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Permeation of pharmaceutical compounds through silicone membrane in the presence of surfactants

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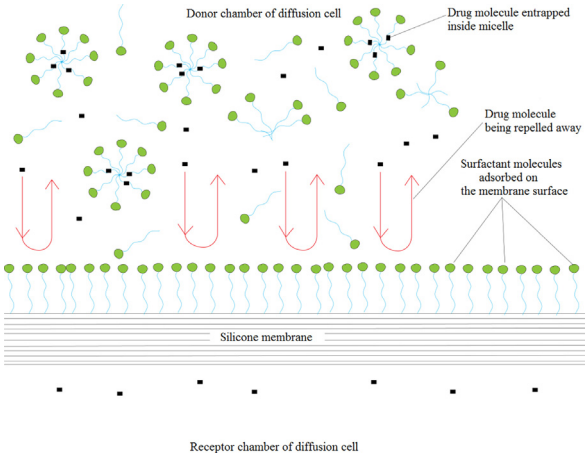
HIGHLIGHTS

- Surfactant charge and concentration can alter permeation through PDMS.
- Surfactant charge effect is dependent on drug ionisation.
- Surfactant concentration is inversely proportional to permeation.

GRAPHICAL ABSTRACT



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ABSTRACT

This study reports the effect of surfactant charge and concentration on the permeation of four model compounds (benzocaine, benzotriazole, ibuprofen and lidocaine). Surfactant charge was systematically varied using a range of surfactants that are known to possess specific head group charges, namely an anionic, a cationic, a zwitterionic and a neutral form over a series of surfactant concentrations, *i.e.* where possible, both above, and below, the critical micellar concentration for each surfactant. It was found that there was almost always a systematic reduction in permeation as the concentration of surfactant increased despite the wide range of physicochemical properties exhibited by the four model compounds studied. Overall, it was concluded that the presence of surfactant does generally seem to reduce permeation, regardless of the compound in question, and that the effect is surfactant concentration, as well as charge, dependent.

1. Introduction

Skin is a natural barrier yet despite this, is often the focus of permeation analysis in both the cosmetic and pharmaceutical industry as the rate, and extent, of transdermal permeation must be quantified irrespective of whether or not it is desired. Factors affecting permeation are complex including the properties of the skin (such as age, location, condition) [1] along with the physicochemical

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properties of the formulation (such as lipophilicity, presence of excipients and molecular size) [2]. Transdermal permeation studies are frequently undertaken using excised human or animal skin although in recent years this has become unfavourable for several reasons, the former mainly for economic reasons and the latter mainly for ethical reasons. Both types of excised skin exhibit notoriously low levels of reproducibility and with recent changes in legislation regarding cosmetic analytical testing, have encouraged the development of synthetic skin mimics [3,4]. These skin mimic systems offer a host of advantages including greater reproducibility, often reduced cost [5] and elimination of the need for ethical approval. One such skin mimic that has become popular for investigating transdermal permeation is a polymer known as polydimethylsiloxane, also known as PDMS or simply as silicone membrane. PDMS is a commonly used polymer that has a wide range of industrial applications, for example, gas and liquid separation [6], pervaporation [7,8] and microfluidic devices [9]. More importantly, PDMS membrane has been reported to produce good correlation with an *in vivo* situation in a case whereby the penetrant lipophilicity was the prime determinant of compound permeation [10]. However, as PDMS is a very simplified model of skin it has the advantage of significantly increasing the level of reproducibility in data acquired yet has the disadvantage of potentially behaving differently to skin under certain conditions. Several factors have already been found to effect permeation including ionisation (as a result of pH) [11], membrane thickness [12] and solvent selection (*i.e.* donor and receptor solution composition) [13].

Formulations can be tailored to permeate skin at a rate suited to their requirements, for example, they can be encouraged to permeate by the addition of permeation enhancers [14,15] or discouraged by the addition of permeation retardants [16]. Interestingly it has been found that a particular compound may act as an enhancer in one formulation yet a retardant in another, further complicating the situation. However, what is not currently fully understood is whether or not skin mimics, such as PDMS, behave in a similar manner to that seen *in vivo* and if there is a pattern in their ability to enhance or retard permeation. Previous research from within our group has investigated the effect of temperature on permeation using PDMS and to a very limited extent, the effect of the presence of two surfactants, namely sodium dodecyl sulfate and Brij 35, on two structurally similar paraben-based compounds [17]. In this study it was found that the effect on permeation for these two compounds differed for the two surfactants implying there was a surfactant-specific effect although general conclusions could not be made from such a limited study.

Surfactants can be divided into four categories, depending upon the overall charge located on the head group of the amphiphilic molecule: anionic, cationic, zwitterionic or non-ionic. Upon reaching a surfactant-specific concentration (the critical micellar concentration, *i.e.* CMC) molecules will spontaneously aggregate to form micellar structures which then display dissimilar properties to the unaggregated molecules. Surfactants are renowned for their ability to modify transdermal permeation [18] yet their behaviour, with respect to PDMS, is not well understood regarding surfactant choice or concentration.

In this paper, a systematic study into the effects of the presence of all four categories of surfactant over a wide range of concentrations with a selection of chemically-diverse model compounds seeks to create a better understanding of the interactions exhibited between permeation and the addition of such molecules.

2. Materials

Polydimethylsiloxane membrane (PDMS) was used as purchased (ATOS Medical, Sweden) with a standard thickness of 130 μm and cut to size as required.

Compound	Purity	Supplier
Benzocaine	>99.0%	Sigma-Aldrich
Benzotriazole	99.0%	Sigma-Aldrich
Brij 35	Proteomics grade	BDH Lab.
CHAPS	>98.0%	Fisher Scientific
CTAB	>98.0%	Sigma-Aldrich
Dipotassium hydrogen phosphate	>98%	Fisher Scientific
Ibuprofen	>97.0%	BASF
Lidocaine	>98.0%	Sigma-Aldrich
Mono potassium dihydrogen phosphate	>99.0%	Fisher Scientific
SDS	>99.0%	Sigma-Aldrich
Tween 80	Super refined grade	Croda International

3. Methods

3.1. Permeation studies

PDMS membrane was soaked in phosphate buffer solution (0.02 M pH 7.4 and 0.15 M NaCl) for 30 min prior to being mounted in the flow-through diffusion cells (PermeGear Inc. USA). After assembly the cells were placed on a cell warmer, maintained at a temperature of 32 °C. To start each permeation experiment, 0.8 mL of the donor solution containing model compound and/or surfactant was added to the cell. In all experiments the concentration of the model compounds in the donor solution was 1 mg/mL with surfactant present at concentrations of 0, 4, 8 or 20 mM for SDS, Brij 35, Tween 80, CTAB and 0, 2, 4 or 20 mM for CHAPS. Phosphate buffer saline was pumped through the cells at 5 mL/h. The samples were collected by means of a fraction collector at the predetermined time intervals (0.75, 1.5, 2.25, 3, 3.75, 4.5, 5.25 and 6 h). Quantification was undertaken using UV spectroscopy (benzoicaine at 258 nm, benzotriazole at 262 nm, ibuprofen at 225 nm and lidocaine at 219 nm). All experiments were conducted in triplicate with the mean value shown with standard deviation based error limits. All flow-through cells used in this study had a diffusion area of 0.554 cm^2. The steady state flux (J) was determined (noting the importance of maintaining sink conditions [19]) from the slope of the best-fit linear plot of the cumulative amount of the drug permeated per unit area versus time where flux is expressed as:

$$J = \frac{C_0 KD}{L} = C_0 K_P$$

where K_P is the permeability coefficient, C_0 is the drug concentration, K is the partition coefficient, D is the diffusion coefficient and L is the thickness of the membrane [20]. All values are expressed as the mean values of three replicates shown with standard deviation based error limits. Statistical analysis was carried out using Minitab software (V.16).

3.2. Characterisation of surfactant-membrane interactions

Two analytical techniques were used to further characterise the surfactant-membrane interactions in an attempt to determine if the interaction only occurs *in situ* or, is a more permanent modification to the surface. Firstly, differential scanning calorimetry (DSC) was undertaken whereby PDMS membrane was cut to an appropriate size for investigation and left overnight in phosphate buffer (pH 7.4) with, or without, the individual surfactants present at a concentration of 20 mM. The samples were then dried with soft tissue to remove excess liquid. DSC scans of the untreated and the treated samples were performed using a DSC 1 (Mettler-Toledo Ltd., Leicester, UK), at a heating rate of 1 °C/min over a range of −60 °C–−20 °C. All DSC thermograms were assessed with regard to the phase transition of PDMS membrane, which was reported to be −40 °C [27].