parsippany, N.J.) under the Cremophor® brand. It is preferred to use the polyethoxylated castor oils classified as PEG-15 to PEG-50 castor oils, and more preferred to use PEG-30 to PEG-35 castor oils. It is most preferred to use those polyethoxylated castor oils known as Cremophor® EL and Alkamuls® EL-620.

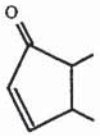
The terms "prostaglandin" and "PG" are generally used to describe a class of compounds which are analogues and derivatives of prostanoic acid (1):



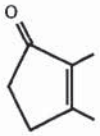
(1)

PG's may be further classified, for example, according to their 5-membered ring structure, using a letter designation:

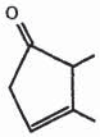
Prostaglandins of the A series (PGA's):



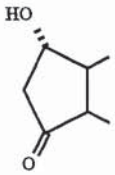
Prostaglandins of the B series (PGB's):



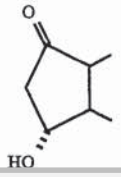
Prostaglandins of the C series (PGC's):



Prostaglandins of the D series (PGD's):



Prostaglandins of the E series (PGE's):



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