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Kee et al.

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[54] **COMPOSITIONS AND METHOD COMPRISING SUBSTITUTED GLYCOSIDES AS MUCUS MEMBRANE PERMEATION ENHANCERS**

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[21] Appl. No.: **31,000**

[22] Filed: **Mar. 12, 1993**

Related U.S. Application Data

[63] Continuation of Ser. No. 745,136, Aug. 13, 1991, abandoned, which is a continuation-in-part of Ser. No. 480,471, Feb. 14, 1990, abandoned.

[51] **Int. Cl.**[5] **A61K 9/10**; A61K 31/715; A61K 31/725; A61K 31/79

[52] **U.S. Cl.** **514/24**

[58] **Field of Search** 514/52, 57, 317, 392, 514/402, 915, 960, 946, 947, 777, 781, 772, 780, 779, 772.3, 24, 25, 42, 53; 536/4.1, 23, 53, 54

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,215,130	7/1980	Sjoerdsma	514/392
4,237,141	12/1980	Shiozawa et al.	514/317
4,558,063	12/1985	Beeley et al.	514/402
4,722,837	2/1988	Cameron	252/174.17
4,725,590	2/1988	Ritchey	514/166
4,742,083	5/1988	Ritchey	514/621
4,921,838	5/1990	Catsimpoolas et al.	514/25
4,923,693	5/1990	Michalos	514/915
4,942,038	7/1990	Wallach	424/450
5,041,450	8/1991	Chiou et al.	514/915
5,062,989	11/1991	Kamegai et al.	252/174.17
5,219,887	6/1993	Andrews et al.	514/881
5,262,178	11/1993	Malfroy Camine et al.	435/212

FOREIGN PATENT DOCUMENTS

1-151528 6/1989 Japan .

OTHER PUBLICATIONS

Tonjum, Asbjorn M., "Permeability of Rabbit Corneal Epithelium in Horseradish Peroxidase After the Influence of Benzalkonium Chloride," *Acta Ophthalmologica,* vol. 53, p. 335 (1975).

Morimoto et al., "Evaluation of permeability enhancement of hydrophilic compounds and macromolecular compounds by bile salts through rabbit corneas in vitro," *J. Pharm. Pharmacol.,* vol. 39, p. 124 (1987).

Schulte, Thomas L., "Ophthalmic compositions containing biphenamine and their use in the treatment or prevention of inflammation," *Chemical Abstracts,* vol. 106, 125931t, p. 402 (1987).

Grass et al., "Mechanisms of Corneal Drug Penetration I. In Vivo and In Vitro Kinetics," *Journal of Pharmaceutical Sciences,* vol. 77, No. 1, p. 3 (Jan., 1988).

Newton et al., "Topically Applied Cyclosporine in Azone Prolongs Corneal Allograft Survival," *Investigative Ophthalmology & Visual Science,* vol. 29, No. 2, p. 208 (Feb., 1988).

Primary Examiner—Ronald W. Griffin
Attorney, Agent, or Firm—Sally Yeager

[57] **ABSTRACT**

The use of substituted glycosides to enhance the penetration of drugs across mucus covered epithelial tissues of humans and animals is disclosed, including enhanced penetrations of topically applied ophthalmic drugs through the corneal epithelium of said humans and animals.

10 Claims, 2 Drawing Sheets

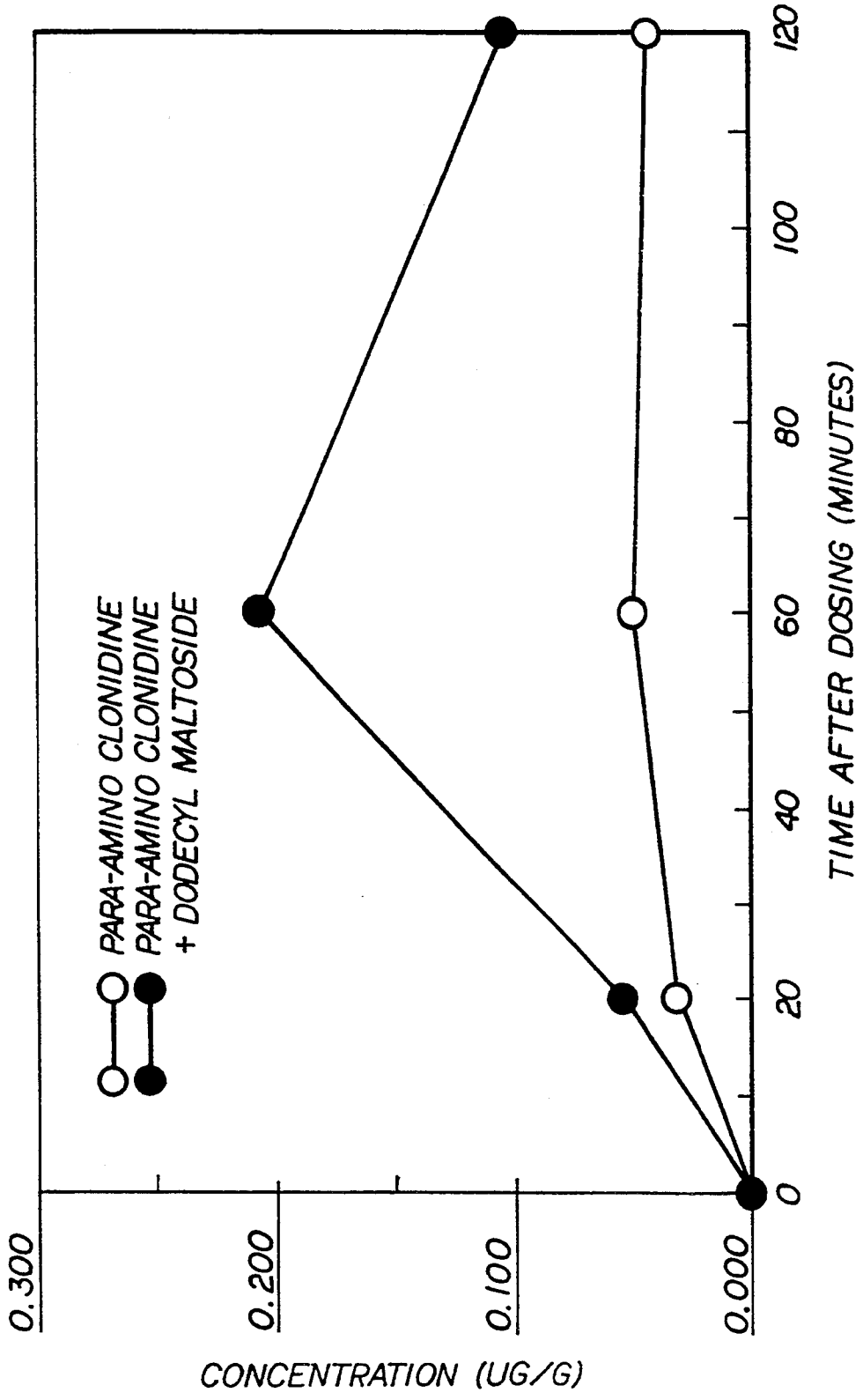


FIG 1

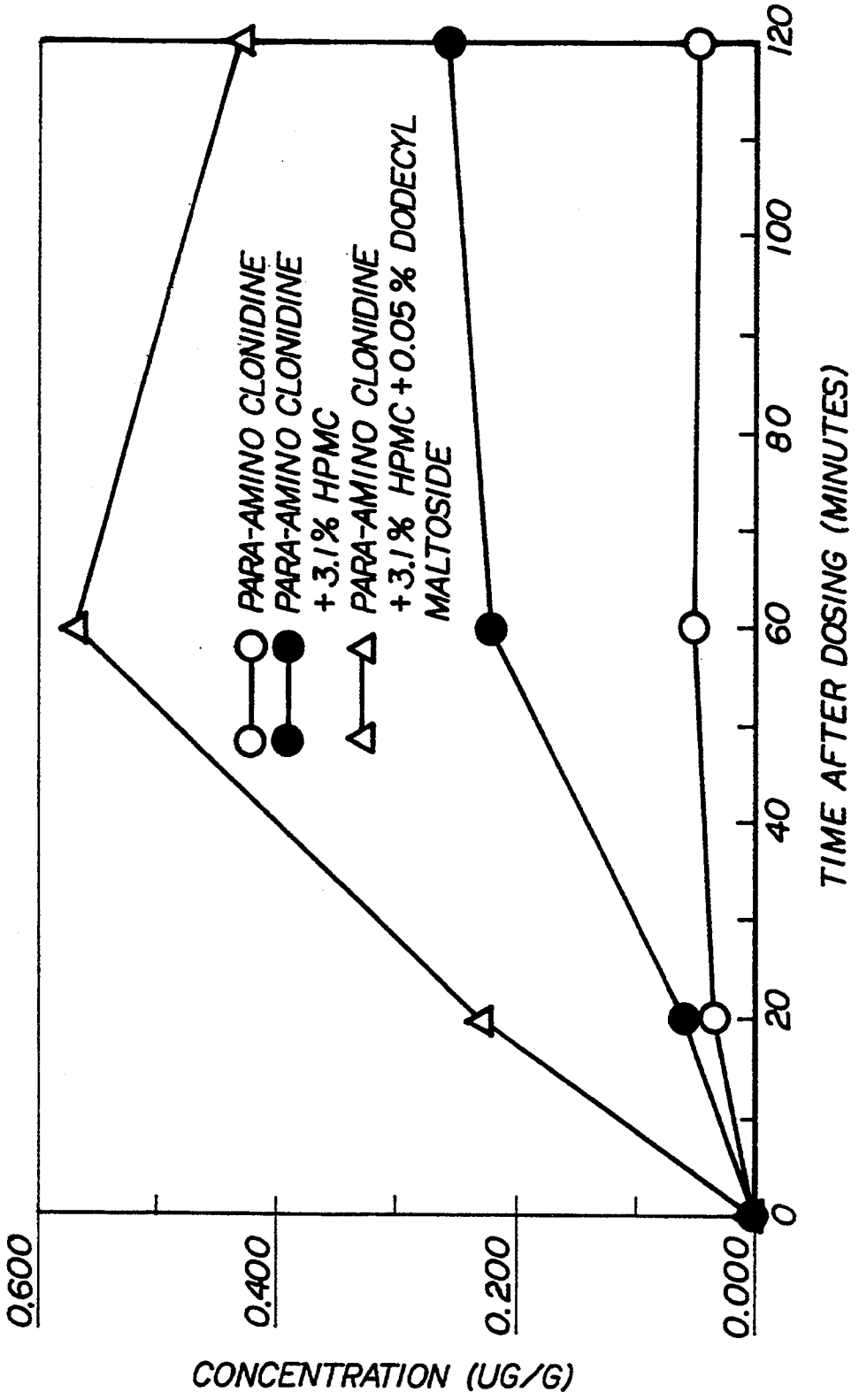


FIG II

COMPOSITIONS AND METHOD COMPRISING SUBSTITUTED GLYCOSIDES AS MUCUS MEMBRANE PERMEATION ENHANCERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation of U.S. Ser. No. 07/745,136, filed Aug. 13, 1991 (now abandoned), which is a continuation-in-part of U.S. Ser. No. 07/480,471, filed Feb. 14, 1990 (now abandoned).

FIELD OF THE INVENTION

This invention relates to substituted glycosides as enhancers for the permeation of therapeutic agents through mucus membranes of humans and animals.

BACKGROUND OF THE INVENTION

The present invention relates to the field of drug delivery across mucus covered epithelial tissues of humans and animals. Such tissues include nasal, pulmonary, rectal, buccal, vaginal, uteral, and gastrointestinal routes for drug administration. More particularly, this invention relates to enhancement of the penetration of ophthalmic drugs and other therapeutic agents through the cornea and other tissues of the eye such as the sclera and conjunctiva of humans and animals.

In order for an ophthalmic drug to be therapeutically effective, it is generally necessary for the drug to penetrate the cornea and be taken up in the aqueous humor, ciliary processes and other tissues in the eye. There are notable exceptions to this general rule, such as drugs or drug products which produce a localized therapeutic effect by acting on the exterior surface of the cornea (e.g., drugs or drug products useful in improving ocular comfort and/or treating dry or irritated eyes). However, the treatment of conditions involving physiological mechanisms within the eye (e.g., glaucoma, diabetic retinopathy, cataracts, etc.) generally does require the permeation of topically applied ophthalmic drugs primarily through the cornea.

In order for a drug to pass through the cornea, it must penetrate three layers of tissue, namely, the epithelium, stroma, and the endothelium. Except for highly lipophilic drugs, the epithelium is the main barrier to drug penetration of the cornea. Penetration of the stroma basically involves diffusion of the drug through a barrier which is approximately 360 microns thick. There are currently no known methods of enhancing drug penetration through the stroma or endothelium. However, it is possible to enhance the penetration of drugs through the epithelium, and thereby enhance the overall absorption of drugs applied topically to the eye. The present invention is directed to such enhancement.

There have been prior attempts to enhance the penetration of drugs through the corneal epithelium. The goal of such attempts has generally been to enhance penetration of drugs through the corneal epithelium to an optimal point at which the stroma alone controls drug transport through the corneas. The prior attempts have included use of chemical agents to enhance the penetration of drugs through the epithelium. It has been reported that benzalkonium chloride (BAC), bile salts, dimethyl sulfoxide (DMSO), ethylenediamine tetraacetate (EDTA) and 1-dodecylazayl-cycloheptan-2-one (AZONE ®) enhance the corneal penetration of certain drugs. The following publications may be referred to for further background concerning the use of such agents to enhance corneal penetration: *Acta Ophthalmologica,* Vol. 53, p.335 (1975); *J. Pharm. Pharmacol.,* Vol.39, p.124 (1987); *Chem. Abstracts,* Vol.106, 125931t, p.402 (1987); *Journal of Pharmaceutical Sciences,* Vol.77, No.1 (Jan.,1988); and *Investigative Ophthalmology and Visual Science,* Vol.29, No.2 (Feb.,1988). Notwithstanding such prior attempts, there continues to be a need for a means of safely and effectively enhancing the penetration of drugs through the cornea.

SUMMARY OF THE INVENTION

A principal objective of the present invention is to provide for a method of enhancing drug delivery across mucus covered epithelial tissues, particularly those of the cornea, sclera and conjunctiva of humans and animals. A further objective of the present invention is to provide topical ophthalmic compositions containing one or more agents for enhancing the penetration of the active ingredient(s) contained therein.

The foregoing objectives and other general objectives of the present invention are satisfied by the provision of a means of enhancing penetration by using a class of compounds collectively referred to herein as substituted glycosides to enhance the penetration of ophthalmic drugs through the corneal epithelium, sclera and conjunctiva. In addition, the objectives of the present invention are furthered when viscosity enhancing polymers are used in conjunction with the substituted glycosides and ophthalmic drugs so that the compositions are retained in the eye for a relatively longer period of time, thus allowing the enhancers more time to facilitate drug transport through the cornea, sclera and conjunctiva.

BRIEF DESCRIPTION OF THE FIGURES

FIG. I compares the amount of a drug, para-aminoclonidine, found in the aqueous humor of rabbits which were administered, the drug with and without the substituted glycoside enhancer, dodecyl maltoside.

FIG. II compares the amount of a drug, para-aminoclonidine, found in the aqueous humor of rabbits which were administered the drug as a solution, or the drug in combination with a viscosity enhancing polymers, hydroxypropylmethyl cellulose (HPMC) and dodecyl maltoside, or the drug with HPMC.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is based on the discovery that substituted glycosides effectively and safely enhance the corneal penetration of ophthalmic drugs. When "corneal penetration" is used herein it includes penetration through the cornea, sclera and conjunctiva of the eye. These penetration enhancers can be used in compositions comprising any ophthalmic drug which, to be effective, must be substantially taken up by the aqueous humor, ciliary processes and other tissues in the eye upon topical administration. Examples of classes of ophthalmic drugs with which the substituted glycosides of the present invention can be used, include: steroids, growth factors, cycloplegics, miotics, mydriatics, therapeutic proteins and peptides, antioxidants, aldose reductase inhibitors, nonsteroidal antiinflammatories, immunomodulators, antiallergics, antimicrobials, angiostatic agents and anti-glaucoma therapeutic agents.

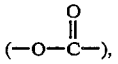
The penetration enhancing substituted glycosides used in the present invention have the following structure:

$$R_1—Z—(R_2)_x$$

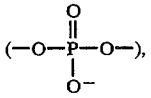
wherein R_1 is a hydrophobic group including saturated and unsaturated aliphatic hydrocarbon groups which range from 8 to 28 carbons in length with 1 to 5 double bonds. The aliphatic hydrocarbon group can be a straight or branched chain and may be substituted by one or more aromatic, cycloaliphatic or hydrophilic (e.g. hydroxyl, thiol, ester or amino) groups. R_2 is a group derived from any cyclic or acyclic saccharide containing 4–7 carbons and their isomers;

X is an integer from 1–10; and

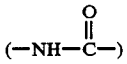
Z is an oxy (—O—), carbonyloxy



phosphoryl



thio (—S—), or carboxamido

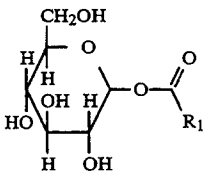


where R_2 covalently bound to such group.

More specifically R_1 can be a straight 8–18 carbon alkyl chain in hemiacetal linkage (glycoside) to the saccharide; and R_2 a group derived from any of a variety of isomeric saccharides containing 5 or 6 carbons. The saccharide can be, for example, an aldehyde-containing saccharide (glucose, mannose, arabinose, galactose, xylose); a ketone-containing saccharide (fructose, xylulose, sorbose); a saccharide alcohol (sorbitol, inositol, xylitol, mannitol); a saccharide acid (glucuronic acid, neuramic acid, mannuronic acid); a deoxysaccharide (deoxy-ribose, rhamnose,); an aminosaccharide (glucosamine, galactosamine). Higher order saccharides being covalently linked in any of a number of ways to form different isomeric structures include for example disaccharides such as maltose, cellobiose, sucrose and lactose and trisaccharides, such as raffinose.

The preferred penetration enhancers are alkyl chain containing glycosidas derived from maltose and glucose with R_1 being 8 to 18 carbons and having the following structures:

[A]



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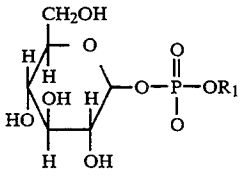
[B]



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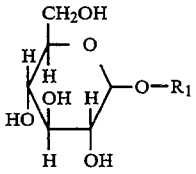

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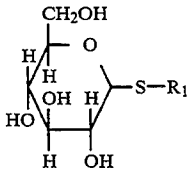

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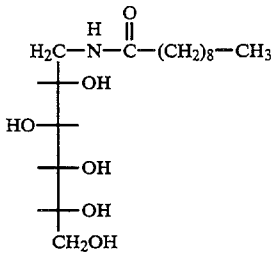
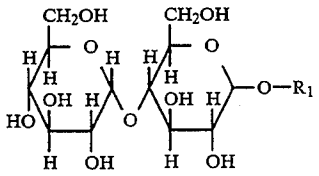
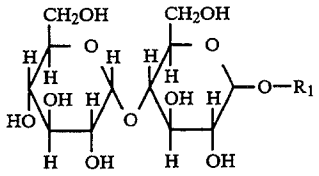


[F]



The most preferred penetration enhancer is:

Dodecyl Maltoside



The substituted glycosides which are useful in the present invention may be described as being "amphipathic", since they include both hydrophilic and hydrophobic groups. While not wishing to be bound by any theory, it is believed that substituted glycosides enhance the corneal penetration of drugs by partition and interaction with protein, glycoprotein and lipid components present in the membrane of the corneal epithelium. Such interaction is believed to alter the degree of order of the proteins and lipids in the membrane, thereby modifying the function of the epithelium as a barrier to drug penetration. Whatever the mechanism, the net result is that drug penetration across the epithelium is enhanced.

The use of substituted glycosides in accordance with the present invention to enhance corneal penetration of drugs significantly increases the amount of drug which

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