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

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8

9 **Abstract**

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

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

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## 30 Introduction

31 Skin is a natural barrier yet despite this, is often the focus of permeation analysis in  
32 both the cosmetic and pharmaceutical industry as the rate, and extent, of transdermal  
33 permeation must be quantified irrespective of whether or not it is desired. Factors affecting  
34 permeation are complex including the properties of the skin (such as age, location,  
35 condition)[1] along with the physicochemical properties of the formulation (such as  
36 lipophilicity, presence of excipients and molecular size)[2]. Transdermal permeation studies  
37 are frequently undertaken using excised human or animal skin although in recent years this  
38 has become unfavourable for several reasons, the former mainly for economic reasons and  
39 the latter mainly for ethical reasons. Both types of excised skin exhibit notoriously low levels  
40 of reproducibility and with recent changes in legislation regarding cosmetic analytical testing,  
41 have encouraged the development of synthetic skin mimics [3, 4]. These skin mimic systems  
42 offer a host of advantages including greater reproducibility, often reduced cost[5] and  
43 elimination of the need for ethical approval. One such skin mimic that has become popular  
44 for investigating transdermal permeation is a polymer known as polydimethylsiloxane, also  
45 known as PDMS or simply as silicone membrane. PDMS is a commonly used polymer that  
46 has a wide range of industrial applications, for example, gas and liquid separation[6],  
47 pervaporation[7, 8] and microfluidic devices[9]. More importantly, PDMS membrane has  
48 been reported to produce good correlation with an *in vivo* situation in a case whereby the  
49 penetrant lipophilicity was the prime determinant of compound permeation[10]. However, as  
50 PDMS is a very simplified model of skin it has the advantage of significantly increasing the  
51 level of reproducibility in data acquired yet has the disadvantage of potentially behaving  
52 differently to skin under certain conditions. Several factors have already been found to effect  
53 permeation including ionisation (as a result of pH)[11], membrane thickness[12] and solvent  
54 selection (i.e. donor and receptor solution composition)[13].

55 Formulations can be tailored to permeate skin at a rate suited to their requirements,  
56 for example, they can be encouraged to permeate by the addition of permeation enhancers[14,  
57 15] or discouraged by the addition of permeation retardants[16]. Interestingly it has been  
58 found that a particular compound may act as an enhancer in one formulation yet a retardant in  
59 another, further complicating the situation. However, what is not currently fully understood is  
60 whether or not skin mimics, such as PDMS, behave in a similar manner to that seen *in vivo*  
61 and if there is a pattern in their ability to enhance or retard permeation. Previous research  
62 from within our group has investigated the effect of temperature on permeation using PDMS  
63 and to a very limited extent, the effect of the presence of two surfactants, namely sodium  
64 dodecyl sulfate and Brij 35, on two structurally similar paraben-based compounds[17]. In this  
65 study it was found that the effect on permeation for these two compounds differed for the two  
66 surfactants implying there was a surfactant-specific effect although general conclusions could  
67 not be made from such a limited study.

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

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

79

## 80 **Materials and Methods**

### 81 **Materials**

82 Polydimethylsiloxane membrane (PDMS) was used as purchased (ATOS Medical,  
83 Sweden) with a standard thickness of 130  $\mu\text{m}$  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

84

### 85 **Methods**

#### 86 **Permeation studies**

87 PDMS membrane was soaked in phosphate buffer solution (0.02 M pH 7.4 and 0.15  
88 M NaCl) for 30 minutes prior to being mounted in the flow-through diffusion cells  
89 (PermeGear Inc. USA). After assembly the cells were placed on a cell warmer, maintained at  
90 a temperature of 32  $^{\circ}\text{C}$ . To start each permeation experiment, 0.8 mL of the donor solution  
91 containing model compound and/or surfactant was added to the cell. In all experiments the  
92 concentration of the model compounds in the donor solution was 1 mg/mL with surfactant  
93 present at concentrations of 0, 4, 8 or 20 mM for SDS, Brij 35, Tween 80, CTAB and 0, 2, 4  
94 or 20 mM for CHAPS. Phosphate buffer saline was pumped through the cells at 5 mL/h. The  
95 samples were collected by means of a fraction collector at the predetermined time intervals

96 (0.75, 1.5, 2.25, 3, 3.75, 4.5, 5.25 and 6 h). Quantification was undertaken using UV  
97 spectroscopy (benzoicaine at 258 nm, benzotriazole at 262 nm, ibuprofen at 225 nm and  
98 lidocaine at 219 nm). All experiments were conducted in triplicate with the mean value  
99 shown with standard deviation based error limits. All flow-through cells used in this study  
100 had a diffusion area of 0.554 cm<sup>2</sup>. The steady state flux ( $J$ ) was determined (noting the  
101 importance of maintaining sink conditions[19]) from the slope of the best-fit linear plot of the  
102 cumulative amount of the drug permeated per unit area versus time where flux is expressed  
103 as:

$$104 \quad J = \frac{C_0KD}{L} = C_0K_p$$

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

### 109 **Characterisation of surfactant-membrane interactions**

110 Two analytical techniques were used to further characterise the surfactant-membrane  
111 interactions in an attempt to determine if the interaction only occurs *in situ* or, is a more  
112 permanent modification to the surface. Firstly, differential scanning calorimetry (DSC) was  
113 undertaken whereby PDMS membrane was cut to an appropriate size for investigation and  
114 left overnight in phosphate buffer (pH 7.4) with, or without, the individual surfactants present  
115 at a concentration of 20 mM. The samples were then dried with soft tissue to remove excess  
116 liquid. DSC scans of the untreated and the treated samples were performed using a DSC 1  
117 (Mettler-Toledo Ltd., Leicester, UK), at a heating rate of 1 °C/min over a range of -60 °C to -  
118 20 °C. All DSC thermograms were assessed with regard to the phase transition of PDMS  
119 membrane, which was reported to be -40 °C [27].

120 FT-IR analysis of the untreated and treated membranes (as described above) was  
121 performed using a Nicolet IR 380 spectrometer. The samples were cut into suitable sizes and  
122 placed in direct contact with the diamond crystal of the spectrometer over the range of 4000-  
123 400 cm<sup>-1</sup> and analysed with Omnic software (version 7.2a).

124

### 125 **Results and Discussion**

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

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

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

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

153  
 154

**Table 1**

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

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

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

158

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

170

171 **Table 2**

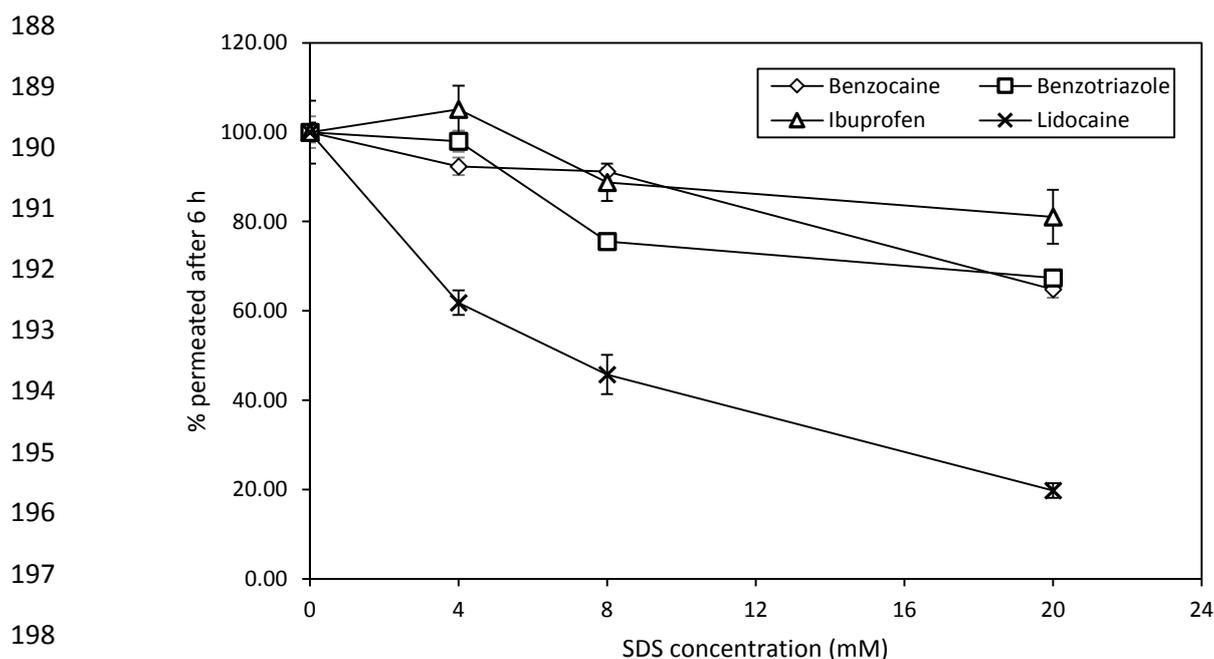
172 Cumulative amount permeated after 6 hours ( $Q_6$ ) of four model compounds in the presence of  
173 various surfactants across PDMS membrane

Surfactant in the donor phase	Amount of compound permeated ( $\mu\text{g}/\text{cm}^2$ ) 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 ± 31.91	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

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

180 Overall, the results here would indicate that the reduction in the amount permeated is  
 181 directly related to the concentration of surfactant. These results are similar to the findings of a  
 182 recent study where Waters and co-researchers reported a decrease in the permeation of  
 183 paraben derivatives with an increase in SDS concentration in the donor solution [17]. It can  
 184 be seen in Fig. 1 that the maximum reduction in permeation of each compound resulted from  
 185 20 mM SDS being present in the donor compartment, with lidocaine experiencing a reduction  
 186 of 80.22 %, being the greatest reduction when compared with other model compounds, and  
 187 ibuprofen having the least reduction of 18.93 %.



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

200

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

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

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

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

250 A second type of surfactant was investigated in this study, namely a cationic  
251 surfactant, cetyltrimethylammonium bromide (CTAB). Fig. 2 shows the permeability profiles  
252 of the compounds in the presence of CTAB. Fig. 2, along with the calculated  $p$ -values ( $<$   
253  $0.05$ ) clearly indicate that the compound fluxes were significantly influenced by the cationic  
254 surfactant being present in the donor solution.

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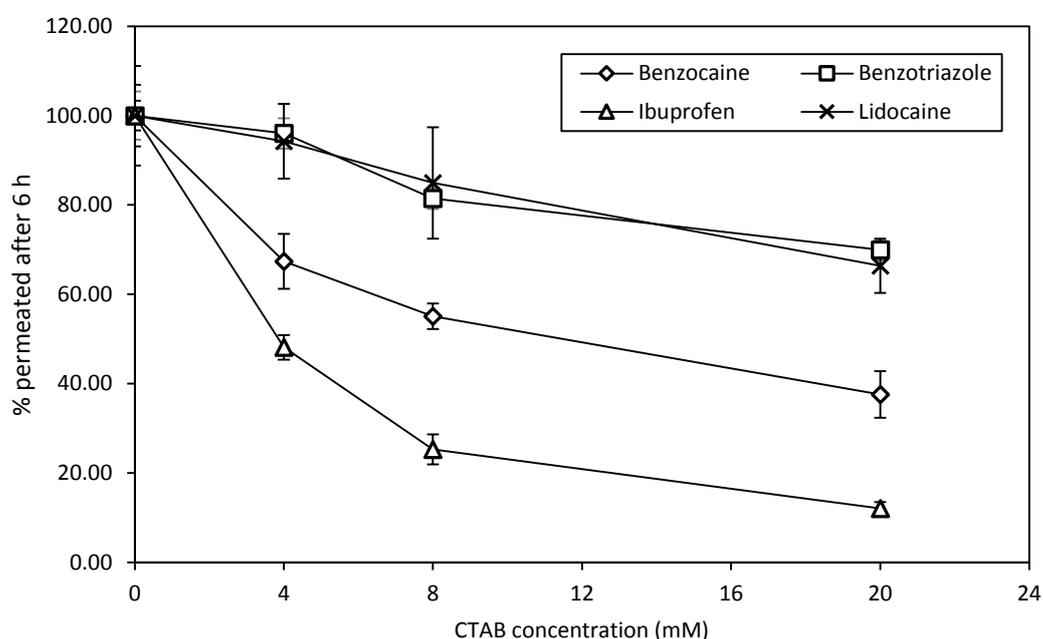
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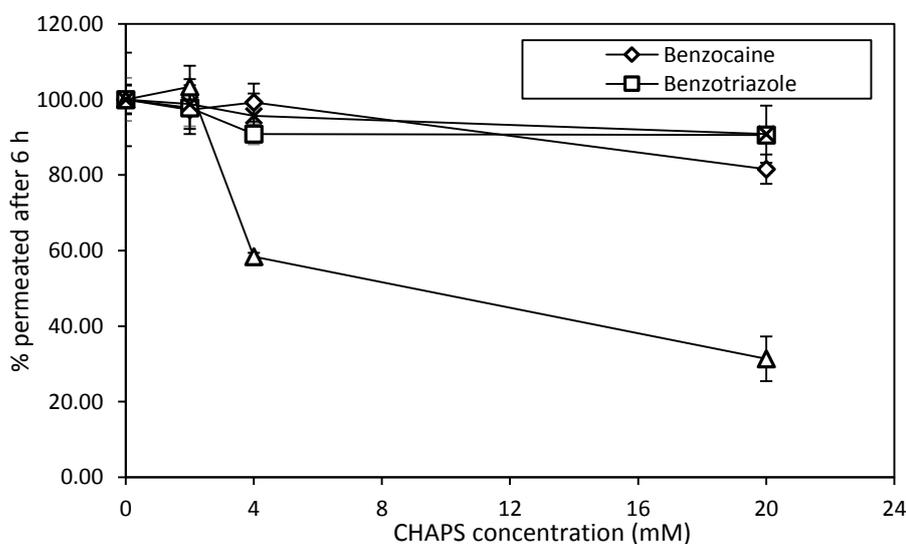
267 **Fig. 2.** Effect of the presence of CTAB on compound permeation across PDMS membrane.

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

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

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

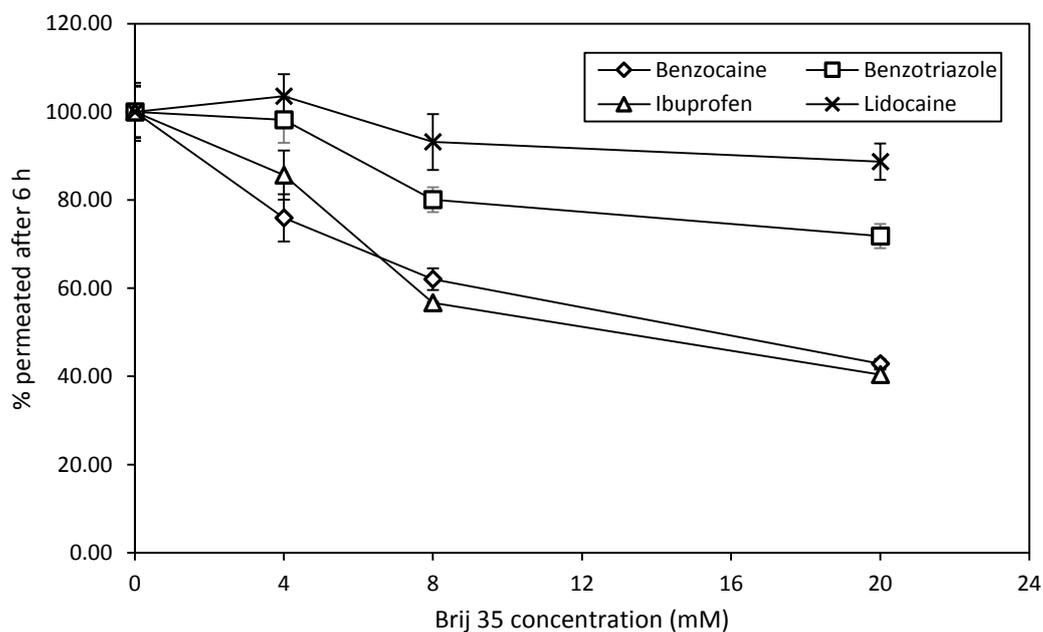
310 The third type of surfactant, investigated in this study, was a zwitterionic surfactant,  
311 namely CHAPS. The effect of CHAPS on compound permeation is shown in Fig. 3.



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

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

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



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

334

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

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

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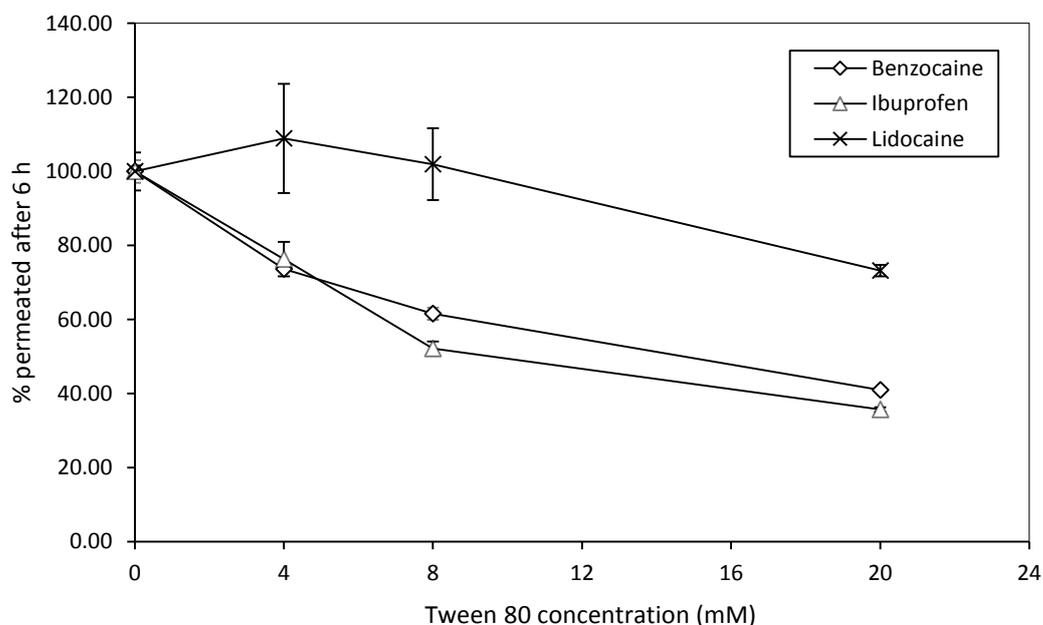
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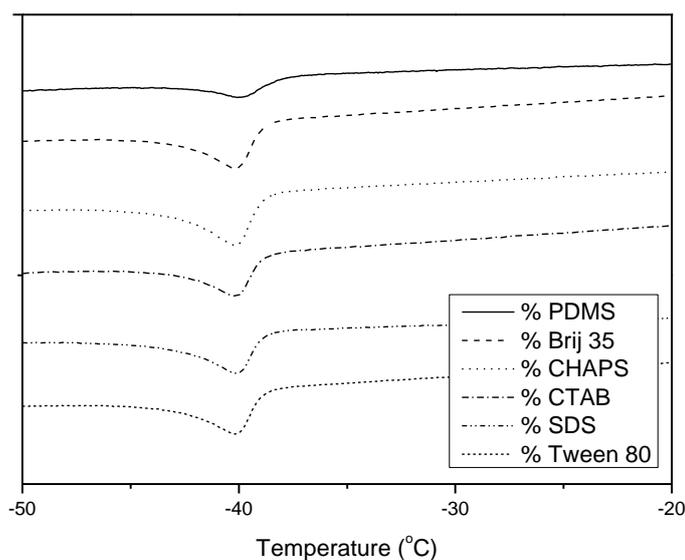


357 **Fig. 5.** Effect of the presence of Tween 80 on compound permeation across PDMS  
358 membrane.

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

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

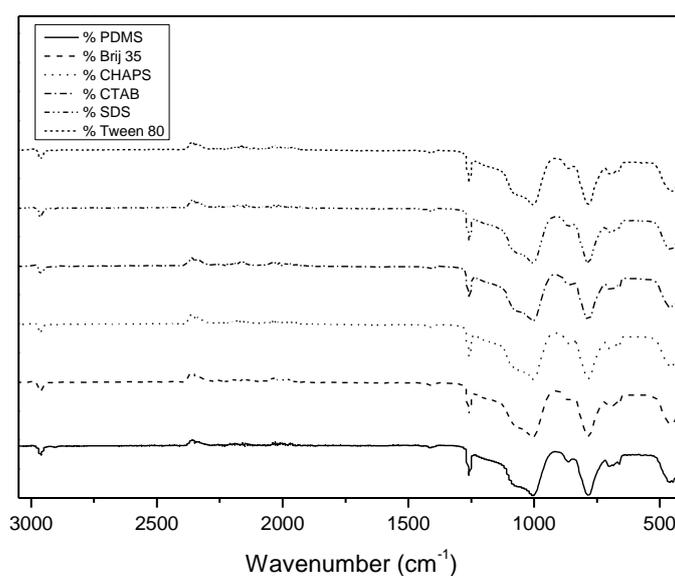
372 To confirm the surfactant-membrane interaction observed was an event that only  
373 occurred *in situ*, i.e. was not the result of a permanent alteration to the membrane surface,  
374 analysis was undertaken to characterise the membrane using DSC and FT-IR. Firstly, DSC  
375 thermograms of untreated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



377

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

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



388

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

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

## 396 **Conclusion**

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

## 407 **References**

- 408 [1] M. Machado, T.M. Salgado, J. Hadgraft, M.E. Lane, The relationship between transepidermal  
409 water loss and skin permeability, *International Journal of Pharmaceutics*, 384 (2010) 73-77.
- 410 [2] M.H. Abraham, H.S. Chadha, R.C. Mitchell, Factors That Influence Skin Penetration of Solutes,  
411 *Journal of Pharmacy and Pharmacology*, 47 (1995) 8-16.
- 412 [3] L.J. Waters, Recent developments in skin mimic systems to predict transdermal permeation.,  
413 *Current Pharmaceutical Design* 21 (2015) 2725 - 2732.
- 414 [4] L. Luo, A. Patel, B. Sinko, M. Bell, J. Wibawa, J. Hadgraft, M.E. Lane, A comparative study of the  
415 *in vitro* permeation of ibuprofen in mammalian skin, the PAMPA model and silicone membrane,  
416 *International Journal of Pharmaceutics*, 505 (2016) 14-19.
- 417 [5] S.F. Ng, J.J. Rouse, F.D. Sanderson, G.M. Eccleston, The relevance of polymeric synthetic  
418 membranes in topical formulation assessment and drug diffusion study, *Archives of Pharmacal*  
419 *Research*, 35 (2012) 579-593.
- 420 [6] M. Fang, H. Zhang, J. Chen, T. Wang, J. Liu, X. Li, J. Li, X. Cao, A facile approach to construct  
421 hierarchical dense membranes via polydopamine for enhanced polyethylene/nitrogen separation,  
422 *Journal of Membrane Science*, 499 (2016) 290-300.
- 423 [7] A. Dobrak, A. Figoli, S. Chovau, F. Galiano, S. Simone, I.F.J. Vankelecom, E. Drioli, B. Van der  
424 Bruggen, Performance of PDMS membranes in pervaporation: Effect of silicalite fillers and  
425 comparison with SBS membranes, *Journal of Colloid and Interface Science*, 346 (2010) 254-264.
- 426 [8] P.V. Naik, R. Bernstein, I.F.J. Vankelecom, Influence of support layer and PDMS coating  
427 conditions on composite membrane performance for ethanol/water separation by pervaporation,  
428 *Journal of Applied Polymer Science*, 133 (2016).
- 429 [9] D. Liyu, S.H. Nematy, A.E. Vasdekis, Solvent-assisted prototyping of microfluidic and optofluidic  
430 microsystems in polymers, *Journal of Polymer Science, Part B: Polymer Physics*, 54 (2016) 1681-  
431 1686.
- 432 [10] G.P. Moss, D.R. Gullick, S.C. Wilkinson, *Predictive methods in percutaneous absorption*, 2015.
- 433 [11] L.J. Waters, A.K.M.M.H. Bhuiyan, Ionisation effects on the permeation of pharmaceutical  
434 compounds through silicone membrane, *Colloids and Surfaces B: Biointerfaces*, 141 (2016) 553-  
435 557.

436 [12] G. Firpo, E. Angeli, L. Repetto, U. Valbusa, Permeability thickness dependence of  
437 polydimethylsiloxane (PDMS) membranes, *Journal of Membrane Science*, 481 (2015) 1-8.  
438 [13] Y. Shahzad, L.J. Waters, C. Barber, Solvent selection effects on the transport of compounds  
439 through silicone membrane, *Colloids and Surfaces A: Physicochemical and Engineering Aspects*,  
440 458 (2014) 96-100.  
441 [14] H. Marwah, T. Garg, A.K. Goyal, G. Rath, Permeation enhancer strategies in transdermal drug  
442 delivery, *Drug Delivery*, 23 (2016) 564-578.  
443 [15] K. Hirata, D. Mohammed, J. Hadgraft, M.E. Lane, Influence of lidocaine hydrochloride and  
444 penetration enhancers on the barrier function of human skin, *International Journal of*  
445 *Pharmaceutics*, 477 (2014) 416-420.  
446 [16] D. Kaushik, P. Batheja, B. Kilfoyle, V. Rai, B. Michniak-Kohn, Percutaneous permeation  
447 modifiers: Enhancement versus retardation, *Expert Opinion on Drug Delivery*, 5 (2008) 517-529.  
448 [17] L. Waters, L. Dennis, A. Bibi, J.C. Mitchell, Surfactant and temperature effects on paraben  
449 transport through silicone membranes, *Colloids and Surfaces B: Biointerfaces*, 108 (2013) 23-28.  
450 [18] A.C. Williams, B.W. Barry, Penetration enhancers, *Advanced Drug Delivery Reviews*, 64,  
451 Supplement (2012) 128-137.  
452 [19] S. Yousef, X. Liu, A. Mostafa, Y. Mohammed, J.E. Grice, Y.G. Anissimov, W. Sakran, M.S.  
453 Roberts, Estimating Maximal In Vitro Skin Permeation Flux from Studies Using Non-sink Receptor  
454 Phase Conditions, *Pharmaceutical Research*, 33 (2016) 2180-2194.  
455 [20] E. Awoonor-Williams, C.N. Rowley, Molecular simulation of nonfacilitated membrane  
456 permeation, *Biochimica et Biophysica Acta (BBA) - Biomembranes*, 1858 (2016) 1672-1687.  
457 [21] D.S. Hart, L.C. Davis, L.E. Erickson, T.M. Callender, Sorption and partitioning parameters of  
458 benzotriazole compounds, *Microchemical Journal*, 77 (2004) 9-17.  
459 [22] M. Dias, J. Hadgraft, M.E. Lane, Influence of membrane-solvent-solute interactions on solute  
460 permeation in skin, *International Journal of Pharmaceutics*, 340 (2007) 65-70.  
461 [23] H.H. Cho, H. Huang, K. Schwab, Effects of solution chemistry on the adsorption of ibuprofen  
462 and triclosan onto carbon nanotubes, *Langmuir*, 27 (2011) 12960-12967.  
463 [24] H. Liu, J. Atkins, R.S. Kass, Common molecular determinants of flecainide and lidocaine block  
464 of heart Na<sup>+</sup> channels: Evidence from experiments with neutral and quaternary flecainide  
465 analogues, *Journal of General Physiology*, 121 (2003) 199-214.  
466 [25] A. Chattopadhyay, K.G. Harikumar, Dependence of critical micelle concentration of a  
467 zwitterionic detergent on ionic strength: Implications in receptor solubilization, *FEBS Letters*, 391  
468 (1996) 199-202.  
469 [26] A.R. Tehrani-Bagha, K. Holmberg, Solubilization of hydrophobic dyes in surfactant solutions,  
470 *Materials*, 6 (2013) 580-608.  
471 [27] M. Dias, J. Hadgraft, M.E. Lane, Influence of membrane-solvent-solute interactions on solute  
472 permeation in model membranes, *International Journal of Pharmaceutics*, 336 (2007) 108-114.  
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