

United States Patent [19]

Glonek et al.

[11] **Patent Number:** **5,578,586**[45] **Date of Patent:** ***Nov. 26, 1996**[54] **DRY EYE TREATMENT PROCESS AND SOLUTION**[75] Inventors: **Thomas Glonek**, Oak Park, Ill.; **Jack V. Greiner**, Winchester; **Donald R. Korb**, Boston, both of Mass.[73] Assignee: **Ocular Research of Boston, Inc.**, Boston, Mass.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,294,607.

[21] Appl. No.: **192,051**[22] Filed: **Feb. 4, 1994****Related U.S. Application Data**

[63] Continuation of Ser. No. 898,375, Jun. 9, 1992, Pat. No. 5,294,607, which is a continuation-in-part of Ser. No. 529,657, May 29, 1990, abandoned, Ser. No. 457,086, Dec. 26, 1989, abandoned, Ser. No. 111,874, Oct. 23, 1987, Pat. No. 4,914,088, and Ser. No. 33,185, Apr. 2, 1987, abandoned.

[51] **Int. Cl.**⁶ **A61K 31/685**; A61K 31/66; A61K 31/20[52] **U.S. Cl.** **514/76**; 514/75; 514/78; 514/558; 514/912[58] **Field of Search** 514/76, 75, 558, 514/912[56] **References Cited****U.S. PATENT DOCUMENTS**

4,421,748 12/1983 Trager et al. 424/199

4,522,803	6/1985	Lenk et al.	424/1.1
4,677,099	6/1987	Shinitzky et al.	514/78
4,804,539	2/1989	Guo et al.	424/450
4,818,537	4/1989	Guo	424/427
4,839,175	6/1989	Guo	424/450
4,866,049	9/1989	Maumenee et al.	514/169
4,908,154	3/1990	Cook et al.	252/314
4,914,088	4/1990	Glonek et al.	514/76
4,938,965	7/1990	Shek et al.	424/450

FOREIGN PATENT DOCUMENTS

16149	1/1978	Australia .
0241376	10/1987	European Pat. Off. .
0391369	4/1990	European Pat. Off. .

OTHER PUBLICATIONS

Hardberger, Hanna and Boyd, "Effects of Drug Vehicles on Ocular Contact Time," Arch. Ophthalmol., vol. 93, Jan. 1975.

Primary Examiner—Zohreh Fay*Attorney, Agent, or Firm*—Robert L. Goldberg[57] **ABSTRACT**

A method and composition for reducing evaporation of an aqueous layer from the surface of the eye. The method comprises applying an admixture of a charged phospholipid and a non-polar oil over the eye, preferably in the form of a meta-stable oil in water emulsion in a dosage not exceeding 100 microliters.

22 Claims, No Drawings

DRY EYE TREATMENT PROCESS AND SOLUTION

CROSS REFERENCE TO RELATED APPLICATIONS

This is continuation of application(s) Ser. No. 07/898,375 filed on Jun. 9, 1992, now U.S. Pat. No. 5,294,607 which is a continuation-in-part of U.S. patent application Ser. No. 07/529,657, filed May 29, 1990, now abandoned and a continuation-in-part of U.S. patent application Ser. No. 07/457,086 filed Dec. 26, 1989, now abandoned and a continuation-in-part, of U.S. patent application Ser. No. 07/111,874 filed Oct. 23, 1987, now U.S. Pat. No. 4,914,088 and a continuation-in-part of U.S. patent application Ser. No. 07/033,185 filed Apr. 2, 1987, now abandoned.

BACKGROUND OF THE INVENTION

1. Introduction

This invention relates to wetting the surface of the eye and/or an ocular prosthesis, providing mechanical lubrication therefor, reducing the evaporation of fluid from the surface of the eye and if desired, delivering a medicant to the ocular surface. More particularly, the invention relates to a composition capable of augmenting and maintaining a stable tear film over the ocular surface and/or delivering a medicant to said surface without causing substantial blurring of vision. In a preferred embodiment of the invention, the invention relates to an ophthalmic composition for dry eye treatment. The invention is especially useful for treatment of individuals wearing ocular prostheses such as contact lenses, as the composition of the invention wets and provides lubrication for both the ocular surface and the surface of the prosthesis in contact with the ocular surfaces.

2. Description of the Prior Art

It is known in the art that an aqueous tear film extends over the ocular surfaces and maintains the ocular surface moist and lubricated. It is also known that dehydration of moisture from the eye may result in discomfort. Further, it is known that compositions are available in the market intended for dry eye treatment. These compositions are primarily aqueous materials that supplement the tear film.

The feeling of discomfort resulting from a dry eye condition may include ocular dryness, grittiness, burning, soreness or scratching, dependent upon the subject and the condition of the subject. Proposed causes for dry eye, treatment and symptoms are described in a compendium of papers edited by Holly, *The Preocular Tear Film in Health, Disease, and Contact Lens Wear*, The Dry Eye Institute, Lubbock, Tex. 1986, incorporated herein by reference.

The most common treatment for dry eye involves temporary alleviation of dry eye symptoms by topical application of a tear substitute that adds a large volume of liquid to the anterior surface of the eye and related adnexa. Typical tear substitute compositions comprise water soluble polymer solutions. Examples of such solutions include saline solutions of polyvinyl alcohol, hydroxypropylmethyl cellulose or carboxymethyl celluloses. U.S. Pat. No. 4,421,748 teaches an artificial tear composition comprising an aqueous hypotonic solution of lecithin and a viscosity adjusting agent such as a solution soluble cellulose.

Methods used to quantify the effectiveness of tear substitutes for dry eye treatment solutions have not been standardized, and many methods used to quantify the results obtained using such tear substitute compositions are often

inaccurate. For this reason, it is known that reported relief of dry eye symptoms using known tear substitutes varies considerably from subject to subject, and regardless of the method used to quantify relief using a tear substitute, relief often does not exceed several minutes.

The symptoms associated with dry eye are often exacerbated with subjects using ocular prostheses such as contact lenses. In some cases, contact lens intolerance is caused in part, or in total, by the condition of dry eye and its symptoms. Further, the rate of evaporation from the eye is accelerated by the nature of the contact lens surface and the physical presence of the contact lens results in meniscii formation with additional physical and evaporative effects, even with subjects having an adequate tear film. For many subjects, contact lens intolerance is not overcome by topical application of tear substitutes. Therefore, there is a need for improved compositions and processes for treatment of the dry eye condition and for improving tolerance to ocular prostheses.

An improved composition for dry eye treatment is the subject of U.S. Pat. No. 4,914,088 incorporated herein by reference. This patent teaches the use of charged phospholipids for the treatment of dry eye symptoms. The addition of a charged phospholipid to the eye assists in replicating the tear film that would naturally occur in the eye. In accordance with the patent, the phospholipid composition, preferably in the form of an aqueous emulsion, is topically applied to the eye where it is believed to disperse over the ocular surface and form a film that replicates a lipid layer that would be formed by the spreading of a naturally occurring lipid secreted principally from the Meibomian glands during blinking. Because the phospholipid, when applied to the eye, carries a net charge, it is believed that aligned molecules repel each other preventing complex aggregate formation thereby resulting in a stable phospholipid film. The patent speculates that the film formed from the charged phospholipid assists in the formation of a barrier film reducing evaporation of the aqueous layer, thereby preserving the tear film.

In copending U.S. patent application Ser. No. 07/529,657, filed May 29, 1990, a further improvement in dry eye treatment is disclosed. In accordance with the disclosure of said application, the dry eye treatment composition of U.S. Pat. No. 4,914,088 is improved by the addition of an essentially non-polar oil to the eye treatment composition. The oil is added to improve the performance of a dry eye treatment composition by increasing the longevity of the tear film formed on the eye following addition of the dry eye treatment solution, presumably by providing and/or thickening the dehydration barrier (the oil layer) on the outer surface of the tear film. Thus, the oil increases the efficacy of the dry eye treatment solution and reduces performance variability from subject to subject.

The use of the dry eye treatment of the referenced application assists in overcoming dry eye symptoms as reported in the application. However, when using the procedures and composition of the application, some subjects experience blurring following addition of the treatment composition containing the oil. The time required for the blur to clear is often unpredictable. In addition, relief of dry eye symptoms was found to vary somewhat from patient to patient.

SUMMARY OF THE INVENTION

The invention disclosed herein is a further improvement over the inventions disclosed in the above referenced U.S.

Pat. No. 4,914,088 and copending application Ser. No. 07/529,657. In accordance with the invention disclosed herein, dry eye treatment compositions and processes are further improved by providing a controlled means for application of a dry eye treatment composition to the eye whereby blurred vision is reduced or eliminated and the residence time of tear film on the eye is prolonged.

The invention herein is the result of several discoveries. First, it has been discovered that the total quantity of oil available to form a film over the ocular surface should be closely controlled. Secondly, and contrary to prior understanding, it has been found that when the dry eye treatment composition is in the form of an emulsion, the emulsion is preferably added to the eye as a meta-stable emulsion, not as a finely divided, stable emulsion. Finally, it has been discovered that the surfactant used in the preparations of the preferred treatment composition be one that enables control of the amount of oil contained in an emulsion and enables rapid formation of an oil film over the ocular surface.

To understand how the treatment compositions of the invention function and the basis for the improvements described herein, it is desirable to understand the mechanism by which a barrier film over the eye is capable of alleviating dry eye symptoms. The description that follows is based upon belief and that reported in the literature.

It is reported that a naturally occurring tear film comprises a complex coating with three separate layers. The inner layer in contact with the ocular surface of the eye is said to be composed primarily of mucous, and renders the hydrophobic epithelial cell surface hydrophilic. The middle layer of the tear film is an aqueous layer. This layer is the thickest portion of the tear film, is a source of moisture and lubrication for the eye and functions as an optical planarizing layer. The outer layer of the tear film, at the interface with the atmosphere, is a non-polar oily, naturally occurring lipid layer. This oily lipid layer is reported to act as a barrier that prevents evaporation of the aqueous layer (Mishima and Maurice: The oily layer of the tear film and evaporation from the corneal surface, Exp. Eye Res. 1961; 1:39-45). Finally, the oily layer is bound to the aqueous layer through a polar interfacial phospholipid layer.

The polar phospholipid and non-polar oily lipid components of the tear film are thought to originate primarily from secretions of the Meibomian glands. The oily layer of the tear film is formed from these secretions and is constantly replenished during blinking by expression of the secretions from the Meibomian glands and then spreading of the same over the surface of the eye by the eyelids. By constantly spreading the polar and non-polar lipids over the eye during blinking, the tear film is maintained and evaporation of the aqueous middle layer of the tear film is minimized.

A cause of dry eye is believed to be a deficiency in the quantity or quality of secretions from the Meibomian glands. It is postulated herein that a cause of dry eye is a deficiency in the polar lipid layer of the tear film, the non-polar oily lipid layer or both. Regardless of the cause of the deficiency, the compromised lipid layer fails to act as an adequate barrier against evaporation of the aqueous portion of the tear film resulting in one form of the dry eye condition.

In accordance with the invention of U.S. Pat. No. 4,914,088, a charged phospholipid is added to the eye, preferably as an oil-in-water emulsion. Upon contact of the emulsion with the eye, it was thought that the phospholipid dispersed over the ocular surface to form a film replicating the lipid layer formed by spreading a naturally occurring lipid secreted from the Meibomian glands during blinking. Where

the phospholipid applied to the eye preferably carries a net charge, it is believed that the aligned molecules repel each other such that complex aggregate formation is prevented and the integrity of the phospholipid film is maintained. It was believed that the film formed from the phospholipid layer acted as a barrier, reducing evaporation of the aqueous layer, thereby preserving the tear film.

In practice, it was found that treatment of dry eye symptoms with the phospholipid compositions claimed in U.S. Pat. No. 4,914,088 resulted in substantial improvement relative to treatment with prior art compositions. Films formed by the application of the phospholipid to the eye were found to be long lasting and application of the treatment composition did not cause blurring of vision any more severe than the blurring resulting from the application of prior art compositions for dry eye treatment or even physiological saline.

Though the use of the dry eye treatment compositions of U.S. Pat. No. 4,914,088 provided relief of dry eye symptoms in the majority of patients treated as stated in said patent, with improved testing procedures developed subsequent to the filing of the application leading to the grant of said patent, it was found that there was variance in efficacy from patient to patient.

In copending U.S. patent application Ser. No. 07/529,657, an improved dry eye treatment composition is disclosed. The invention of the application was the discovery of the desirability of adding an oil to the eye for treatment of the dry eye condition. Thus, the invention of the copending application involved supplementing dry eye treatment by addition of an essentially non-polar oil to the eye. In a preferred embodiment of the invention, dry eye treatment involved adding a combination of a charged phospholipid and an essentially non-polar oil to the eye. In accordance with said application, though the charged phospholipid and the non-polar oil could be separately applied to the eye, it was preferred that the two components be combined in a single treatment composition, most preferably in the form of a finely divided stable oil-in-water emulsion. A stable emulsion was desired for long term storage in a container. Upon application of the phospholipid and oil to the eye, whether as separate additions or as a single treatment composition, it was postulated that the negatively charged phospholipid layer formed an aligned film over the aqueous tear film with charged ends dissolved in the aqueous layer and hydrophobic ends furthest removed from the aqueous layer available to bond with the non-polar oil layer. This caused the oil layer to disperse over the top surface of the eye as a thin, continuous and stable layer that functioned as an evaporation barrier. Recognizing that the tear film naturally occurring in the eye may be deficient in the phospholipid component, the oil component, or both, the preferred embodiment of the treatment composition of said application replenished both components of the tear film, thereby reducing variations in efficacy from patient to patient.

Use of the treatment compositions of the copending application results in formation of a tear film over the eye that alleviates dry eye symptoms and increases patient tolerance for ocular prostheses as described in said application. However, as a consequence of treatment with the solution, some subjects experienced blurred vision both initially upon application of the treatment composition to the eye, and in some cases over a prolonged time. In accordance with the invention described herein, the dry eye compositions alleviate dry eye symptoms at least as effectively as those of the above-referenced copending application, enhance patient tolerance to ocular prostheses, and provide

the further advantage of essentially avoiding prolonged blurred vision. In addition, in accordance with the subject invention, the residence time of the film is increased.

In accordance with the invention, it has been found that the above described improvements are realized if any one or more of the following is practiced:

- (1) the total amount of oil comprising the film over the ocular surface is controlled;
- (2) the treatment composition is added to the eye in the form of a meta-stable emulsion; and
- (3) the treatment composition, in the form of an emulsion, contains a surfactant that permits increase in the oil content of an emulsion with decreased phospholipid content and enables rapid formation of a film of the efficacious components of the treatment composition over the ocular surface. With regard to control of the amount of oil comprising the film over the eye, it should be recognized that the oil layer is a thin film and the total volume of oil required to form this thin film is extremely small. If the oil component of the tear film is excessively thick or irregular (beaded), the patient will experience prolonged blurred vision. The problem is exacerbated when the oil is a polar oil rather than the preferred non-polar oil.

The process of formation of a tear film following addition of a treatment composition to the eye is a dynamic process with many steps involved. If the treatment composition is in the form of an emulsion, several processes are simultaneously set in motion immediately following the addition of the emulsion to the eye. The emulsion begins to differentiate while the dispersed oil phase spreads over the ocular surface. In addition, the amount of a fluid additive retained by the eye is up to about 10 microliters (ul). It is believed that if the volume of a fluid additive increases above about 10 ul, excess fluid moves to the canthi and rapidly enters the tear duct or is expressed from the eye as tears. This can occur within four to five blinks following addition of the treatment composition to the eye. Discharge of excess fluid will result in discharge of treatment components of the fluid from the eye, making them unavailable to form and sustain the tear film. This problem is exacerbated if the fluid is in the form of an emulsion which does not rapidly differentiate liberating treatment components. Consequently, the concentration of the treatment components of the emulsion must be sufficient to treat the eye and compensate for that lost by discharge from the eye but should not be excessive and cause blurring.

In accordance with the invention, recognizing that the formation of a tear film is a dynamic process as described above, the total amount of oil available for formation of a film preferably does not exceed 25 ul, more preferably varies between about 1 and 10 ul and most preferably varies between about 1 and 5 ul. Of this amount, only a small portion will be available to form the oil layer over the ocular surface. As the amount of oil available for film formation exceeds about 10 ul, the oil film formed over the eye becomes excessively thick or, alternatively, oil globules may form on the surface of the eye and not spread evenly over the eye. In either case, the patient is likely to experience blurring due to excessive oil. The amount of oil beyond which blurring will occur varies from patient to patient and is dependent upon the specific oil uses.

The treatment compositions of the invention are desirably formulated to permit self administration by a patient. It is difficult for a patient to self-administer low volumes of treatment composition—i.e., amounts of from 1 to 10 ul. Therefore, to render the formulations suitable for self-

administration, it is desirable to disperse the active compounds of the formulation in a suitable vehicle that permits administration of larger volumes by the patient. To control the volume of oils available for formation of the tear film without excessive discharge of treatment composition from the eye and to provide water to augment the aqueous portion of the tear film, the total amount of a liquid treatment composition added to the eye per treatment per eye preferably does not exceed 100 microliters (ul) (about 2 drops) and more preferably varies between about 25 and 50 ul. Since it is desired to limit the total volume of treatment composition added to the eye while recognizing that excess is discharged from the eye by blinking, and that the total volume of oil must be controlled, it is apparent that the concentration of oil in the treatment solution must be adjusted to provide the desired small dosage of oil to the eye and compensate for that lost due to discharge of excess treatment composition.

For reasons stated above, rapid formation of the oil film over the corneal surface is desirable. If the film does not form rapidly, oil in the treatment composition may be discharged from the eye before it can form a satisfactory film. When oil is added in the form of an emulsion, the emulsion should differentiate rapidly on entering the eye to provide oil for formation of a film before excessive oil is discharged from the eye with excess treatment composition. The formation of the oil film is desirably assisted by use of a surfactant in the treatment composition which assists in spreading the oil over the eye. The surfactant should be one that enables rapid phase differentiation and further, should be one compatible with composition components and physiologically compatible with the eye—i.e., it should not be toxic nor cause stinging.

From the above discussion, it is apparent that it is undesirable to provide a treatment composition in the form of an excessively stable emulsion for several reasons. An emulsion is often optically opaque due to the presence of distinct dispersed phases. Therefore, an emulsion over the surface of the eye is expected to cause blurring. The duration of blur is dependent upon the time required for the emulsion to differentiate and form separate layers replicating a tear film. Consequently, blurring is likely to occur until the emulsion differentiates. In addition, and as discussed above, if the emulsion is too stable, excess emulsion will be discharged from the eye. Discharge of the emulsion from the eye will result in discharge of efficacious components of the treatment solution from the eye before a tear film can be formed and these components will not be available for formation of the tear film. Therefore, in accordance with this invention, it is preferred that the emulsion be stable for long term storage, but rapidly differentiate in the eye. This is difficult to achieve with existing technology and for purposes herein it is desired that the emulsion be meta-stable where a meta-stable emulsion is defined as a composition that is sufficiently stable to provide a uniform dose to the eye but is relatively unstable and rapidly differentiates upon contact with the eye, preferably differentiating within about 5 blinks following application of the composition to the eye, more preferably in a time of less than about 30 seconds. Blurring may occur during the time required to move the bulk of the excess liquid to the canthi and discharge the same from the eye.

In accordance with the copending application, non-polar oils were used for dry eye treatment because the use of polar oils caused substantial blurring. It is a further discovery of this invention that though non-polar oils are preferred, polar oils may be used to alleviate dry eye symptoms without significant blurring if their volume available for film formation is carefully controlled within the most preferred con-

centration range of from 1 to 5 ul, more preferably 1 to 3 ul or if the polar oils are diluted with non-polar oils.

Based upon the above, the invention described herein comprises treatment of the eye with either a charged phospholipid, an oil, preferably an essentially non-polar oil, or both, in amounts and in a treatment solution form that reduces or eliminates blurring and prolongs the residence time of an artificially formed replicated tear film on the eye.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The treatment compositions of the invention comprise a charged phospholipid and an oil. They are applied by topical application to the eye. Topical application is by application of each component separately or preferably by single treatment composition containing the two components in a single liquid vehicle such as an emulsion. More preferably, the emulsion is an aqueous oil-in-water, meta-stable emulsion where the oil comprises the dispersed (organic) phase of the emulsion.

Phospholipids suitable for purposes of the invention are known in the art to be complex and to carry a net positive or negative charge under conditions of use. The preferred materials are those carrying a net negative charge because the negatively charged material will be repelled by the negatively charged ocular surface thereby permitting the maintenance of a relatively thick aqueous layer. The positively charged phospholipid will be attracted to the negatively charged ocular surface thus compressing the tear film. Hence the positively charged phospholipids operate in a different manner than the negatively charged phospholipids and are lesser preferred.

It is known that complex phospholipids contain a polar group at one end of their molecular structure and a non-polar group at the opposite end of the molecular structure. A discussion of phospholipids can be found in Leninger, *Biochemistry*, 2 ed., Worth Publishers, New York, pp. 279-306, incorporated herein by reference.

Many complex phospholipids are known in the art. They differ in size, shape and the electric charge of their polar head groups. Phosphoglycerides are compounds where one primary hydroxyl group of glycerol is esterified to phosphoric acid, and the other two hydroxyl groups are esterified with fatty acids. The parent compound of the series is, therefore, the phosphoric acid ester of glycerol. This compound has an asymmetric carbon atom and, therefore, the term phosphoglycerides includes stereoisomers.

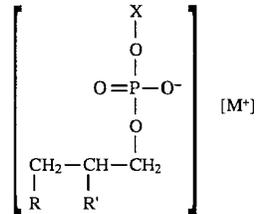
All phosphoglycerides have a negative charge at the phosphate group at pH 7, and the pK_a of this group is in the range of 1 to 2. The head groups of phosphatidylinositol, phosphatidylglycerol including diphosphatidylglycerols (having the common name cardiolipins) and the phosphatidylsugars have no electric charge, and all are polar because of their high hydroxyl group content. Because of the negative charge of the phosphate group and the absence of a charge in the head group, the net charge of each of these materials is negative, and these materials are within the scope of the invention. Likewise, the head group of phosphatidylserine contains an alpha-amino group ($pK_a=10$) and, a carboxyl group ($pK_a=3$) and therefore, the molecule contains two negative charges and one positive charge at pH 7.0, giving it a net negative charge whereby this compound is also within the scope of the invention.

Complex phospholipids having a net positive charge are also within the scope of this invention but are lesser pre-

ferred for reasons given above and because of the high price and scarcity of these compounds. Examples of positively charged complex phospholipids within the scope of the invention are those containing the basic acyl amino acid groups. Such compounds are a subgroup within the family of the o-aminoacylphosphatidylglycerols.

In contrast to the charged phospholipids, the head groups of phosphatidylethanolamine and phosphatidylcholine (lecithin) have a positive charge at pH 7, and, thus, at this pH, these two phosphoglycerides are dipolar zwitterions with no net electric charge. Such compounds are not within the scope of this invention unless chemically reacted to impart a negative charge to the material.

Of the phospholipids discussed above, the net negatively charged phosphoglycerides are preferred. A more preferred class of phosphoglycerides are represented by the following formula:



where R' and R are each fatty acid residues preferably having from 8 to 24 carbon atoms; X is hydrogen, a polyol or a 3'-O -aminoacylphosphatidylglycerol; and M is one equivalent of a countercation. R and R' are typically common natural fatty acids having an even or odd number of carbon atoms; they may be the same or may differ from each other; and they may be saturated, monounsaturated or polyunsaturated. Examples of fatty acid residues include laurate, myristate, palmitate, stearate, oleate, linoleate, octanoate, dodecate, lignocerate, etc.

Phospholipids are available from a variety of sources such as egg yolks, soy beans, etc. as is known in the art. These sources typically contain a mixture of components including natural lipids as exemplified by glycerides, cholesterol and cholesterol esters; phospholipids having a net charge of zero as exemplified by phosphatidylcholine, phosphatidylethanolamine; various unsaturated and saturated fatty acids; and charged phospholipids such as phosphatidylglycerol and phosphatidylinositol. The charged phospholipids are typically contained in these naturally occurring products in minor concentration, typically varying from below one percent up to 10 to 15 percent of the total composition.

Accordingly, the concentration of the charged phospholipid from such a natural source would likely be insufficient for purposes of treatment in accordance with the invention, and a complex phospholipid having a net charge, preferably a net negative charge, would be added to such a phospholipid source to increase the total concentration of the complex charged phospholipids to a concentration required for treatment in accordance with the invention. Obviously, if a phospholipid from a natural source is negatively charged, a negatively charged phospholipid would be added to supplement the concentration of the same whereby the total net charge remains negative.

The most preferred phospholipid for purposes of this invention is a polyol with a net negative charge. The most preferred polyol phospholipids are the phosphatidylglycerols, including cardiolipins and phosphatidylinositols. Without wishing to be bound by theory, it is believed that the hydroxyl groups of the head groups of these phospholipids

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