Surfactant and temperature effects on paraben transport through silicone membranes

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Abstract

This study investigates the effects of two surfactants (one anionic and one non-ionic) and controlled modifications in temperature (298 K to 323 K) on the permeation of two structurally similar compounds through a silicone membrane using a Franz diffusion cell system.

In all cases the presence of an anionic surfactant, namely sodium dodecyl sulphate (SDS), reduced the permeation of both compounds (methylparaben and ethylparaben) over a period of 24 hours. The degree of permeation reduction was proportional to the concentration of surfactant with a maximum effect observed, with an average reduction of approximately 50%, at the highest surfactant concentration of 20 mM. Differences were seen around the critical micelle concentration (CMC) of SDS implying the effect was partially connected with the favoured formation of micelles. In contrast, the presence of non-ionic surfactant (Brij 35) had no effect on the permeation of methylparaben or ethylparaben at any of the concentrations investigated, both above and below the CMC of the surfactant. From these findings the authors conclude that the specific effects of SDS are a consequence of ionic surfactant-silicone interactions retarding the movement of paraben through the membrane through indirect modifications to the surface of the membrane.

As expected, an increase in experimental temperature appeared to enhance the permeation of both model compounds, a finding that is in agreement with previously reported data. Interestingly, in the majority of cases this effect was optimum at the second highest temperature studied (45 °C) which suggests that permeation is a temperature-dependent phenomenon.

Keywords

Silicone membranes; surfactant; temperature; paraben; skin permeability; in vitro

1. Introduction

When applying compounds to the skin it is important to be aware of their ability to penetrate transdermally, regardless of whether this is the desired effect or not. If a compound is found to exhibit transdermal penetration then this may influence the pharmaceutical and/or cosmetic applications and commercial usage. The outermost layer of human skin (*stratum corneum*) is the main barrier the body has against external compounds entering the internal system and this must be overcome if a compound is to be used as a transdermal product. In the last twenty years a variety of chemical penetration enhancers have been developed which employ compounds targeted for transdermal delivery using a range of modes of action [1]. Formulations are often developed using specific groups of excipients that have a known human skin penetration effect (HSPE). These include terpenes [2], fatty acid esters [3], pluronic gels [4], liposomes [5] and nanoemulsions [6]. One group of compounds that have shown an ability to alter the permeability characteristics of human skin is surfactants [7, 8] where they are known to intercalate with lipid bilayers in the *stratum corneum*, thus increasing fluidity. Previous studies have investigated the effects of surfactants on skin penetration using a wide range of compounds including ionic and non-ionic based systems [9]. One recent study, using surfactants as penetration enhancers in transdermal drug delivery found that the penetration of the surfactant molecule into the lipid lamellae of the *stratum corneum* is strongly dependent on the partitioning behaviour and solubility of the surfactant [10]. Findings such as these confirm that there is no doubt surfactants can, and have, been used to enhance the extent of penetration of compounds intended for transdermal delivery.

Similar, yet more complex, surfactant based systems have also been developed; these include the formation of elastic vesicles [11] and the use of surfactants in combination with

iontophoresis to enhance transdermal drug delivery [12]. Literature reports that there are clear relationships observed between the physicochemical properties of the compound under investigation and the surfactant choice, resulting in some circumstances where only a minimal enhancement is observed. One such example is the attempted enhancement of methotrexate using different types of surfactants, where sodium lauryl sulphate did not show a significant enhancement effect for this particular drug [13]. In summary, the presence of enhancers, such as surfactants, along with other variables, are known to affect compound permeation through human skin, though only a limited amount of research has considered the impact of such changes with respect to a frequently used *in vitro* skin mimic, namely silicone membrane. Synthetic membranes, such as the aforementioned silicone membrane, are often used to simulate the *stratum corneum* in drug diffusion studies, for example, in Franz-type diffusion studies. More specifically, polydimethylsiloxane (PDMS) has become an accepted *in vitro* skin mimic and is frequently employed to aid prediction of the movement of drugs alongside its use for the quality assessment of compounds [14, 15]. Comparisons with results obtained using human or animal skin are numerous, often highlighting differences between their ability to transport solutes through their molecular structures [16] with faster permeation rates often observed with silicone membranes [17]. Unsurprisingly, in recent years, alternatives to the more traditional methods have been developed [18] yet Franz-type diffusion cells still remain a leading experimental strategy for predicting the movement of compounds through skin.

One group of compounds that is widely used in cosmetic and pharmaceutical products applied to the skin is the parabens, specifically the methyl (MP), ethyl (EP), propyl (PP) and butyl (BP) derivatives, which are used alone or in a variety of combinations as preservatives. These compounds have previously been investigated to determine their transdermal permeation

using animal skin [19] and human skin [20, 21] and therefore they are ideal when requiring a model set of compounds for analysis, as in this study. The Scientific Committee on Consumer Safety (SCCS) reported in March 2011 that these same four paraben based compounds are safe to the consumer in finished cosmetic products as long as the sum of their individual concentrations does not exceed 0.19% [22]. However, these particular compounds have the ability to both permeate through and accumulate in skin, giving rise to some concern for what their potential toxic and carcinogenic properties may impart [23].

To probe these model compounds, this study comprises an investigation into the effects of surfactants on the transport of paraben derivatives through silicone membrane. Surfactant molecules contain both hydrophobic and hydrophilic regions and are known to spontaneously aggregate to form micellar systems upon reaching a certain concentration and temperature. Surfactants have been employed in a variety of analytical techniques including chromatographic systems [24] and calorimetric systems [25] yet very limited research has focused on the effect of surfactants on transport through silicone membranes. One study has considered the effect of the addition of 6% sodium lauryl sulphate on the diffusion of pentachlorophenol and found that this additive gave rise to reduced absorption and opposed dermal transport [26].

Transdermal permeation, through both human skin and silicone membrane, is a thermodynamic event and therefore also known to be influenced by temperature modifications. Model penetrants, including methylparaben and ethylparaben, have been investigated to determine the effect of heat on transdermal delivery with differences observed in permeation kinetics [27, 28] using human skin and cellulose membrane. A similar study found that for methylparaben in the presence of butanol and heptanol a break point in diffusion coefficient was observed around 20 ºC, highlighting the importance of temperature control [29, 30] with similar

studies identifying the role of solvent uptake [31]. In addition, temperature dependence has been observed for skin permeability with respect to activation energies with some differences observed between model predictions and experimental data [31, 32].

Although various surfactants have been used to enhance drug permeability, little research has focused on drug-surfactant interactions in conjunction with surfactant-membrane interactions. One study has considered a similar interaction for the former, namely determining *in vitro* permeability coefficients for three model drugs using regenerated cellulose dialysis membrane [33] with the extent of interaction described either by hydrophobic effects or electrostatic effects, depending upon the charge associated with the chosen drug. Thus, for the two drugs without a significant hydrophobic surface area (timolol and cefoxitin) their interactions were dictated by electrostatic (charge) effects whereas for the third compound (that was far more hydrophobic), interactions were dictated by hydrophobic effects.

In this paper, studies of the transport of methylparaben and ethylparaben are investigated using Franz-type diffusion cells in the presence of two surfactants over a range of temperatures. Data acquired provides an insight into the nature and extent of movement for each compound through PDMS silicone membrane. Moreover, experiments will provide an insight into the interactions not only between the model compounds and the surfactants, but also between the surfactants and the silicone membrane over a range of temperatures.

2. Experimental

2.1 Materials

Two model compounds were considered, namely methylparaben (methyl 4-hydroxybenzoate) and ethylparaben (ethyl 4-hydroxybenzoate), obtained from Sigma-Aldrich,

Dorset, UK. These compounds were investigated in conjunction with sodium dodecyl sulfate (SDS) (Sigma-Aldrich, Dorset, UK) and Brij 35 (Fisher Scientific, Loughborough, UK) in a pH 7.4 buffer solution composed of mono-potassium hydrogen phosphate and di-sodium hydrogen phosphate (Sigma-Aldrich, Dorset, UK) with sodium chloride (Fisher Scientific, Loughborough, UK) to control the ionic strength. Silicone membrane (PDMS) was purchased from ATOS Medical, Horby, Sweden and used as received.

2.2 Franz cell experiments

In all experiments the paraben derivative concentration in the donor solution was initially 5 mM with either SDS or Brij 35 also present at concentrations of 0, 4, 8 or 20 mM for the former and 1.0 or 10 mM for the latter, i.e. either below, equal or above the critical micellar concentration of each surfactant. The receptor compartment of each cell was filled with pH 7.4 phosphate buffer and stirred constantly whilst placed in a temperature controlled water bath at 25, 30, 37, 45 or 50 ºC containing a submerged stirrer plate and left to equilibrate. The donor solution containing paraben derivative and/or surfactant was then added to the cell, separated by silicone membrane from the receptor solution. Samples were routinely removed from the receptor compartment and replaced with fresh buffer stored at the same experimental temperature. Extracted samples were analysed using UV spectroscopy (λ=245nm) over a period of 24 hours to quantify the model compounds. All experiments were conducted in a minimum of triplicate with the mean value presented with standard deviation based error limits. All diffusion cells used in this study were based on an experimental diffusion area of 1.03cm^2 and a cell volume of 4 mL.

3. Results & Discussion

3.1 Effect of the presence of Sodium Dodecyl Sulfate on paraben derivative transport

As a control, the transport of methylparaben through silicone membrane was analysed at 25 °C with no SDS present in the donor phase over a period of twenty four hours. Three further solutions were then prepared containing 4, 8 and 20 mM SDS and the transport of methylparaben through the membrane measured (Figure 1).

It can be seen in Figure 1 that the presence of SDS significantly affects the transport of methylparaben through silicone membrane over a period of twenty four hours with an approximate halving in the amount permeated after this period at the highest concentration investigated. Overall, it would appear that there is a direct relationship between the concentration of surfactant and the reduction in the amount permeated. Unexpectedly though, the amount permeated after twenty four hours for the 8 mM SDS solution appeared slightly greater than that for 4 mM. This may be a result of reaching the critical micellar concentration (CMC), at which point the surfactant behaves differently with respect to transport rate through the membrane. A similar result was also observed for ethylparaben, i.e. a clear relationship can be seen where an increase in SDS concentration likewise decreased the amount of paraben permeated (Figure 2). Overall though, the total amount of ethylparaben permeated is less than that for methylparaben which is expected as the ethyl derivative is the more hydrophobic of the two.

In addition to the presence of surfactant, the effect of temperature was also investigated to ascertain the influences it may have on the permeation of the model compounds. Firstly, the system was considered in the absence of surfactant at 25, 30, 37, 45 and 50 °C (Figure 3) where

it can be seen that temperature changes do indeed affect the transport of methylparaben through silicone membrane.

There is no doubt that temperature changes do play an influential role in the transport process; for example, from 25 °C to 45 °C the amount permeated after twenty four hours increased from an average of 311 to 592 μg/cm^2, i.e. an increase of an additional 90% permeated. As with the effect of the presence of surfactant, a similar relationship was observed for ethylparaben where an overall increase in permeation was observed with increased temperature (Figure 4).

The combined effects of the presence of surfactant and controlled modifications in experimental temperature are shown to affect the cumulative amounts of paraben permeated over a period of twenty four hours with SDS concentrations of 4 mM and 20 mM (Figures 5 and 6 respectively).

Through comparing the results presented in Figures 3, 5 and 6 it is possible to observe that an increase in experimental temperature enhanced the transport of methylparaben, regardless of surfactant concentration. With no SDS, 4 mM SDS or 8 mM SDS, the maximum amount permeated appeared to occur at 45 °C, rather than the highest temperature studied; indicating this temperature to be the optimum for methylparaben transport. However, it can also be seen that the previously observed trend continues - where an increase in the concentration of SDS reduces methylparaben permeation over all temperatures studied. Again, similar results were observed with SDS and ethylparaben (data not shown). In summary, these findings confirm that both

temperature and SDS play a significant role in the transport of methylparaben and ethylparaben across silicone membrane.

3.2 Effect of the presence of Brij 35 on the transport of paraben derivatives

Previously it has been shown that the anionic surfactant SDS dramatically reduced the transport of methylparaben and ethylparaben through silicone membrane over a range of experimental temperatures. To confirm if this phenomenon is a result of the SDS in particular (or a more widely observed trend) a further study was conducted focusing on the transport of the model compounds in the presence of the non-ionic surfactant Brij 35. Firstly, the transport of methylparaben was investigated at 25 °C in the presence of three concentrations of the non-ionic surfactant to determine if they had the same ability to reduce permeation through silicone membrane over twenty four hours (Figure 7).

Figure 7 clearly shows that the presence of this non-ionic surfactant does not retard the transport of methylparaben in a similar manner to that observed for the anionic surfactant previously investigated. Again, a comparable effect was seen for ethylparaben, i.e. no significant reduction in the amount permeated was observed over the course of the experiment (data not shown).

As previously discussed, temperature can influence the transport of compounds through silicone membrane and therefore a systematic increase in temperature was introduced to the system, as summarised in Figure 8.

In line with Figure 7, it would appear that there is no alteration in the amount of methylparaben permeated after twenty-four hours at any temperature investigated with any amount of this surfactant present. Moreover, with an increase in temperature there is an appreciable increase in the amount of methylparaben permeated with a maximum amount recorded at 45 °C, in agreement with that observed in the absence of SDS.

In summary, the transport of both methylparaben and ethylparaben across PDMS membrane is influenced by the presence of SDS yet not by the presence of Brij 35. With only 20 mM of SDS present the amount of compound permeated after twenty-four hours had been reduced by approximately half, indicating that the anionic surfactant was preventing the paraben esters from moving through the membrane and passing into the receiver compartment. In contrast to this, the presence of a non-ionic surfactant had no appreciable effect on the movement of paraben esters through the membrane into the receiver phase. These findings imply that SDS is creating a barrier effect, preventing movement through the silicone membrane – a situation not apparent with Brij 35. As it is widely known that the membrane is a predominantly hydrophobic structure, it can postulated that the hydrophobic regions of the anionic surfactant are submerged within the membrane which will, in turn, result in the charged head groups being present at the membrane surface exposed to the aqueous buffer solution of the donor phase. As the paraben derivatives are regarded as neutral species, they may be reluctant to approach the SDS impregnated PDMS surface as it presents a negatively charged environment thus repelling the paraben away from the membrane resulting in a reduction in transport through to the receiver phase. The fact that the amount permeated for 4 mM after twenty-four hours is less than that for 8 mM may indicate that the surfactant experiences an equilibrium between associating with the membrane surface or existing freely in solution as micelles. Therefore, at 8 mM the SDS

preferentially exists as the micellar form as it approaches the CMC, leaving little 'spare' surfactant to interact with the membrane surface. Given the surface area of the membrane available, it is plausible that in all cases the surfactant concentration exceeds that required to saturate the membrane surface, yet this requires the presence of free surfactant monomer. Results for the 20 mM SDS show a greater retardation in permeation than all others thus suggesting a complex equilibria between free monomer, monomer-surface interactions and micellisation must coexist in the solution. As Brij 35 does not possess a charged head group the same phenomenon would not occur to repel the parabens away from the silicone surface, and hence no reduction in transport would result.

The second factor considered in this study was temperature and, in agreement with previously reported literature [27], in all cases an expected general increase in permeation through the membrane was observed with an increase in experimental temperature between 25 and 45 ºC. From previous publication in this area, a single mechanism for solute diffusion through membranes appears to operate from 16 up to 45 ºC [31] in which the transport of solute increases with increasing temperature. In this case this general trend is observed from our experimental temperatures from 25 to 45 ºC. However, above 45 ºC the transport of both parabens through the membrane is more complex.

For both SDS and Brij 35 studies involving a modification in the experimental temperature an important point to note is that the effect of the change on the CMC should not be ignored. It is widely recognised that the CMC for a surfactant is temperature dependent and is dictated by the change in heat capacity of micellisation and the fractional degree of counterion binding[34]. For the purpose of this study however, it is assumed such influences are minimal on the overall process and the surfactant-membrane interaction is the dominant factor.

4. Conclusion

Overall it can be seen that the presence of a particular anionic surfactant reduced the transport of both methylparaben and ethylparaben through silicone membrane. Moreover, there was a clear inverse relationship between the amount of compound permeated and SDS present. This phenomenon was not observed for Brij 35 implying the effect is related to the head group charge of the surfactant under investigation. Based on this theory it is plausible that a result similar to that observed for SDS would also be observed in the presence of a cationic surfactant, such as hexadecyltrimethylammonium bromide (CTAB). In this hypothetical case, a positively charged surface would form on the membrane thus reducing the likelihood the neutral paraben molecule would permeate through.

With respect to temperature, a relationship was observed between the amount of paraben derivative permeated through the membrane and an increase in temperature. Unexpectedly, for the majority of cases a maximum effect was observed at 45 ˚C rather than the higher temperature of 50 ˚C. The reasons for this observation are currently unclear and are the focus of current work, for example, firstly through pre-treating the membrane and secondly saturating the donar solution - thus normalising surfactant-paraben interactions and permitting calculation of permeability coefficients. In addition, it would have been beneficial to study further paraben based compounds in the series such as propylparaben but their reduced solubilities prevented such experiments to be undertaken.

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