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

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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.

Keywords: silicone; PDMS; transdermal; permeation; surfactant; charge

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 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.

Materials and Methods

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

Methods

Permeation studies

PDMS membrane was soaked in phosphate buffer solution (0.02 M pH 7.4 and 0.15 M NaCl) for 30 minutes 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:

$$J = \frac{C_0 K D}{L} = C_0 K_P$$

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).

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 to -20 °C. All DSC thermograms were assessed with regard to the phase transition of PDMS membrane, which was reported to be -40 °C [27].

FT-IR analysis of the untreated and treated membranes (as described above) was performed using a Nicolet IR 380 spectrometer. The samples were cut into suitable sizes and placed in direct contact with the diamond crystal of the spectrometer over the range of 4000-400 cm^{-1} and analysed with Omnic software (version 7.2a).

Results and Discussion

Four model compounds were analysed to investigate the permeation effect of surfactant charge across PDMS membrane. The model compounds were benzocaine, benzotriazole, ibuprofen and lidocaine, having a diverse range of lipophilicities ranging from a log P of 1.2 for benzotriazole[21] to 3.6 for ibuprofen[11]. The surfactants were chosen to include all four categories, namely SDS (anionic), CTAB (cationic), CHAPS (zwitterionic) and Brij 35 (non-ionic).

As a control, the permeation of the model compounds through silicone membrane were assessed at 32 °C with no surfactant present in the donor solution over a period of 6 hours. Three additional solutions were then prepared containing the surfactants at three different concentrations (4, 8 and 20 mM for SDS, CTAB, Brij 35 and Tween 80, and 2, 4 and 20 mM for CHAPS), and the permeation of the model compounds was measured. The

concentrations of the surfactants were chosen to be either below, equal or above the critical micellar concentration (CMC). Two permeation parameters, namely, steady-state flux (J) and the cumulative amount of compound permeated after 6 hours (Q_6), were calculated from the data obtained using a flow-through diffusion cell system and are summarised in Tables 1 and 2. The steady-state flux (J) values of the compounds were analysed statistically using One-way ANOVA to determine p-values to confirm whether the variability in surfactant type and/or concentration caused a significant difference in compound permeability.

In a simple scenario, all donor solutions of the same penetrant should yield an identical steady-state flux across a membrane, not depending on the composition of the vehicle, provided that the formulation components do not interact with the membrane [22]. Therefore, the steady-state flux of a compound from donor solutions from any of the surfactant-containing vehicles would be anticipated to be same. However, the data presented in Table 1 demonstrate that the flux values of the penetrants are not identical. In all cases, interactions between either surfactant and membrane, or drug and surfactant were observed that could possibly have altered the compound flux across the membrane, i.e. these interactions were affected by surfactant concentration and surfactant type.

Table 1

Steady-state flux values of four model compounds in the presence of SDS, CTAB, CHAPS and Brij 35 across silicone membrane

Surfactant in the donor phase	Steady-state flux (μg/cm^2/h) of compound			
	Benzocaine	Benzotriazole	Ibuprofen	Lidocaine
SDS 0 mM	97.92 ± 2.22	18.33 ± 0.80	26.25 ± 1.95	69.70 ± 1.12
SDS 4 mM	89.80 ± 1.70	17.94 ± 0.43	27.53 ± 1.40	43.07 ± 1.70
SDS 8 mM	89.16 ± 0.85	13.75 ± 0.23	23.37 ± 1.27	31.69 ± 3.10
SDS 20 mM	62.87 ± 1.84	12.21 ± 0.26	21.29 ± 1.55	13.54 ± 1.08
CTAB 0 mM	104.59 ± 3.22	9.96 ± 0.58	21.15 ± 1.46	56.98 ± 6.64
CTAB 4 mM	70.77 ± 6.79	9.51 ± 0.27	9.82 ± 0.55	52.93 ± 4.63
CTAB 8 mM	56.71 ± 2.94	8.00 ± 0.25	5.12 ± 0.75	47.77 ± 6.77
CTAB 20 mM	38.82 ± 5.48	6.88 ± 0.23	2.37 ± 0.31	37.66 ± 3.23
CHAPS 0 mM	107.95 ± 3.99	10.46 ± 0.53	32.13 ± 1.12	55.28 ± 6.64
CHAPS 2 mM	105.10 ± 6.75	10.14 ± 0.51	32.48 ± 1.76	54.68 ± 3.73
CHAPS 4 mM	106.75 ± 5.42	9.45 ± 0.26	18.50 ± 0.39	52.62 ± 3.05
CHAPS 20 mM	87.53 ± 4.10	9.47 ± 0.18	9.90 ± 1.93	49.94 ± 4.01

Brij 35 0 mM	102.07 ± 6.88	13.30 ± 0.09	31.00 ± 1.83	64.84 ± 3.66
Brij 35 4 mM	77.54 ± 5.67	13.04 ± 0.73	26.50 ± 1.69	66.96 ± 3.09
Brij 35 8 mM	63.29 ± 2.61	10.62 ± 0.43	17.49 ± 0.12	60.48 ± 4.07
Brij 35 20 mM	43.36 ± 1.15	9.58 ± 0.37	12.29 ± 0.33	57.44 ± 2.57

To understand the effect of individual surfactant type and concentration, the cumulative amount of compound permeated after 6 h was also considered (Table 2). It can be seen from Table 2 that the amount of the model compounds permeated after 6 hours varies with a change in surfactant concentration and type. Moreover, the compounds' permeability profiles were shown as percentage permeated after 6 h, graphically, in Figs. 1 – 4 in an attempt to provide a comprehensive understanding of the relationship between the surfactant concentration and the reduction in the amount permeated. In all of the figures (Figs. 1 – 4) the amount permeated after 6 h for the control solution was normalised to 100 %, with values for other solutions calculated accordingly. Such presentations offer a convenient way of comparing different active compounds in terms of the effect on their permeation by a surfactant.

Table 2

Cumulative amount permeated after 6 hours (Q_6) of four model compounds in the presence of various surfactants across PDMS membrane

Surfactant in the donor phase	Amount of compound permeated (μg/cm^2) after 6 h			
	Benzocaine	Benzotriazole	Ibuprofen	Lidocaine
SDS 0 mM	570.65 ± 13.00	110.80 ± 3.90	155.67 ± 10.95	410.35 ± 8.29
SDS 4 mM	526.98 ± 11.19	108.55 ± 2.60	163.60 ± 8.24	253.74 ± 11.36
SDS 8 mM	520.29 ± 4.56	83.72 ± 1.33	138.18 ± 6.53	187.76 ± 17.99
SDS 20 mM	370.01 ± 10.93	74.63 ± 1.24	126.20 ± 9.45	81.17 ± 6.68
CTAB 0 mM	611.95 ± 20.24	60.06 ± 3.23	126.09 ± 8.67	333.97 ± 37.25
CTAB 4 mM	412.35 ± 37.75	57.66 ± 2.03	60.67 ± 3.51	314.68 ± 27.91
CTAB 8 mM	336.94 ± 17.46	48.92 ± 1.40	31.88 ± 4.27	283.63 ± 41.67
CTAB 20 mM	229.99 ± 31.91	41.99 ± 1.41	15.23 ± 1.80	221.73 ± 20.32
CHAPS 0 mM	635.17 ± 23.38	62.59 ± 3.57	188.30 ± 7.40	322.81 ± 39.99
CHAPS 2 mM	617.92 ±	61.18 ± 3.07	194.57 ± 10.60	318.98 ± 21.29

	41.17			
CHAPS 4 mM	630.04 ± 31.97	56.85 ± 1.67	109.94 ± 1.93	308.78 ± 19.19
CHAPS 20 mM	517.98 ± 24.85	56.72 ± 1.16	59.05 ± 11.19	293.14 ± 24.37
Brij 35 0 mM	600.99 ± 39.63	80.90 ± 0.64	185.47 ± 10.62	380.52 ± 22.63
Brij 35 4 mM	456.40 ± 32.33	79.45 ± 4.24	158.84 ± 10.30	394.04 ± 18.87
Brij 35 8 mM	372.96 ± 14.80	64.79 ± 2.29	105.09 ± 0.51	354.49 ± 24.16
Brij 35 20 mM	257.46 ± 6.52	58.10 ± 2.22	74.88 ± 2.15	337.36 ± 15.73

In the first set of experiments, permeation of benzocaine, benzotriazole, ibuprofen and lidocaine through silicone membrane from the donor solutions containing SDS (an anionic surfactant) at three different concentrations (4, 8 & 20 mM) were evaluated. It can be seen in Fig. 1 that the presence of the anionic surfactant significantly ($p < 0.05$) affected the transport of all compounds over a period of 6 h with the lowest percentage permeated observed at the highest concentration of surfactant examined.

Overall, the results here would indicate that the reduction in the amount permeated is directly related to the concentration of surfactant. These results are similar to the findings of a recent study where Waters and co-researchers reported a decrease in the permeation of paraben derivatives with an increase in SDS concentration in the donor solution [17]. It can be seen in Fig. 1 that the maximum reduction in permeation of each compound resulted from 20 mM SDS being present in the donor compartment, with lidocaine experiencing a reduction of 80.22 %, being the greatest reduction when compared with other model compounds, and ibuprofen having the least reduction of 18.93 %.

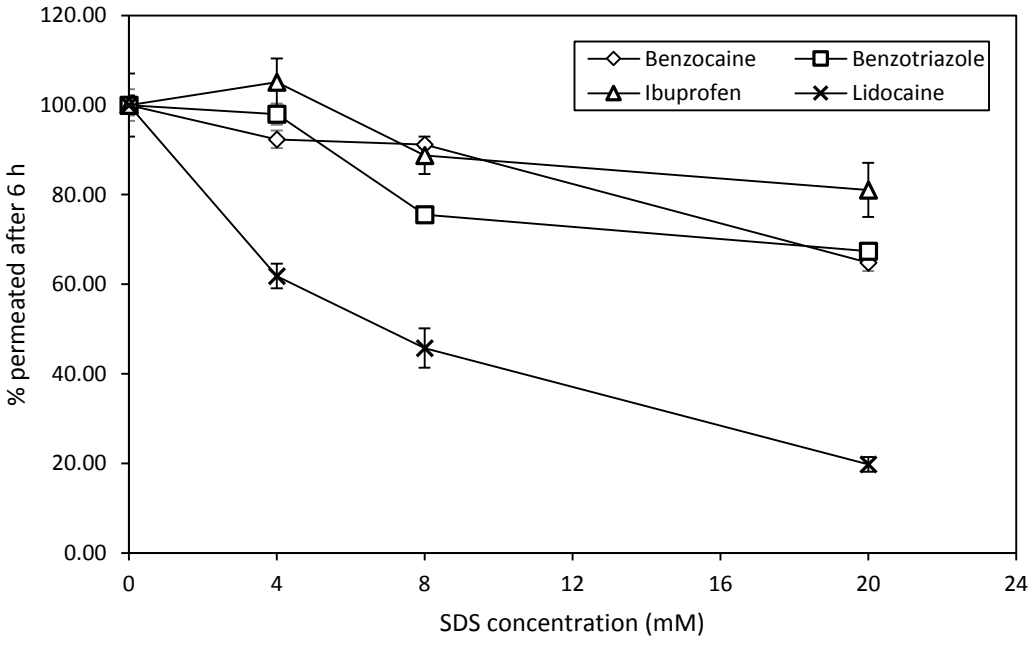

Fig. 1. Effect of the presence of SDS on compound permeation across PDMS membrane.

The other noticeable phenomenon in Fig. 1 is that the permeability profiles of benzocaine, benzotriazole, and ibuprofen, position themselves, more likely, to be part of a group whereas lidocaine is very distinctive in this regard. From a physicochemical perspective, lidocaine is basic in nature whereas the other three compounds are regarded as acidic. Thus, upon ionisation in buffer solution, lidocaine produces cations while benzocaine, benzotriazole, and ibuprofen, produce anions. Hence, the compounds, in donor solutions, would exist as ionised (charged) species and unionised (neutral) species. As PDMS membrane is predominantly hydrophobic in nature, only the neutral species can pass through the membrane while the charged species stay in the donor solution. Although both the neutral and charged (anionic and cationic) species can interact with SDS, the interaction of SDS with an anion could not be the same as that with a cation, and this variation might result in the compounds experiencing dissimilar effects in the presence of SDS.

It is clear that the influence on compound permeability can result from a multidimensional interaction or a mixture of interactions, such as, surfactant-membrane, and/or surfactant-drug interactions. One previous study from our group suggested surfactant-membrane interaction to be a triggering factor in the reduction of compound permeation[17]. That study assumed that the hydrophobic tail of SDS was submerged within PDMS membrane, thus, resulting in the charged head group exposed to the donor solution. Therefore, it was proposed that the SDS impregnated membrane surface create a negatively charged environment which would, in turn, repel the neutral species of compound. This study found 20 mM SDS to produce a greater hindrance in permeation than all others (0, 4 and 8 mM SDS) which, was suggested, was because of the coexistence of free monomer, monomer-membrane surface interactions and micellisation. It is noticeable that the above-mentioned mechanisms offer a comprehensive explanation of SDS effect on the overall reduction in compound permeation. However, the fact that SDS produces a dissimilar effect for different compounds, cannot be addressed by applying these mechanisms.

If only the unionised form of compound can permeate through PDMS membrane, the extent of permeation depends on the availability of compounds in unionised form in the donor compartment of the diffusion cell. In solution, an equilibrium exists between unionised and ionised forms while maintaining a specific ratio between the two forms depending on the pH of the solution. For example, in a buffer solution of pH 7.4, ibuprofen (p*K*a = 4.9[23]) would have 0.32 % of total as the neutral (unionised) and 91.68 % as the anionic (ionised) species whereas lidocaine (p*K*a = 7.8[24]) would have 24.02 % as the neutral and 75.98 % as the cationic species. This ratio gives the actual percentage of species in the donor solution, provided that they do not interact with other components such as surfactant. However, this might not be the case for lidocaine. As lidocaine produces cations in the solution, a portion of these ions might weakly bond the anionic head groups of SDS. In other words, a portion of cationic lidocaine molecules, from the bulk solution, will migrate to the SDS-submerged membrane surface. Therefore, to maintain the equilibrium ratio between two species (ionised and unionised) in the bulk solution a certain number of unionised species would be converted to the ionised form which, in turn, decreases the number of neutral (unionised) lidocaine molecules available to diffuse through the membrane. In the case of a micellar surfactant solution, an additional interaction can happen where the cationic lidocaine species interacts with SDS head groups in the micelles thus further decreasing the number of neutral lidocaine

molecules that would pass through the membrane. In both cases, the permeation of lidocaine would be further reduced. These scenarios might not be observed for benzocaine, benzotriazole and ibuprofen, as upon ionisation they produce anions which would be repelled by the SDS head group, and stay in the bulk solution i.e. the equilibrium ratio of ionised and unionised forms would not be affected.

A second type of surfactant was investigated in this study, namely a cationic surfactant, cetyltrimethylammonium bromide (CTAB). Fig. 2 shows the permeability profiles of the compounds in the presence of CTAB. Fig. 2, along with the calculated *p*-values (< 0.05) clearly indicate that the compound fluxes were significantly influenced by the cationic surfactant being present in the donor solution.

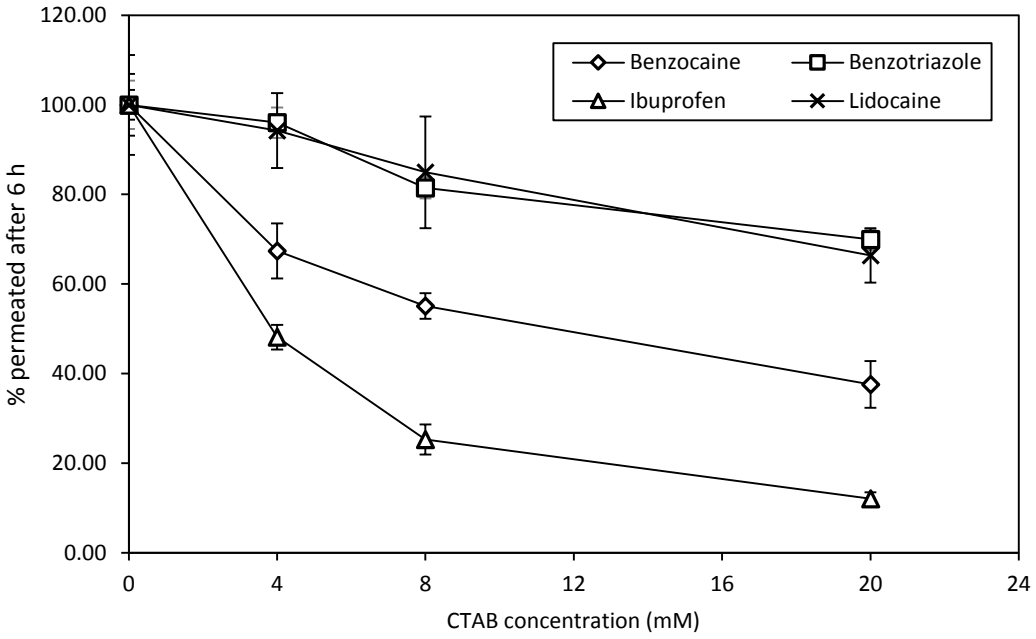

Fig. 2. Effect of the presence of CTAB on compound permeation across PDMS membrane.

Such an effect of CTAB was hypothesised in a previous study where it was assumed that CTAB would reduce the transport of paraben derivatives (the model compounds considered in the study) across PDMS membrane[17]. The hypothesis stated that CTAB would create a positively charged membrane surface i.e. the hydrophobic tail of CTAB would be submerged within PDMS membrane thus exposing the cationic head group to the donor solution, and consequently, this would reduce the likelihood of the permeation of neutral paraben molecules through the membrane. The same mechanism could be observed in this study. In other words, the positively charged CTAB-submerged membrane surface could repel the compound molecules away from the membrane resulting in an overall reduction in permeation. As mentioned earlier (in the case of SDS), though this mechanism may explain the reduction of compound permeation in general, it cannot clarify the inter-difference amongst the compounds in terms of percentage reduced. It can be seen from Fig. 2 that the percentage of the amount reduced by CTAB is different for each compound.

Although both SDS and CTAB create a barrier effect in compound permeability, the overall trend they follow is different. From Fig. 1 and 2, if the percentages of overall

reduction are placed in an order, then for CTAB the order appears as ibuprofen > benzocaine > lidocaine > benzotriazole whereas, for SDS it becomes lidocaine > benzocaine > benzotriazole > ibuprofen. In general, the reduction effect of both these surfactants on compound permeation is different for each drug. Previously, it was mentioned that the difference produced by SDS was because of the interaction between its anionic head groups and ionised compound species in the donor solution. In the case of CTAB, the difference in compound reduction can be the result of the interaction between its cationic head groups and ionised species of the compounds. If the hydrophobic regions of CTAB are submerged in PDMS membrane this will expose the cationic head groups to the donor solution, making a positively charged membrane surface. A portion of anionic species, which are formed upon ionisation of acid compounds, may migrate to the positively charged membrane surface, and weakly bond the cationic head groups of CTAB. Consequently, to maintain the equilibrium ratio between ionised and unionised forms of acid compounds in the bulk solution, a number of unionised species are converted to the ionised (anionic) species, thus, decreasing the total available number of neutral molecules to be transported across the membrane. In the case of a micellar solution, the number of neutral molecules can be further decreased because of the interaction between the anionic form of the compound and the cationic head group of CTAB. In both scenarios, the compound would experience a reduction in transport through PDMS membrane. However, the aforementioned circumstances may not be observed for lidocaine as it forms a cation upon ionisation which is repelled by the cationic CTAB head. Unexpectedly, even though benzotriazole forms an anion upon ionisation, it was not affected by the scenarios mentioned above. One possible explanation for this anomaly is the comparatively high pKa of benzotriazole, indicating it is a very weak acid, compared with benzocaine and ibuprofen. Although this difference did not appear to be an influential factor when SDS was present, it may be significant enough to result in benzotriazole behaving in a similar way to lidocaine in the presence of CTAB. Alternatively, this anomaly may be the result of a complex chemical interaction which is currently unclear and the focus of current study.

The third type of surfactant, investigated in this study, was a zwitterionic surfactant, namely CHAPS. The effect of CHAPS on compound permeation is shown in Fig. 3.

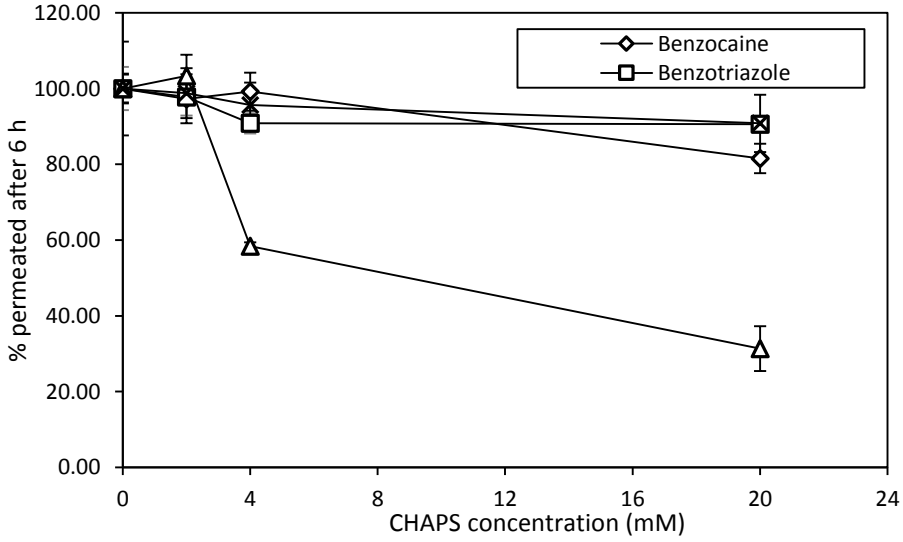

Fig. 3. Effect of the presence of CHAPS on compound permeation across PDMS membrane.

Figure 3 indicates that the overall permeation of compounds, except for ibuprofen, was not significantly affected by CHAPS. Additionally, the permeation of ibuprofen was reduced only in the presence of CHAPS being present at, and above its CMC which is between 4 and 6 mM[25]. At 2 mM, i.e. below the CMC, CHAPS did not affect ibuprofen permeation. This may be the result of an interaction between the ibuprofen molecules and CHAPS micelles as upon reaching the CMC, the surfactant forms micelles. The formation of surfactant micelles creates a hydrophobic core which contains the hydrophobic regions of surfactant and it is known that the hydrophobic core of micelles can strongly interact with hydrophobic molecules and entrap them inside the core [26]. A similar mechanism can be observed in this study where ibuprofen, with a log P value of 3.6[11], strongly interacted with the hydrophobic core of CHAPS micelles and became trapped inside them thus reducing the number of ibuprofen molecules available to cross through PDMS membrane. Consequently, there would be a reduction in ibuprofen permeation. As the other three compounds are relatively less hydrophobic, they might not as strongly interact with CHAPS micelles and hence, their fluxes would not be as significantly affected.

This study also investigated the effect of a non-ionic surfactant, namely Brij 35, on drug transport across PDMS membrane. The results (Fig. 4) indicate that the presence of this non-ionic surfactant significantly retarded the overall transport of all compounds except for lidocaine. It can also be seen that the permeation of lidocaine and benzotriazole remain unaffected in the case of 4 mM Brij 35.

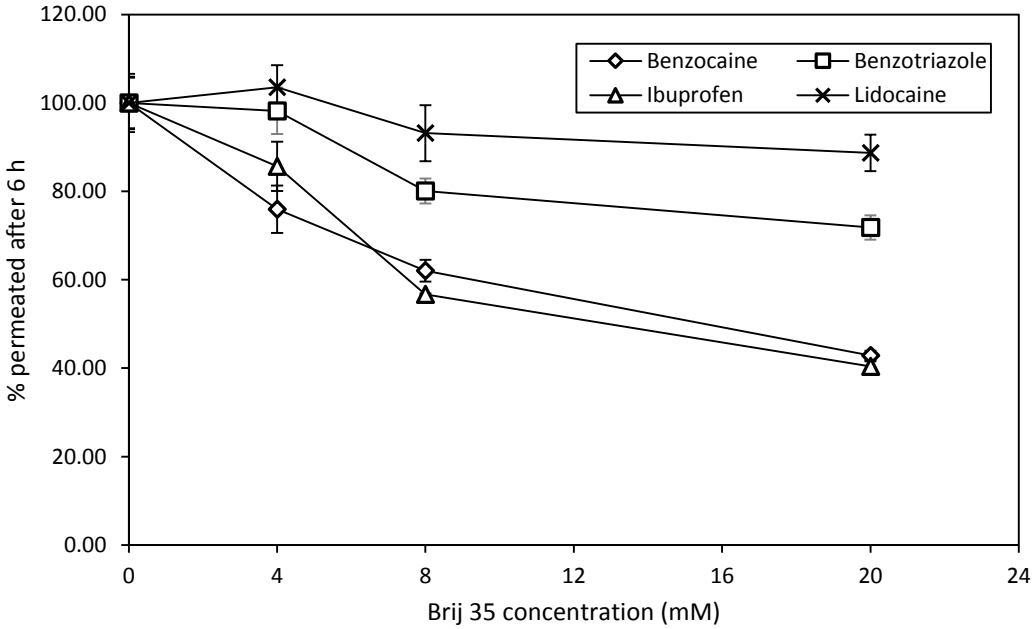

Fig. 4. Effect of the presence of Brij 35 on compound permeation across PDMS membrane.

In general, an increase in the concentration of Brij 35 resulted in a decrease in the flux of the compounds. Interestingly, this finding appears to be different than that observed in a recent study[17]. In that study Brij 35 was reported not to have a significant effect on compound permeation through PDMS membrane. The study considered paraben derivatives, namely, methylparaben and ethylparaben as model compounds. However, to confirm if this

phenomenon is a result of Brij 35 in particular (or a more broadly observed trend of non-ionic surfactant) a further study was carried out focusing on the permeation of three model compounds (benzocaine, ibuprofen and lidocaine) in the presence of another non-ionic surfactant, namely Tween 80 (Figure 5).

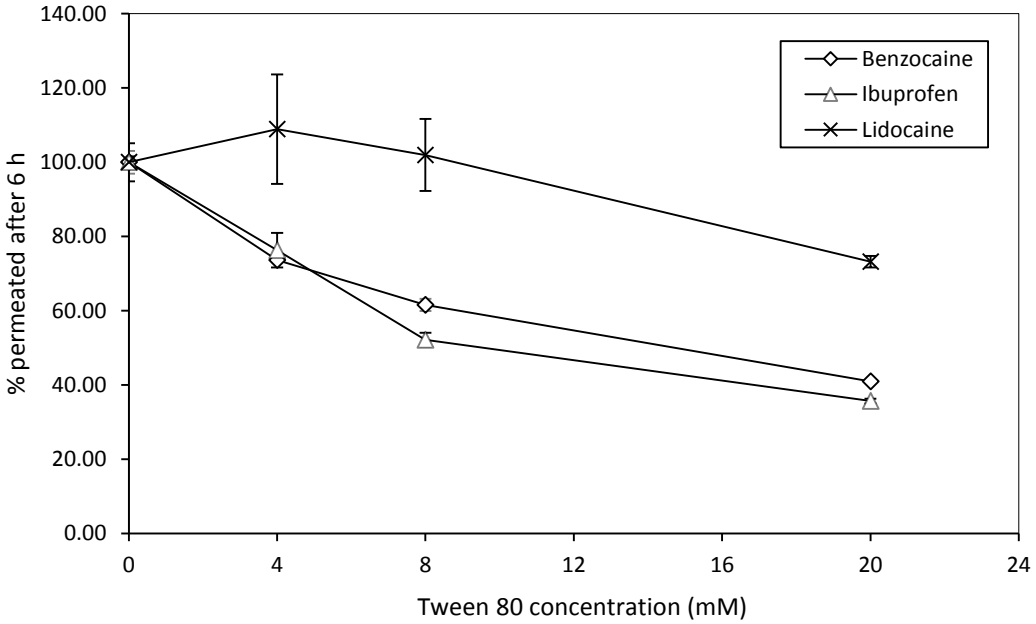

Fig. 5. Effect of the presence of Tween 80 on compound permeation across PDMS membrane.

Fig. 5 clearly shows that the presence of this non-ionic surfactant retards the permeation of the compounds in a similar trend to that observed for Brij 35. Therefore, it can be inferred that in the presence of this (and other) non-ionic surfactants does affect compound permeation.

In summary, the current study demonstrates that all five surfactants investigated here had a significant effect on compound permeation. Comparing different concentrations of various surfactants, it is obvious from Table 1 that the solution containing 20 mM surfactant leads to the lowest flux of compound across PDMS membrane. However, while the surfactants show the greatest reduction effect at 20 mM, clear differences can be found in their effect at this concentration. It also appears that among the four surfactants tested, CTAB facilitates the lowest flux in the case of all compounds, except for lidocaine – the lowest flux of lidocaine was obtained in the presence of SDS and that the same trend was observed for the surfactants being present in the donor solution at a concentration of 4 mM.

To confirm the surfactant-membrane interaction observed was an event that only occurred *in situ*, i.e. was not the result of a permanent alteration to the membrane surface, analysis was undertaken to characterise the membrane using DSC and FT-IR. Firstly, DSC thermograms of untreated membrane, along with surfactant pre-treated membrane, are shown in Figure 6.

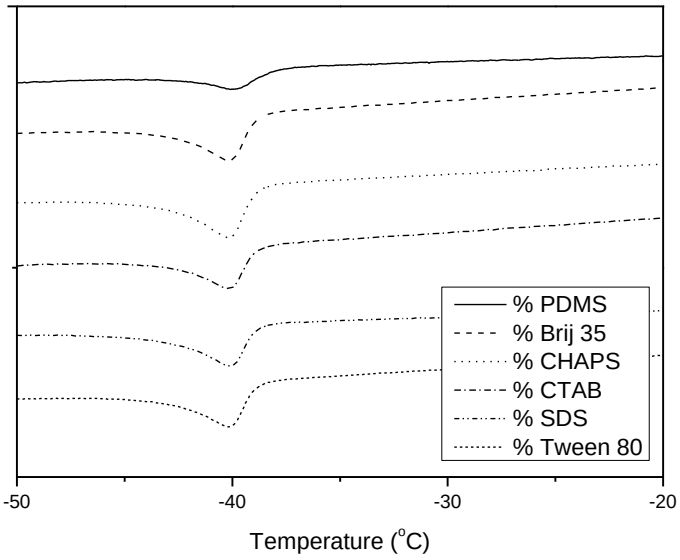

Fig. 6. DSC thermograms for PDMS membrane with the addition of surfactants.

Previous research has observed a significant shift in the silicone membrane phase transition when the membrane has been pre-treated with certain solvents, indicating there has been a permanent interaction between those particular solvents and membrane[27]. In this work no such shift in phase transition temperature, i.e. melting transition temperature of the crystalline phase, was observed with all transitions at -40 °C thus confirming the interaction between surfactant and membrane in all cases is temporary and limited to occurring *only* when an aqueous solution of surfactant is in direct contact with PDMS. To further confirm this hypothesis, FT-IR analysis was undertaken for PDMS membrane and all surfactants, as summarised in Figure 7.

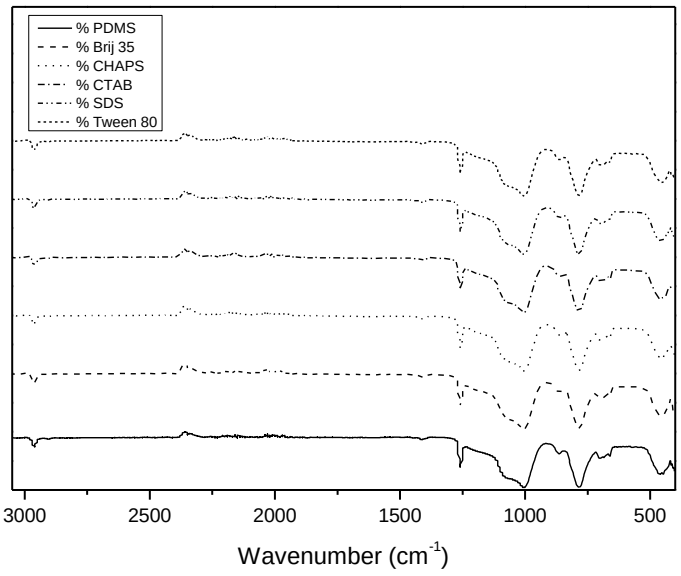

Fig. 7. FT-IR spectra for PDMS membrane with the addition of surfactants.

Once again, it is apparent from Figure 7 that all of the spectra are very similar confirming that there had been no change in chemical structure as a result of pre-treating the membrane surface with each surfactant. Furthermore, as a study to consider the effects of a range of surfactants on permeation through PDMS, this work has shown that it is uniquely possible to observe the effects of surfactants on the membrane *in situ* which were not observable using standard analytical techniques, such as DSC or FT-IR.

Conclusion

In conclusion, there is a clear surfactant effect on compound permeation across silicone membrane. The surfactants examined in this study appear to reduce the transport of four model compounds through the membrane. Overall, there was an inverse relationship between surfactant concentration and the amount of compound permeated. It was also observable that the effect of surfactant on compound permeation was different for different surfactant types, and also for different compounds. This variance was thought to result from a variation in the interaction of the charged and neutral compound species with the surfactant head group, and/or the surface and core of the surfactant micelle. Comparing all four surfactants, CTAB appeared to facilitate the lowest flux of compound through silicone membrane.

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