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Influence of membrane–solvent–solute interactions on solute permeation in model membranes

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Abstract

The interaction of the components of topical formulations with the skin is an important consideration for effective drug delivery and efficacy. The relative importance of solubility parameters and other solvent properties on membrane diffusion processes has not been fully elucidated in the literature. In this paper, the effect of different vehicles on the permeation of caffeine, salicylic acid and benzoic acid through silicone membranes was evaluated. Polydimethylsiloxane membranes were used as model membranes for comparing the release characteristics of saturated solutions of model permeants because of their homogeneity and uniformity. Log P (octanol–water partition coefficient) and solubility parameter values were calculated for the compounds under study. In vitro diffusion studies indicated that the permeation profiles of all solutes showed a similar pattern. The permeation rates of benzoic acid and salicylic acid through silicone membrane from saturated solutions were higher than those for caffeine reflecting the more lipophilic nature of these compounds in comparison with caffeine. Solvent uptake studies confirmed that the vehicles that were highly sorbed by the membrane altered its properties and hence the flux. Vehicles that were not sorbed by the membrane showed similar steady-state fluxes for the model drugs. This suggests that the diffusion process is mainly influenced by the interactions between the vehicles and the membrane. Solubility parameter alone cannot explain the interactions between the membrane and the vehicles in all cases. Rather, it is likely that membrane flux reflects a combination of different solvent and solute characteristics, such as size, shape and charge distribution.

Keywords: Solubility parameter; Vehicle; Dermal; Transdermal; Permeation; Flux

1. Introduction

Methods of quantifying solvent–drug and solvent–membrane interactions using solubility parameters (δ) have been suggested as useful in predicting drug flux (J). The theory of the solubility parameter was first developed by Hildebrand and co-workers based on regular solution theory (Hildebrand and Scott, 1950). A number of authors have considered the role of solubility parameter in skin permeation for example Liron and Cohen (1984) and Sloan et al. (1986). The solubility parameter is defined as the square root of the cohesive energy densities, which corresponds to the energy of vaporisation per unit volume (Eq. (1)).

$$\delta = \left(\frac{\Delta E_v}{V_m}\right)^{1/2} \quad (1)$$

where V_m represents the molar volume and E_v is the energy of vaporisation.

The solubility of a solid in a vehicle can be expressed by the following equation (Martin, 1993):

$$-\ln X_2 = \frac{\Delta H_f}{RT}\left(\frac{T_0 - T}{T_0}\right) + \frac{V_2 \Phi_1^2}{RT}(\delta_1 - \delta_2)^2 \quad (2)$$

where X_2: molar fraction solubility; Φ_1: volume fraction of solvent; V_2: molar volume of solute; R: gas law constant; T: temperature in degrees Kelvin; T_0: melting point of the solid; (H_f: molar heat of fusion; δ_1: the solubility parameter of the solvent; δ_2: the solubility parameter of drug

For a particular temperature, the first term of the equation is constant. Therefore, the solubility would be expected to increase with the decrease in the difference $(\delta_1 - \delta_2)^2$.

Permeation of a solute through a membrane is influenced by the solute activity gradient in the membrane and also by its mobility within the membrane. Solute and/or solvent

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interactions with the membrane can alter the membrane physicochemical properties. This will lead to a modified permeation through the membrane that will result from the diffusivity and partitioning of the drug in the altered membrane.

Garrett and Chemburkar (1968) reported that with increasing ethanol content, an increase in the diffusion rate of 4-aminopropiophenone through silicone membrane from saturated water/ethanol solutions was observed. Twist and Zatz (1988a,b) studied the permeation of methyl paraben through silicone membrane from saturated solutions of a series of alcohols and found that the permeation rate was not constant; uptake of neat alcohol was well correlated with the flux data. In addition, these vehicles mainly affected the partition of the drug in the membrane with less influence on the diffusion coefficient. In a further investigation (Twist and Zatz, 1990) it was observed that an increase in the paraben concentration reduced the alcohol activity, its uptake by the membrane and consequently the partition coefficient of the paraben. Therefore, it is important to have an understanding of the physical and chemical properties of the vehicles and their potential to interact with both permeant and membrane for rational design of dermal and transdermal formulations.

The aim of the present work was to investigate the effect of different vehicles on the permeation of caffeine, salicylic acid and benzoic acid through silicone membranes. Solubility parameters were calculated for the model compounds and for all vehicles studied. Polydimethylsiloxane membranes were used as model membranes for comparing the release characteristics of different formulations because of their homogeneity and uniformity. The interaction of the different solvents with the membrane was also investigated by gravimetric and calorimetric measurement.

2. Materials and methods

2.1. Materials

Caffeine was obtained from May and Baker Ltd. (UK), benzoic acid from Fisons (UK). Isopropyl myristate was obtained from Croda Universal Ltd., decanol, mineral oil and butyl acetate from Aldrich (UK), glycerol from ICN biochemicals. Propylene glycol, octanol, butanol and salicylic acid were obtained from Fisher Scientific (UK). Isopropyl lactate, butyl lactate, ethyl lactate and ethyl hexyl lactate were obtained from Purac Biochem, Gorinchem (Netherlands). Polydimethylsiloxane membranes with a thickness of 400 μm were purchased from Samco (St. Albans, UK).

2.2. Solubility parameter and Log P (octanol–water partition coefficient)

The three dimensional solubility parameters were calculated using the cohesive energies determined by the group contributions method according to Van Krevelen and Hoftyer (1976). The Log *P* (octanol–water partition coefficient) values were determined using Advanced Chemistry Development Labs. (Toronto, Canada) software.

2.3. Solubility studies

Excess drug was added to each solvent or co-solvent mixture and stirred with a magnetic bar for 48 h in a water bath maintained at 32 °C. Solutions were centrifuged for 10 min at 5000 rpm. The supernatant solution was then diluted and assayed either by HPLC (caffeine) or UV spectroscopy (benzoic acid salicylic acid). Experiments were performed in triplicate and mean values with S.D. and CV were calculated.

2.4. Diffusion cell studies

Diffusion studies of a variety of solutions of caffeine, benzoic acid and salicylic acid across silicone membrane were performed using Franz type diffusion cells with a receptor phase of 2.5 ml and a diffusional area of 1 cm^2. Sheets of silicone membrane were cut to size and soaked overnight in the receptor solution. The membrane was then placed between the two compartments of the diffusion cells and silicone grease used to produce a leakproof seal between the membrane and compartments.

The receptor compartment was filled with pH 7.4 phosphate buffered saline (PBS) and saturated solutions of the drugs were placed in the donor compartment. Excess solute was present to maintain saturation throughout the experiment. Uniform mixing of the receptor phase was obtained with a magnetic stirrer that was placed in the receptor compartment. The diffusion cells were placed on a stirring bed immersed in a water bath at 37 °C to maintain a temperature of ∼32 °C at the membrane surface.

At predetermined times 0.4 ml of the receptor phase was removed through the arm of the cell and replaced with pre-warmed buffer. Samples were analyzed by HPLC for quantification of caffeine. The whole content of the receptor phase was withdrawn at each sampling interval for UV analysis for benzoic and salicylic acid. The receptor phase was then refilled with pre-warmed buffer. Diffusion experiments were performed under occluded conditions by covering the donor compartment with microscope cover slips (this also ensured that volatile solvents did not evaporate significantly. Experiments were performed in quadruplicate for 12 h. Flux values were calculated by monitoring the cumulative amount of drug diffused and measuring the slope of the graph once steady state diffusion was reached. At least three points were plotted on the linear part of the graph. Lag times were close to zero for salicylic acid, less than 30 min for benzoic acid and less than 3 h for caffeine.

2.5. Solvent uptake

Uptake of vehicles into silicone membrane was determined gravimetrically. Silicone membrane was cut to size and weighed using a balance (Sartorius Research, 10 μg accuracy). The membranes were then placed in a sample bottle containing the vehicle and soaked overnight. The membranes were blotted dry with tissue paper and reweighed. To facilitate monitoring of solvent uptake, the experiments were performed at room temperature in triplicate. The amount of vehicle taken up into the membrane was expressed as weight percent.