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Transdermal iontophoretic delivery of a liquid lipophilic drug by complexation with an anionic cyclodextrin

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ABSTRACT

Iontophoresis is now established as one of the methods of enhancing transdermal delivery of drugs. However, its application to enhance the delivery of highly lipophilic compounds is limited due to lack of any charge and poor water solubility of molecules. Propofol, a sedative and anesthetic drug was chosen as a model lipophilic drug in this study. Propofol was complexed with sulfobutyl ether-β-cyclodextrin (SCD), a β-cyclodextrin derivative carrying ionizable groups to render propofol amenable to iontophoresis. The phase solubility studies of propofol with SCD revealed an A_L type curve indicating a stoichiometry of 1:1. The complex was characterized by UV-spectrophotometry and ^{1}HNMR. Transport studies were performed using Franz diffusion cells across porcine epidermis. The passive permeation flux of propofol was enhanced by fourfold due to complexation with SCD. Application of iontophoresis (0.5 mA/cm^2) to SCD-propofol solution enhanced the transport of propofol by an additional fourfold. The enhancement in the transport of propofol after complexation was found to be due to multiple mechanisms such as transport of intact complex, enhanced thermodynamic activity of drug at the interface and prolonged recovery of barrier disrupted due to iontophoresis. The pharmacokinetic studies were performed in Sprague–Dawley rats to assess the feasibility of transdermal iontophoretic delivery *in vivo*, of a lipophilic drug complexed with SCD.

1. Introduction

Transdermal delivery of therapeutic agents provides several advantages which include avoidance of first pass metabolism, easy termination of dose by removal of patch, easy application for extended period of time by controlling the drug release and many more. Research so far in the area of drug delivery into the skin has clearly shown that the drug substance should possess enough lipophilicity (log P 1-2) and molecular weight of <500 Da to cross the skin passively, because of the excellent barrier property of rigid lamellar structures of stratum corneum (SC) [1]. Therefore, several research groups are focusing on investigating different passive and active techniques to enhance the delivery of therapeutics across the skin. The use of chemical permeation enhancers (CPEs) in combination with active technique is one of the advanced approaches to achieve the delivery of higher doses or larger size molecules [2,3].

Cyclodextrins (CDs) are commonly used as pharmaceutical excipients, mainly to solubilize the drugs that are poorly water soluble. CDs are cyclic oligosaccharides with a hydrophobic central cavity and hydrophilic outer surface. In aqueous solutions, CDs are capable of forming inclusion complexes with many therapeutic agents. Formation of inclusion complexes offers a variety of physicochemical advantages including increased water solubility and solution stability [4,5].

Propofol (2,6-diisopropylphenol) is an anesthetic usually administered through the intravenous route. Propofol is widely used clinically because of its unique therapeutic advantages such as rapid onset and cessation of effects upon single bolus injection or after infusion. Due to its clinical safety and efficacy, it is widely used in the pediatric population [6,7]. Propofol is a clear to slightly yellow oily liquid at room temperature and is highly lipophilic. Due to its poor water solubility, initially propofol was formulated as 1% aqueous solution in 16% cremophor EL surfactant. This formulation was reported to cause several side effects including hypersensitivity, pain and anaphylactic reactions [8]. Therefore, the drug was eventually reformulated as a lipid based emulsion. Since, this new propofol emulsion is generally prepared with lipidic substances such as soybean oil and egg phosphatide, the patient suffers from side effects associated with high lipid intake and pain at the site of injection [9]. Therefore, there is a need for the development of an alternate mode of delivery to avoid the side effects associated with the invasive parenteral mode of administration. Iontophoresis is a non-invasive active technique that involves driving of drug ions by the way of application of a mild electric current. Iontophoretic delivery could be a programmable system in which the rate of delivery of drugs could be regulated by adjusting the applied electrical

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dose (time × current density) [10]. Therefore, iontophoretic mediated transdermal delivery is one of the most suitable approaches for the delivery of drugs with a narrow therapeutic window like, propofol. However, the iontophoretic delivery is not possible due to the lack of charge on the propofol molecule. One of the simplest approaches could be to introduce an ionizable group on the propofol molecule. Recently, a phosphate salt of propofol was synthesized and delivered transdermally by iontophoresis [2]. In this approach, there is a potential concern that the conversion of lipophilic drug to hydrophilic salt might affect its brain bioavailability and distribution [11]. Therefore, there is a need for an approach to render the drug amenable to iontophoresis without altering its structure.

Therefore, the objective of the present study was to investigate, if cyclodextrin derivatives carrying ionizable groups could be utilized to complex with the non-polar lipophilic drug, propofol to render it amenable to transdermal delivery by iontophoresis. Sulfobutyl ether-β-cyclodextrin (SCD), a derivative of β-cyclodextrin with an average molecular weight of 2164 Da and seven negative charges due to an ionizable sulfate group on its surface was chosen as the complexing agent. This study on transdermal iontophoretic delivery of charged CD (SCD) complexed with liquid lipophilic drugs appears to be first of its kind.

2. Materials and methods

2.1. Materials

Captisol® (Sulfobutyl ether-β-cyclodextrin) (SCD) was provided by Ligand Pharmaceuticals, La Jolla, CA and rhodamine labeled Sulfobutyl ether-β-cyclodextrin (R-SCD) was obtained from CycloLab Ltd, Budapest, Hungary. Propofol, deuterium oxide, deuterated chloroform, menthol, ethanol, oleic acid and propylene glycol were purchased from Sigma-Aldrich Corporation, St. Louis, MO. Ag wire was purchased from Alfa Aesar, Ward Hill, MA. Isopropyl myristate and dialysis membrane molecular weight cut off (MWCO) 1000 Da was from Spectrum Chemicals, New Brunswick, NJ. All other chemicals used were of research grade.

2.2. Methods

2.2.1. Phase solubility studies

Phase solubility studies were performed according to the standard protocol [12]. Solubility measurements were carried out at constant temperature (25 °C) using different concentrations of aqueous solutions of SCD. A large excess of propofol (200 mg) was added to 3 ml of water with an accurately weighed amount of SCD and diluted to concentrations of 0.02, 0.04, 0.08, 0.1 and 0.15 M in screw capped scintillation vials. The resulting solution was vortexed for 5 min and was shaken for 5 days using a rotary Labquake™ tube shaker (Labindustries, Inc. Berkeley, CA). Then, an aliquot of aqueous phase from each mixture was withdrawn, centrifuged for 15 min at 13,000 rpm and the supernatant was discarded and the remaining content was filtered through 0.45 μm cellulose acetate membrane filter [13]. A portion of clear filtrate was diluted appropriately and analyzed using high performance liquid chromatography (HPLC).

2.3. Preparation of propofol–captisol® complex

Propofol:Captisol (PC) inclusion complex was prepared by freeze-drying method. The aqueous solution of PC complex was prepared by dissolving propofol (100 mg) in 10 ml of 18% w/v solution of SCD in distilled water. The resulting mixture was vortexed for 15 min and sonicated for 20 min followed by setting aside at 25 °C for 48 h to attain equilibrium solubility. The clear solution was then subjected to freeze-drying for 24 h to obtain white powder.

2.4. UV-spectrophotometric studies

Samples were prepared by dissolving freeze-dried complex and neat propofol (control) in distilled water. The samples were analyzed using a UV spectrophotometer and any shift in the λ_{max} or absorption intensity was recorded.

2.5. NMR spectroscopy

Inclusion complex of PC was characterized by high-resolution nuclear magnetic resonance spectra (^{1}H NMR). Samples of propofol and PC complex were prepared by dissolving, a portion of freeze-dried powder in deuterium oxide (D_2O) and propofol in deuterated chloroform ($CDCl_3$). Spectra were recorded on a Brucker Ultraspec 400 MHz/100 MHz spectrometer (Brucker Biospin Corporation, Woodlands, TX). Chemical shifts were reported in parts per million (δ) and ^{1}H NMR signals were quoted as s (singlet), d (doublet), t (triplet), and m (multiplet).

2.6. In vitro transport studies

2.6.1. Preparation of porcine epidermis

Freshly excised porcine belly skin was obtained from the local abattoir. The obtained skin was washed carefully with saline followed by removal of subcutaneous fat and the pieces of the skin were wrapped in aluminum foil and heated to 60 °C for 2 min. Then the epidermis was gently peeled off the skin and stored at 4 °C until further use [14].

2.6.2. General experimental setup

A vertical Franz diffusion apparatus (Logan Instruments, Somerset, NJ) was used for all resistance, transport and mechanistic studies. A piece of epidermis was placed between the donor and receiver compartments with temperature maintained at 37 ± 1 °C using a water circulator. Effective surface area for transport studies was kept constant at 0.64 cm^2. The receiver compartment was filled with 5 mL of freshly prepared phosphate buffered saline (PBS) (pH 7.4) with 30% methanol and donor compartment with 0.5 mL of permeant solution. The electrical resistance of epidermis was measured with the help of an electric circuit consisting of a waveform generator and digital multimeter (Agilent Technologies, Santa Clara, CA). An epidermis with a resistance of ≥20 k Ω cm^2 was considered for permeation studies. One mL of sample from the receiver compartment was withdrawn at pre-determined time points and estimated for propofol using HPLC.

2.6.3. Transport studies across porcine epidermis

In vitro passive permeation studies were carried out using the experimental setup described in the above section. PC complex at 10 mg/mL concentration in the donor compartment was used for transport studies across the porcine epidermis, whereas propofol dissolved in 30% methanol was used as control at the same concentration. Permeation studies were carried out for a period of 8 h and samples were analyzed for propofol using HPLC technique. The details of analytical method are discussed in Section 2.9.

For *in vitro* iontophoretic permeation of the PC complex, the experimental setup remained the same as described in the above section. Additionally, constant current cathodal iontophoresis was performed using a Phoresor® iontophoresis unit (Iomed, Salt Lake City, UT) at a current density of 0.5 mA/cm^2.

2.7. Trans-epidermal transport of R-SCD

In vitro iontophoretic and passive permeation of rhodamine labeled SCD (R-SCD) was carried out across the porcine epidermis. 0.5 mL of 18% w/v of R-SCD was placed in the donor compartment. The experimental setup remains the same as described under Section 2.6.2. Samples from the receiver compartment were collected and the amount of