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Original Research Paper

Effect of the glyceryl monooleate-based lyotropic phases on skin permeation using *in vitro* diffusion and skin imaging

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ABSTRACT

Glyceryl monooleate (GMO) is a polar lipid that can exist in various liquid crystalline phases in the presence of different amounts of water. It is regarded as a permeation enhancer due to its amphiphilic property. Various phases of GMO/solvent system containing sodium fluorescein were prepared to compare permeability using confocal laser scanning microscopy (CLSM). GMO was melted in a vial in a water bath heated to 45 °C. Propylene glycol and hexanediol were homogeneously dissolved in the melted GMO. Sodium fluorescein in aqueous solution was diluted to various ratios and thoroughly mixed by an ultrasonic homogenizer. Each GMO/Solvent system with fluorescein was applied onto the epidermal side of excised pig skin and incubated overnight. CLSM was performed to observe how the GMO/solvent system in its different phases affect skin permeability. Cubic and lamellar phase formulations enhanced the fluorescein permeation through the stratum corneum. A solution system had the weakest permeability compared to the other two phases. Due to the amphiphilic nature of GMO, cubic and lamellar phases might reduce the barrier function of stratum corneum which was observed by CLSM as fluorescein accumulated in the dermis. Based on the results, the glyceryl monooleate lyotropic mixtures could be applied to enhance skin permeation in various topical and transdermal formulations.

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1. Introduction

Glyceryl monooleate (GMO) is a well-known molecule commonly used as an emulsifying agent, biocompatible controlled-release material, and a food additive. It is considered as a nontoxic, biodegradable, and biocompatible material classified as "generally recognized as safe" (GRAS). It is included in the FDA Inactive Ingredients Guide and present in nonparenteral medicines in the United Kingdom [1].

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GMO is a polar lipid with the ability to form various liquid crystalline phases in the presence of different amounts of water. In the presence of a small amount of water, GMO forms reversed micelles characterized by an oily texture. As more water is added, a mucous-like system is formed that corresponds to the lamellar phase. A large isotropic phase region dominates when more water is added (20 ~ 40%). This phase, known as the cubic phase, is highly viscous. In addition, the temperature and ratio of weight to water plays a role in the various phases of GMO. In the presence of high amounts of water in temperatures ranging from 20 ~ 70 °C, the cubic phase might exist in a stable condition [2]. The cubic phase is said to be bicontinuous since it consists of a curved bilayer extending in three dimensions, separating two congruent water channel networks. The water pore diameter is about 5 nm when the cubic phase is fully swollen. The presence of a lipid and an aqueous domain gives special properties to the cubic phase such as the ability to solubilize hydrophilic, hydrophobic, and amphiphilic substances [3].

Previous research has demonstrated that the liquid crystalline phases of GMO such as the cubic and reversed hexagonal phase, increased transdermal drug delivery [4]. The advantages of the formulations for transdermal drug delivery system might include biocompatibility and the ability to self-assemble their structure. The cubic phase of GMO can be dispersed in a water-rich environment and form a dispersion containing nanometer-sized particles. GMO's interaction with phospholipid bilayers might suggest why it is known as a permeation enhancer [5].

In the current study, effects of various formulations of GMO/water system on skin permeability were evaluated using Franz-diffusion cells and confocal laser scanning microscopy (CLSM). To test the permeability of each formulation, sodium fluorescein was added to the mixture that was applied on excised pig skin. Even though the influence of GMO on the percutaneous absorption through hairless mouse skin has been studied [6], differences between the GMO/water formulations and how they affect permeability and distribution throughout the layers of the skin have not been investigated. This study might provide an insight to understand the effects of formulation on the skin permeation.

2. Material and methods

2.1. Materials

Glyceryl monooleate (GMO), propylene glycol, hexanediol, paraformaldehyde, sodium chloride, potassium chloride, potassium phosphate monobasic, potassium phosphate dibasic, and sodium fluorescein were purchased from Sigma–Aldrich Co. (St. Louis, MO, USA). Excised pig skin obtained from PWG Genetics Korea, Ltd. (Pyeongtaek, Gyeonggi, Korea). FSC 22 Frozen section media was purchased from Leica Biosystems (Wetzlar, Hesse, Germany). Hydrophobic PTFE membrane was purchased from Pall Corporation (New York, NY, USA). Hydrophilic nitrocellulose membrane was purchased from EMD Millipore (Billerica, MA, USA).

2.2. Preparation of formulations

Three different formulations were prepared for the current study (Table 1). Lyotropic liquid crystalline phases (cubic and lamellar phases) were produced by melting GMO in a vial at 45 °C and then propylene glycol and hexanediol were dissolved in the melted GMO. Propylene glycol was utilized in order to slow down the drastic increase of viscosity during the cubic phase formation by mixing GMO and water. A small amount of hexanediol was added to prevent bacterial growth in the mixture and prolong the shelf-life. An aqueous solution of fluorescein was produced by dissolving hexanediol and sodium fluorescein in deionized water. The aqueous solution of sodium fluorescein was slowly added to the mixture while it was strongly agitated by an ultrasonic homogenizer to form lyotropic liquid crystalline phases.

2.3. In vitro diffusion studies with membranes

In vitro diffusion study was carried out using Franz-type diffusion cells assembled with hydrophobic PTFE membrane and hydrophilic nitrocellulose membrane between the donor and receptor chambers. The volume of each chamber was 12.5 ml and the diffusion area was 1.82 cm^2. Pore size of the membranes was 0.45 μm. To simulate a skin's lipid-bilayer, hydrophobic membranes were dipped in melted GMO and soaked in receptor medium for 30 min before diffusion studies. After the membranes were soaked, the hydrophobic membrane was attached to the hydrophilic membrane and both remained attached during the diffusion experiment.

The receptor chamber was filled with phosphate buffered saline (pH 7.4). The donor chamber containing the cubic phase, lamellar phase, or solution samples with 1 mg/ml of the sodium fluorescein were applied on the upper surface of the hydrophobic membrane. Receptor components were continuously stirred with a magnetic stirrer and samples were withdrawn at predetermined time intervals (1, 2, 3, 4, 6, 8, and 12 h). After withdrawing samples from the receptor, the receptor was replaced with the same volume of fresh phosphate buffered saline to maintain sink condition. The content of sodium fluorescein was analyzed by multi-mode microplate reader. The cumulative amount of sodium fluorescein released per surface area was obtained using the following equation:

$$Q = \left\{ C_n V + \sum_{i=1}^{n-1} C_i S \right\} \Big/ A$$

where Q is the cumulative amounts of sodium fluorescein released per surface area of the membrane (μg/cm^2) and *Cn*

Table 1 – Compositions of cubic, lamellar, and solution formulations for the current study.

Component	Cubic phase	Lamellar phase	Solution
Water	0.199	0.119	0.969
Glyceryl monooleate	0.650	0.850	–
Propylene glycol	0.120	–	–
Hexanediol	0.030	0.030	0.030
Sodium fluorescein	0.001	0.001	0.001

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