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# Alcohol enhanced permeation in model membranes. Part I. Thermodynamic and kinetic analyses of membrane permeation

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ABSTRACT

While it is well recognised that formulation components influence drug permeation, few studies have addressed the influence of vehicles on drug transport in artificial or biological membranes Previously we have investigated the effects of temperature on the uptake of model vehicles (i.e. alcohols) into silicone membrane. The present study evaluates the permeation of the model drug methyl paraben in the presence of butanol or heptanol. Drug permeation through silicone membranes was studied at different temperatures for each vehicle. Thermodynamic and kinetic analyses of the permeation data were conducted to elucidate the possible mechanisms of drug transport. Independent examination of the partition and diffusion coefficients estimated for the permeation studies at different temperatures showed a break point occurring near 20 °C for butanol, but not heptanol. This transition temperature separated two different mechanisms of solute diffusion and partitioning, which may be associated with a change in the properties of the solvent. This was not observed from an analysis of flux data, owing to compensatory influences on the diffusion and partition behaviour of the drug. The study underlines the importance of appropriate temperature control when studying drug permeation.

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## 1. Introduction

Drug permeation through biological membranes depends not only on the physicochemical properties of the drug, but also on the formulation. The use of excipients that interact with the membrane, changing their physicochemical properties and consequently modulating solute transport, is a common strategy to improve dermal delivery. In this context, understanding the physicochemical determinants of vehicle-membrane interactions is crucial for selection of optimal penetration enhancers and effective formulation design.

*In vitro* studies using human skin are ideal for monitoring drug delivery and evaluation of formulations, and provide a good representation of the processes *in vivo* (Franz, 1975). Nevertheless, these studies are associated with several difficulties and limitations for assessing the effects of formulation components, particularly because of the complex nature of biological tissue and inter- and intra-individual variability of skin samples. Artificial model membranes offer a simple and reproducible alternative to study the basic physicochemical mechanisms of drug permeation, and provide a basis for understanding more complex interactions with human skin. The utility of such models, particularly of silicone membranes, for the screening of topical formulations and assessing their contribution to the overall mechanisms of drug transport across human skin is well documented in the literature (Nakano and Patel, 1970; Pellett et al., 1997; Dias et al., 2007; Watkinson et al., 2009a,b). Notwithstanding this, a recent inter- and intra-laboratory silicone membrane transport study (Chilcott et al., 2005) has reported a significant coefficient of variation between laboratories (~35%), with a fourfold difference in the highest and lowest average flux values. If artificial membranes such as silicone are to have utility as models for membrane transport then the reasons underlying this variability must be understood. Membrane-solvent interactions have been investigated using solvent uptake by many workers, including Twist and Zatz (1988). High solvent sorption can alter the physicochemical properties of the membrane and result in changes in the partition and diffusion properties of the drug, and thus modified permeation. Twist and Zatz (1988) correlated the alcohol uptake into polydimethylsiloxane (silicone) membranes with enhanced permeation of methyl and propyl paraben from the corresponding saturated alcohol solutions. Their findings related flux enhancement to increased drug solubility in the membrane and, to a lesser extent, increased diffusivity. An optimum balance between solute and vehicle concentrations was required for maximum permeation, owing to reduced solvent activity (and hence membrane sorption) of the solvent, as the solute concentration increased (Twist and Zatz, 1990). However, the authors did not address the actual

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mechanism of the alcohol–membrane interactions and the possible implications for membrane transport.

We have previously investigated the uptake of a homologous series of aliphatic alcohols with 2–10 carbon numbers into silicone membranes at different temperatures by a gravimetric method (McAuley et al., in press). An increase in alcohol membrane sorption with carbon number from ethanol to butanol (4 carbon atoms), was observed after which sorption decreased exponentially with increasing aliphatic chain length. The results were generally in agreement with the findings of Twist and Zatz (1988) obtained at 37 °C, but the highest membrane uptake was observed for butanol rather than propanol. A van't Hoff analysis of the equilibrium constants estimated at different temperatures was conducted for the alcohols with higher uptake (propanol, butanol, pentanol, hexanol, heptanol and octanol). Similar plots were obtained for all alcohols and two individual linear trends in the profiles were evident, separated by a break point occurring near 17 °C. Non-linearity in the van't Hoff plots reflected, in this case, a change in the mechanism of alcohol sorption possibly associated with the properties of the silicone-solvent system. Below the transition temperature the process was entropy driven whereas above it was dominated by the significant associated enthalpy. Additionally, changes in membrane volume related with solvent uptake suggested a different organization of the alcohol molecules inside the silicone membrane for temperatures above and below the transition temperature, which is likely to impact on the partitioning of solutes into the membrane.

The present investigation builds on the findings of the earlier study and explores the implications for butanol or heptanol uptake on membrane transport of methyl paraben. Butanol exhibited the highest uptake of all the alcohols in the previous study and heptanol was selected as representative of alcohols with a chain length >4. Thermodynamic and kinetic analyses of the membrane transport data obtained at different temperatures are evaluated to gain a mechanistic understanding of the processes involved in the solute transport across the membrane.

## 2. Materials and methods

### 2.1. Materials

Methyl paraben (methyl-4-hydroxybenzoate, puriss. ≥99%, Fluka) was supplied by Sigma–Aldrich, UK. Butan-1-ol (AnalaR® grade, BDH) and ethanol (99.7–100% v/v AnalaR® grade, BDH) were supplied by VWR UK, and 1-heptanol (98%, Aldrich) was supplied by Sigma–Aldrich, UK. Silicone membranes (250 μm thickness) were obtained from Samco, Nuneaton, UK. All solvents used in the HPLC analysis were HPLC grade and supplied by Fisher Scientific, UK.

### 2.2. Solubility studies

Saturated solutions of methyl paraben were produced by adding excess amounts of the solute to each alcohol in a glass vial containing a Teflon coated magnetic flea. The vials were allowed to equilibrate with stirring for at least 24 h at 32 °C (±0.5 °C) to produce saturated solutions with visible excess chemical. The saturated suspensions were then sampled and filtered using a syringe and filtration unit (13 mm PTFE filter media device, 0.2 μm pore size, Whatman®) previously conditioned at the same temperature to avoid further precipitation/solubilisation of the drug. The obtained saturated solutions were suitably diluted with ethanol and quantified by HPLC.

### 2.3. Permeation studies using silicone membranes

Permeation studies were conducted in Franz-type diffusion cells using pre-treated silicone membranes and "symmetric" conditions (same solvent in both donor and receptor compartments) to prevent changes in the membrane thickness during the experiment and to avoid the existence of solvent gradients across the membrane. Donor solutions of methyl paraben in 1-butanol and 1-heptanol were prepared at a concentration of 1.52 mg/ml (0.01 M). The silicone membranes were cut to appropriate size and pre-treated with the solvent for 24 h at the experimental temperature before starting the experiment. The donor and the receptor phase were also equilibrated at the experimental temperature. The receptor phase was degassed for ~3 min in a Hilsonic ultrasonicator (Hilbre Ultrasonics Ltd, England) prior to the permeation studies. Permeation experiments were conducted at 40, 30, 20, 15, 10 and 5 (±1)°C. The pre-treated membranes were carefully blotted with absorbent paper tissue before mounting in the Franz cells which were equilibrated for 30 min before starting the experiment. The actual temperature of the membranes once mounted in the Franz cells was also measured (Digitron TM-22 Differential Digital Thermometer, RS Components, Corby, UK) for the range of experimental temperatures tested. The volume of donor solution used was 1 ml and the donor compartment was covered with Parafilm® during the experiment to prevent evaporation. Collections of 200 μl were taken every 5, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110 and 120 min, with volume replacement using fresh receptor phase. At the end of the experiment, the membranes were carefully blotted to remove excess solvent and the thickness was measured (Electronic Outside Micrometer, 0–25 mm, 0.001 mm, RS Components, UK).

### 2.4. HPLC analysis

The HPLC System comprised of a Hewlett Packard HP1050 Series injector, HP1050 Series quaternary pump, HP1100 Series degasser and a HP1050 Series UV Detector. The data acquired with PRIME Software version 4.2.0 (HPLC Technology Co. Ltd). Quantification of methyl paraben was achieved by injecting 20 μl of the sample in the HPLC system equipped with a reverse-phase $C_{18}$ column (Phenomenex® Synergi 4 μm Fusion-RP 80A) and eluting the sample at room temperature with a methanol:water (60:40 v/v) mobile phase (flow rate 1.0 ml $min^{-1}$). Detection of the analyte was at 254 nm. The method was validated and proved to be suitable for accurate quantification of methyl paraben (coefficient of variance ≤10–15%; $r^2 \geq 0.999$) within the concentration range from 0.063 to 70 μg $ml^{-1}$. The estimated lower detection limit was 0.02 μg $ml^{-1}$, and the tailing factor was below the maximum acceptable value (Twist and Zatz, 1988). The method also showed good injection reproducibility (coefficient of variance < 5%, $n = 3$).

### 2.5. Data analysis

Permeation data was fitted to a finite dose model expressed as a Laplace transform (Eq. (1)) using Scientist©(Micromath, St. Louis, USA).

$$\overline{\text{Amount}} = \frac{C_v \cdot V \cdot K\sqrt{\frac{D}{s}}}{s^2 \cdot \left[A \cdot K \cdot \sqrt{\frac{D}{s}} \cdot \cosh\left(\sqrt{\frac{s \cdot h^2}{D}}\right) + V \cdot \sinh\left(\sqrt{\frac{sh^2}{D}}\right)\right]} \quad (1)$$

where $s$ is the Laplace variable, $K$ and $D$ are the partition and diffusion coefficients, $h$ is the thickness and $A$ is the area of the membrane, $V$ is the volume of donor phase, and $C_v$ is the drug concentration in the vehicle. This allows the determination of $D$, the membrane diffusion coefficient and $K$, the partition coefficient of methyl paraben when applied in the specific vehicle. Permeability coefficients ($k_p$), steady-state fluxes ($J_{ss}$) and lag times ($t_{lag}$) can also be calculated, following Eqs. (2), (3) and (4), respectively.

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