Gelatin-Stabilised Microemulsion-Based Organogels Facilitates Percutaneous Penetration of Cyclosporin A *In Vitro* and Dermal Pharmacokinetics *In Vivo*

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ABSTRACT: Gelatin-stabilised microemulsion-based organogels (MBGs) are very useful in transdermal and topical delivery of hydrophobic drugs because of their lipophilic nature. MBGs systems possessing a potentially improved skin bioavailability of Cyclosporin A were designed and explored for some characteristics. The release characteristics of drug from MBGs were studied according to drug concentration. As the concentration of drug increased, the release of drug from gel increased, showing concentration dependency. Percutaneous penetration studies using rat skin *in vitro* showed that the deposition of Cyclosporin A was significantly improved by MBGs compared to the control. We also evaluated the therapeutic advantage of dermal administration of Cyclosporin A in rat model. Local (subcutaneous and skin), systemic concentrations and organ distribution (liver and kidney) were evaluated serially following topical and oral application of the drug. In rat dermal applied with the MBGs containing Cyclosporin A, the deposition of the drug into skin and subcutaneous fat was, respectively, almost 55- and 3-fold higher than the concentrations compared with oral administration. Systemic distribution in blood, liver and kidney was much lower following topical than following oral administration. With high local concentrations and minimal distribution to other organs via the circulation, topical applied MBGs loaded with Cyclosporin A might deliver maximal therapeutic effect to local tissue while avoiding the side effects seen with systemic therapy. The histopathological findings revealed that the new MBGs vehicle was a safe vehicle for topical drug delivery systems. J Pharm Sci 96:3000–3009, 2007

Keywords: microemulsion-based organogels; skin; topical; Cyclosporin A; *in vivo*

INTRODUCTION

Cyclosporin A (CysA) is a nonpolar cyclic oligopeptide consisting of 11 amino acids.[1] Over the past years, CysA has been evaluated for numerous potential applications in dermatology. It is effective in the treatment of alopecia areata and psoriasis, when administered systemically by i.v. injection or oral application.[2,3] However, long-term systemic administration of CysA has been noted to produce harmful effects such as hypochromic, granulomatous, hypatitis and proximal renal tubular cell damage.[4,5] In the treatment of skin disorder, topical therapy is often preferred to oral drug administration. In fact, the required concentration for immunity activity at the skin target site may be more easily achieved after topical dosing, if good drug release and penetration are ensured. To attain the same local drug concentration, a higher oral dose generally needs to be administered, hence increasing the risk of adverse effect. Usually, topical administration

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results in much more lower systemic levels, thus reducing the possible toxicity of the drug.

However, topical delivery of CysA is hindered by its physicochemical properties and the barrier property of stratum corneum (SC).[6,7] Many studies have used physical and chemical techniques to disrupt the stratum corneum barrier.[8–13]

A number of researchers have trapped proteins, cells, and drugs in hydrogels matrices.[14,15] However, this method is not very useful for hydrophobic drugs because of their limited solubility in hydrogels. Another potential disadvantage of directly dissolving the drug molecules in the polymerization mixture is the possibility that drug molecules may become involved in the polymerization reaction and lose their functionality. These disadvantages can be overcome by gelatin-stabilised microemulsion-based gels (MBGs).

The preparation of MBGs was first reported in 1986 and a number of papers which describe their physical/structural characterizations have since appeared.[16,17] A schematic representation of the proposed structure for the high water content organogel is shown in Figure 1. The model, suggested by Atkinson et al. was based principally on neutron scattering and conductivity data.[18] The MBGs were proposed to consist of an extensive, rigid, interconnected network of gelation/water rods stabilised by a monolayer of surfactant, in coexistence with a population of 'conventional' w/o microemulsion droplets.

In the present study, MBGs were formulated by pharmaceutically acceptable surfactants and oil. The release characteristics and the percutaneous penetration of CysA from MBGs were studied *in vitro*. Furthermore, we compared the local deposit and organ distribution of oral administration and topical administration of CysA, using rats as an animal model.

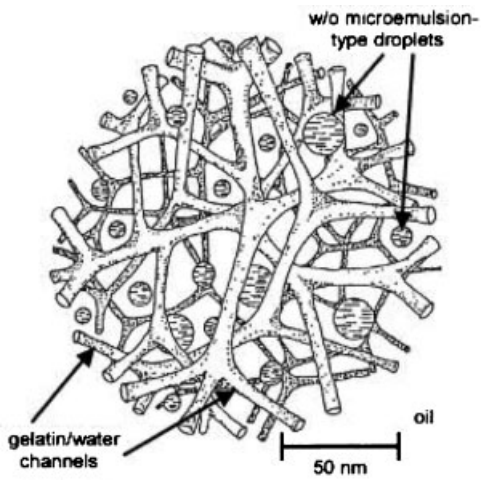

Figure 1. Proposed MBGs structure based on small angle neutron scattering by Atkinson et al.

MATERIALS AND METHODS

Materials

Cyclosporin A (CysA), Aerosol-OT (AOT) and gelatin (Bloom300) were procured from Sigma Chemical, isopropyl myristate (IPM) was obtained from Shanghai Chemical Reagent Corporation Shanghai, China,Tween85 as co-surfactant was from Tianjin Bodi Chemical Company. Hydroxypropyl celluse (Klucel®) was purchased from Hercules, Inc. (Wilmington, DE). The chemicals were used without any further purification. Distilled water was used in preparing MBGs. All other chemicals were of either reagent or high-performance liquid chromatography (HPLC) grade.

Preparation of MBGs Containing CysA

Gelatin was allowed to swell for 2 h in a known amount of distilled water at room temperature. This solution was kept at 55°C for 10 min in order to achieve dissolution of the polymer. Extended heating was avoided because gelatin rapidly hydrolyzed which caused the gel point to shift to higher polymer concentrations. AOT and Tween85 were mixed with weight ratio 2:1 to obtain stock surfactant mixture at room temperature for 24 h. Then CysA in IPM was added and the system was thoroughly stirred for 2 min at 55°C. After cooling, clear or turbid sols and gels were observed, depending on temperature, polymer concentration with respect to the mass of the whole sample (c, %gelatin), water to surfactant concentration molar ratio (w_0) or surfactant concentration (c_s, %). All concentrations were expressed in weight/weight percent. The microemulsion-based organogel formulations were selected at different component ratios as described in Table 1.

Electric Conductivity Measurements

Conductances were measured using a Mettler Toledo MC 226 (Mettler, Switzerland) conductivity meter with a Mettler Toledo Incab 730 electrode.