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Establishing the importance of oil-membrane interactions on the transmembrane

diffusion of physicochemically diverse compounds

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Abstract

The diffusion process through a non-porous barrier membrane depends on the properties of the drug, vehicle and membrane. The aim of the current study was to investigate whether a series of oily vehicles might have the potential to interact to varying degrees with synthetic membranes and to determine whether any such interaction might affect the permeation of co-formulated permeants: methylparaben (MP); butylparaben (BP) or caffeine (CF). The oils (isopropyl myristate (IPM), isohexadecane (IHD), hexadecane (HD), oleic acid (OA) and liquid paraffin (LP)) and membranes (silicone, high density polyethylene and polyurethane) employed in the study were selected such that they displayed a range of different structural, physicochemical properties. Diffusion studies showed that many of the vehicles were not inert and did interact with the membranes resulting in a modification of the permeants' flux when corrected for membrane thickness (e.g. normalized flux of MP increased from 1.25 ± 0.13 $\mu gcm^{-1}h^{-1}$ in LP to 17.94 ± 0.25 $\mu gcm^{-1}h^{-1}$ in IPM). The oils were sorbed differently to membranes (range of weight gain: 2.2 ± 0.2 % for polyurethane with LP to 105.6 ± 1.1 % for silicone with IHD). Membrane interaction was apparently dependent upon the physicochemical properties, size, shape, flexibility and the Hansen solubility parameter values of both the membranes and oils. Sorbed oils resulted in modified permeant diffusion through the membranes. No simple correlation was found to exist between the Hansen solubility parameters of the oils or swelling of the membrane and the normalized fluxes of the three compounds investigated. More sophisticated modelling would appear to be required to delineate and quantify the key molecular parameters of membrane, permeant and vehicle compatibility and their interactions of relevance to membrane permeation.

1. Introduction

For a drug to be delivered passively via the skin, it is generally accepted that it should ideally have adequate lipophilicity (partition coefficient between 1-3) and also a low molecular weight (below 500 Da) (Yano et al., 1986; Bos & Meinardi, 2000). Such requirements have limited the number of commercially available medicinal products that are dependent on transdermal or dermal delivery. As such various strategies have emerged to achieve the absorption of drugs in sufficient quantity to elicit a therapeutic response. One of these strategies is the use of vehicles which may enhance the delivery of the applied drug. Several studies have investigated vehicle uptake into membranes with a view to establishing the effects on drug diffusion, in particular involving both aqueous- and alcohol-based vehicles (Twist & Zatz, 1988a&b; Flynn, 1990; 70 Twist & Zatz, 1990; Dias et al., 2007; Oliveira et al., 2010). Many currently employed pharmaceutical and cosmetic topical formulations incorporate an oil or a combination of oils, but little attention has been given to the nature of such vehicle itself on drug transport.

The principal rationale for the inclusion of oils within topical vehicles has been driven historically by cosmetic concerns and requirements; including 'consumer-feel' and emolliency. Some consideration has also been given to the ability of oils to solubilize incorporated drug(s), and moreover to modify the release and partitioning of drugs into the skin (Kreilgaard, 2002; Saroj et al., 2012). However, although oils are usually incorporated and applied to the skin as supposedly inert vehicles/excipients, some may have a direct affect upon membrane structure (Yamane, et al., 1995; Williams & Barry, 2004). For example, the partition of isopropyl myristate and oleic acid, when applied after dissolution

in a vehicle, has been reported to promote membrane lipid fluidity (Pillai et al., 2004; Brinkmann & Muller-Goymann., 2005; Lane, 2013). This can contribute to the increased disorder of the stratum corneum and thus enhance the permeability of the bilayer structure (Lane, 2013). Any oil residue remaining in contact with the skin can also reduce epidermal water loss; possibly further modifying skin permeability characteristics.

It is accepted that the flux of a permeant across a membrane is identical from different vehicles, provided the vehicles are saturated with permeant (i.e. having a thermodynamic activity of 1) (Higuchi, 1960; Twist & Zatz, 1986). However, such an acceptance is premised on the assumption that the vehicle components do not alter the barrier properties of the membrane. It is now widely known that vehicles can interact with barrier membranes either to alter diffusivity or to enhance the partitioning behaviour into the membrane (Twist and Zatz, 1988; Cross et al., 2001; Dias et al., 2007; Zhang et al., 2011; Oliveira et al., 2012; Lane, 2013). A method to screen for vehicle-membrane interactions would be desirable in order to explore the permeation processes. The solubility parameter of the vehicle has been reported to be one important predictor of the flux of the drug through a membrane (Cross et al., 2001; Dias et al., 2007). The concept of solubility parameter was first developed by Hildebrand and Scott (1950) based on regular solution theory and was extended to describe multi-component Hansen solubility parameters (HSPs, Hansen, 1967). Solubility parameters are derived from the molecular volatilization energy (molecular cohesive energy). Solubility parameters are an important predictor of behaviour of molecules in mixed systems and have been related to the interaction of drugs and vehicles with membranes (Dias et al., 2007; Abbott, 2012).

The stratum corneum is a complex membrane comprising both hydrophobic and hydrophilic diffusion media. Synthetic membranes represent a convenient alternative for pre-screening studies, eliminating the requirement for use of human skin (Pellett et al., 1997) and offering improved reproducibility (Karadzovska & Riviere, 2013). Polydimethylsiloxane (silicone), high density polyethylene (HDPE) and polyurethane (PU) membranes have all been used to investigate diffusion mechanisms of permeants in screening studies (Aminabhavi & Khinnavar, 1993; Jiang et al., 1998; Sloan et al., 2013). The use of a range of membranes also provides materials ranging in their solubility parameters (17.4 – 20.8, Table 1), to overlap with the stratum corneum itself (20.5; Liron & Cohen, 1984). Reports relating solubility parameters to dermal permeation typically employ the Hildebrand solubility parameter (δ) (e.g. Dias et al., 2007). However, δ fails to account for the diversity of dispersive, polar and H-bonding interaction forces of the corneocytes and lipidic permeation routes in stratum corneum. HSPs provide a means to model the skin as a multicomponent mixture (i.e. the summated HSPs; $\delta_D, \delta_H, \delta_P = 17, 8, 8$ (Abbott, 2012)). A range of membranes with similar δ but differing in the ratio of $\delta_D{:}\delta_H{:}\delta_P$ may provide an ability to enhance the relevance of synthetic membranes.

Despite their wide use for cosmetic and pharmaceutical purposes, the barrier-alteration properties of oily vehicles are poorly understood. The aims of the current study were to obtain data relating diffusion of compounds from a range of oils through barrier membranes with a view to developing an understanding of the means by which oily vehicle components interact with membranes and affect the permeation of co-formulated drug molecules.

2. Materials and Methods

2.1. Materials

Methanol, acetonitrile and hexadecane (HD) were obtained from Merck chemicals, Germany;orthophosphoric acid from Riedel-de-Haen Chemical, Germany;potassium hydroxide from Scharlau Chemical, Spain; methyl paraben (MP), butyl paraben (PB), caffeine (CF) and triethylamine from Sigma Chemical Co., UK; oleic acid (OA) and liquid paraffin (LP) from Sigma, Germany; isopropanol from BDH Laboratory Supplies, UK; isopropyl myristate (IPM) from Uniqema, Malaysia; isohexadecane (IHD) from Uniqema, UK; and silicone membrane (0.32 mm in thickness) from Samco Ltd., UK. High density poly ethylene (HDPE) membrane (pharmaceutical grade package material, 0.20 mm in thickness) and poly urethane (PU) membrane (0.25 mm in thickness) were donated by TQ pharma, Jordan and Exopack, UK, respectively. All membranes were measured for thickness in multiple locations across the membranes prior to permeation testing. In addition, flux measurements were assessed for conformity to literature values for quality control purposes to assess for intra-membrane and inter-membrane variability.

2.2. Hansen solubility parameters and modelling of miscibility

Hansen solubility parameters (HSPs, Hansen, 1967) are determined empirically or by calculation (Stefanis & Panayiotou, 2008; Abbott et al., 2013) and divide the total Hildebrand value (δ) into three parts: a dispersive force component (δ_D), hydrogen bonding component (δ_H) and a polar component (δ_P), :

$$\delta^2 = \delta^2_D + \delta^2_P + \delta^2_H \qquad\qquad\qquad \text{Equation 1}$$

According to HSP theory, a molecular substance can be represented by a point in a tridimensional space, whose orthogonal axes are the HSPs (i.e. $x=\delta_D$, $y=\delta_P$, $z=\delta_H$). Any solvent that can interact with this molecule (e.g. by dissolving or swelling) is located at a point in HSP space that lies inside the circumference of molecule's Hansen sphere. There is a degree of uncertainty in the estimation of a Hansen sphere's radius (interaction radius), from empirical and computational trials (Hansen, 2007). A useful parameter for comparing two substances is the HSP Distance:

$$\text{Distance}^2= 4(\delta_{DA}-\delta_{DB})^2+(\delta_{PA}-\delta_{PB})^2+(\delta_{HA}-\delta_{HB})^2 \qquad \text{Equation 2}$$

Where δ_{DA}, δ_{DB} are the energy of the dispersion forces of compound A and B respectively; δ_{PA}, $\delta_{PB,}$ δ_{HA} *and* δ_{HB} are the corresponding energies of the polar and hydrogen bond forces of the compounds. Hansen Solubility Parameters in Practice (HSPiP) software version 4.1.0.3 was used to extract the Hansen solubility parameter (HSP) values of the oily vehicles and test membranes, and to derive a graphical plot of the Hansen spheres of the membranes. The HSP distance from the centre of the sphere to the oil was calculated using Equation 2.

2.3Solubility studies

Solubility studies were conducted by adding an excess amount of each model permeant separately to deionized water, phosphate buffer (pH 7.0; 50mM), IPM, IHD, LP, HD and OA. The suspensions were vortexed briefly and further agitated at 32°C in a shaking water bath at 110 rpm for around 48 h. After equilibration, the suspensions were filtered through

0.25 µm pore-size Teflon membrane filters (chosen to achieve minimal permeant adsorption) and the resultant solutions diluted. The IPM, OA and IHD samples were diluted with isopropanol; HD with n-hexane:isopropanol (50:50) and LP with IHD:isopropanol co-solvent (20:100). The concentration of the permeant in each sample was determined using UV spectrophotometry and processed using Thermo electron vision pro software V4.20 (Thermo, Germany). Using a 1 mL quartz cuvette, calibration curves were constructed by plotting the absorbance as a function of concentration of standards. The wavelengths of detection (nm) were: 254, 256 and 270 for MP, BP and CF respectively. Experimental data represent the mean ($\pm$ SD) value ($n \geq 4$).

2.4 HPLC chromatographic conditions for model permeants

A Class VP 2010 LC Pump with Auto sampler connected to a UV Absorbance Detector were employed (Shimadzu Japan). The column used for all permeants was a Symmetry 5µ BDS (C18), 150 x 4.6 mm (5 µm) (Waters, USA). The mobile phase for MP consisted of 35% v/v acetonitrile/65% phosphate buffer (50 mM KH_2PO_4 containing 1% w/v triethylamine, then adjusted to pH 3.5 with orthophosphoric acid). The mobile phase for the assay of BP was 50% acetonitrile/50% phosphate buffer (50 mM KH_2PO_4 adjusted to pH 3.0 with orthophosphoric acid) and for CF was 15% v/v acetonitrile/85% phosphate buffer (50 mM KH_2PO_4 adjusted to pH 3.0 with orthophosphoric acid). The flow rate was maintained at 1 mL min^{-1} and injection volumes were 10 µL for MP and BP and 50 µL for CF. The wavelength of detection (nm) was 254, 256 and 270 for MP, BP and CF respectively ($n \geq 4$).

2.5Franz cell studies

The permeation of MP, BP and CF through different membranes from the saturated suspensions was determined using individually (volume) calibrated Franz cells. The donor compartments were prepared by adding excess drug to 6 g of oil. The flask containing the suspension was placed in a shaking water bath overnight at 32˚C. Diffusion experiments were carried out using (volume) calibrated Franz cells with a receptor phase of 2 mL and a diffusional area of 0.65 cm^2. Before the experiment the membrane was immersed and soaked in the receptor medium overnight. The membrane was cut into circular discs and placed between the donor and the receptor compartments of the Franz cell. The receptor compartment was filled with phosphate buffer pH 7.0, after which the receptor temperature was maintained at 32°C by immersion in a temperature-controlled water bath. A small Teflon-coated magnetic bar was included in the receptor compartment such that stirring occurred throughout the duration of the experiment. After allowing the membrane to equilibrate with the receptor fluid, 200 µL of the oily suspension (the sample contained undissolved/suspended solids of permeants at 32°C) of model permeant was then introduced into the donor. The experiments were conducted under occlusion (covering the donor compartment with parafilm) using suspensions of MP, BP and CF respectively. The duration of each experiment was 7, 6 and 6 h when HDPE, silicone and PU membranes were employed, respectively. At appropriate time intervals, 200 µL samples were withdrawn from the receptor compartment and immediately replaced with an equal volume of fresh phosphate buffer, (pH 7.0). Each sample was analysed for drug by HPLC. The concentration of the permeant in the receptor solution at any time point was corrected for previous sample removal. The cumulative amounts (per unit surface area of membrane) of

permeant which diffused across silicone membrane were plotted against time (t). The slope of the linear plot was taken as the flux ($\mu g cm^{-2} h^{-1}$) of the permeant. The flux values were normalized to account for the differences in membrane thickness by multiplying across by their measured thicknesses: PDMS (0.32 mm), HDPE (0.02 mm) and PU (0.02 mm) (normalized flux; $\mu g cm^{-1} h^{-1}$).

2.6 Uptake studies

2.6.1 Membrane weight

Uptake of vehicles into different membranes was determined gravimetrically. Membranes were cut to size and the samples were then immersed in vehicle in a sealed glass vial, and soaked overnight in a temperature-controlled water bath at around 32°C. The membranes were blotted dry with tissue paper and reweighed. The percentage weight difference *(% ΔW)* was calculated according to Equation 3:

$$\% \, \Delta W = \frac{(W_a - W_b)}{W_b} * 100 \hspace{3cm} \text{Equation 3}$$

where W_a and W_b are the weights of membrane after and before soaking, respectively.

The amount of oil (m_{upt}, mg per gram) sorbed by each membrane was calculated according to Equation 4:

$$\mathbf{m}_{upt} = \frac{\Delta \text{ weight of membrane weight (mg)}}{\text{original weight of membrane (g)}} \hspace{2cm} \text{Equation 4}$$

2.7 Statistical analysis

Data reported in this study are usually (unless otherwise stated) the mean of $n \geq 3$, with the standard deviation (SD) given. In order to establish differences in the parameters measured in this study, statistical tests were conducted. The analysis of variance (ANOVA) method and Student's t-test were used as the major statistical tests where applicable. When ANOVA was employed, *post hoc* comparisons of the means of individual groups were performed using Tukey's test, and the level of significance was taken at $p \leq 0.05$ in all cases.

3. Results

3.1 Physicochemical characterisation of permeant and oily vehicle systems

In order to elucidate the factors affecting the oily components' interactions with membranes and their effect on diffusion of co-formulated drug molecules, five structurally unrelated oils with different solubility parameters, shape and size were required. The oils identified for the study were IPM as an example of an oil ester, OA as an example of *cis*-fatty acid, IHD as a branched oil, HD as an example of a linear oil and LP, the commonly-used mixture of linear and branched chain molecules. The membranes used have a range of different HSPs which leads to difference in hydrophilicity of the membranes. The properties of the oils and membranes are found in Table 1.

MP, BP and CF have been postulated to traverse the human skin via different routes (Akomeah et al., 2004) although the exact permeation routes remain unconfirmed. For the current study MP, BP and CF were chosen since they possess similar molecular masses, but possess a diverse relative balance of $\delta_D, \delta_H, \delta_P$ values (Table 1) in order to probe

membrane-specific changes in the permeation barrier due to interactions with oily vehicles. The molecular weight and Log P values of the permeants employed in this study are shown in Table 2, as are the solubility values of the model permeants in different oils, deionised water and buffer. The solubility of permeants in the aqueous vehicles was in the order of CF>MP>BP, which is in accordance with the relative permeant hydrophilicity. While in oily vehicles the solubility of all permeants in OA and IPM was shown to be higher than in IHD, LP and HD. There was no significant difference in the solubility of each permeant, considered individually in HD, IHD or LP.

3.2 Permeation of molecules from oily vehicles across synthetic barrier membranes

The cumulative amount of permeant diffused across the synthetic membranes was plotted versus time; and the flux was derived from the slope of the linear portion of the curve. Fig. 1 shows an example of one such cumulative plot of MP permeating across the three different membranes from saturated solutions in IHD. The fluxes through the membranes from IHD were in the order silicone>PU>HDPE. The curve shows a typical lag time phase followed by a linear portion corresponding to the steady state flux. The shapes of the cumulative amount of BP and CF flux curves were similar to MP.

The derived flux results of the *in vitro* diffusion studies across different membranes are shown in Fig. 2 for MP, BP and CF. The highest measured normalized fluxes of permeants from oils were obtained for diffusion of the compounds through silicone membrane. The diffusion of MP through silicone membrane was in the order of IPM>IHD>HD>OA>LP=Buffer, while BP diffusion was in the rank order of

IHD>IPM>HD>LP=OA> Buffer. CF diffusion through silicone membrane was in the order IPM>IHD>HD>LP=buffer=OA. All oils enhanced the permeation of MP and BP when compared to the buffer, but there was no significant difference between the fluxes of CF from LP, OA or buffer.

All oils enhanced the permeation of MP through HDPE compared with buffer. The fluxes of MP from LP and OA through HDPE were not significantly different from each other, but although low in magnitude, the fluxes of MP from both were higher than from buffer. The rank order of oil enhancement of MP flux across HDPE membranes was IPM>IHD>HD>OA=LP>buffer. Generally oils enhanced BP permeation through HDPE membrane compared with buffer. With an order of enhancement IHD=IPM>OA> HD=LP>buffer. In addition, all oily vehicles enhanced the permeation of CF through HDPE membrane compared with the buffer. There were no differences in the fluxes of CF from either OA or HD through HDPE, the enhancement rank order being IPM>IHD>OA=HD>LP>buffer. In contrast, the flux of CF from saturated buffer solutions was significantly higher than from oily solutions through PU membrane. Despite there being no difference in the flux of CF from HD, IHD, LP or OA through PU, IPM showed an enhancement of the flux of CF when compared with the other oils. The flux of MP across PU membranes was only improved compared to buffer when IPM was the vehicle, with the ranking of flux from the other vehicles as OA>IHD>HD>LP. In contrast, when PU was employed as the membrane, the flux of BP from the buffer was higher than its flux from OA. The oils demonstrated an enhancement of the BP flux across PU in the order IHD=IPM>HD>LP>buffer>OA.

3.3 Swelling data for synthetic barrier membranes in oily vehicles

The absolute amounts of oils sorbed to the different membranes are shown in Table 3. Membranes sorbed oils to different extents with the order being silicone>HDPE>PU for IPM, HD and IHD. OA was highly sorbed to PU; however it appeared to act as a plasticizer for the membrane and the PU membrane was observed to change in its rigidity, becoming sticky when soaked in the oil. Generally the difference in membrane weight after being soaked in the buffer was the lowest, when compared with the resultant weight gain after incubation with oils. The difference between membrane weight after incubating with buffer at 32°C was 0.06 ± 0.05 % for silicone membrane, 18.16 ± 0.72 % for HDPE and 1.01 ± 0.40 for PU.

3.4 Hansen Solubility Parameter valuesas indicators of vehicle-membrane interactions

The various HSP parameters and the molar volume of the different oils are shown in Table 1. LP displays the highest molar volume (*Mvol*), while HD and IHD have the lowest *Mvols*. The δ_D values for all oils were of similar magnitude. IHD and HD are pure hydrocarbons therefore the δ_P and δ_H are zero. OA displays a higher value of δ_H compared with other oils this is because OA has both hydrogen donor and acceptor groups.

A Hansen sphere plot provides a means to visualize the likely miscibility of a substrate in a solvent. In the current study, if a solvent (i.e. oily vehicle) resides inside the sphere for a polymer then it is likely to be miscible with that polymer and the closer it is to the centre,

the more effective it is in its solvency. Two examples of such Hansen spheres are presented in Fig.3, which shows that the solubility parameters of all oils laid inside the Hansen sphere generated for silicone membrane, indicating that they might be expected to swell the silicone membrane. It should be borne in mind that the radius of the Hansen sphere is also a function of the experimental data used for their calculation in the HSPiP software. Failure to study a sufficiently wide range of solvents may underestimate the true radius of the sphere, compared to when a more extensive range of solvents are studied. Since the accuracy of miscibility predictions is compromised by a reduced dataset, the HSPiP software indicates where inadequacies in the empirical miscibility dataset exist for solutes (Hansen, 2007). Accordingly the miscibility (i.e. swelling of a membrane due to a vehicle) predicted by HSPiP may not reflect the true extent of interaction between oily vehicles and a given membrane. For example, the Hansen sphere for HDPE is presented in Fig.3, which shows an example where the solubility parameters of the oils were sited outside the sphere radius for HDPE (a similar observation was made for PU). This indicated that these oils were not perfect solvents for the membranes. However from the experimental results of swelling, these oily vehicles did possess a sufficient degree of solvency power for both PU and HDPE membranes. Therefore, in order to provide comparison for a rank order of miscibility between membranes, the HSP distances were calculated between the membranes and oils using Equation 2 (Table 4).

Generally if two components are chemically similar then it would be expected that their HSP values would be the same; and when the sum of the absolute differences of the three HSP values is calculated, the difference would be 0 (zero) $MPa^{1/2}$ for the perfect solvent.

If the two components are chemically compatible then it would be expected that their HSP values would be similar, and the differences would be small, although not necessarily zero. Comparing the distance values for the same oil between membranes, the general order was silicone<HDPE<PU. This corresponds to the same order of oil uptake for IPM, IHD and HD; however OA and LP were not sorbed in the predicted order. This was possibly due to the non-linear shape of OA and the high *Mvol* of LP. In general IHD produced the highest HSP distance values when compared with the other oils (Table 4) however it was nevertheless highly sorbed into all the membranes. Its greater uptake might be due to physicochemical factors including molecular shape, flexibility, volume and homogeneity of its molecular polarity in comparison to linear hydrocarbons.

4. Discussion

The stratum corneum comprises a complex molecular and supramolecular structure composed primarily of a mixture of lipids and proteins. The extent to which a vehicle is sorbed and interacts with these structures, can affect the penetration kinetics of any topically applied drug. However, due to the complex number and diverse nature of types of interactions possible between vehicles, the stratum corneum and drug, the interpretation of transcutaneous diffusion data with a view to identifying the key factors affecting these interactions is not simple. The use of simpler membranes, with distinctive barrier properties such as silicone, HDPE and PU membranes might provide one means of identifying some of the prime parameters controlling the overall transport process through the markedly more complex stratum corneum. To understand the effect of structure and solubility properties,

the membranes and vehicles which were selected for study possessed different structural and physicochemical properties and HSP values.

The measurement of the solubility of the permeants in phosphate buffer (pH 7.0) was essential in determining whether that medium could be used as receptor fluid, so as to ensure the maintenance of sink conditions during diffusion studies. The selection of phosphate buffered saline as receiver fluid was consistent with several previous studies that employed the three model permeants (Kitagawa et al., 1997; Dias et al., 1999; Akomeah et al., 2004; Lopez et al., 2004 & 2005; Chilcott et al., 2005). Measurement of the solubility of drug in the vehicle is an important parameter for both the drug permeation studies and in determination of the degree of saturation. CF, a relatively hydrophilic molecule was shown to be more soluble in an aqueous solvent than in the oily vehicles. Since MP has moderate lipophilicity compared to BP and CF it was found to have intermediate solubility in both the aqueous and oily vehicles, but for both MP and BP, their solubility was lowest in the hydrocarbons (LP, HD and IHD) than in the ester (IPM) and the *cis*-unsaturated fatty acid (OA). The solubility trends agreed with previous reports for the model compounds (Dias et al., 2007; Akomeah et al., 2004).

The vehicles used in these studies were all permeant-saturated solutions, and in all cases contained sufficient excess solute to maintain a constant donor concentration during the experimental time frame. In an ideal situation all saturated solutions of the same permeant in any solvent system should produce an equal flux through a membrane that is independent of solute concentration (Higuchi, 1960). The restriction of the study run time to 6-8 h was

known to be sufficient for steady-state diffusion to be established with synthetic membranes (Akomeah et al., 2004; Ansari et al., 2006; Oshima et al., 2012; Oliveira et al., 2012). Examination of the flux results shows that flux of permeants from saturated solutions differed depending on the oily vehicle in question, and between different membranes. The direct implication of this result is that for all of the situations investigated, there was some interaction between the vehicle and the membrane. Such an interaction may involve diffusion of the solvent into the membrane where it alters the partition and/or diffusion coefficient of the solute. Alternatively, it is possible the vehicle may act as an extraction solvent and remove some components of the membrane, e.g. a plasticizer, thus modifying its resistance to permeation of the solute in the membrane. In addition, any sorbed vehicle component(s) may increase the solubility of the incorporated drug in the membrane (Crawford & Esmerian, 1971; Amnuaikit et al., 2005; Alexander et al., 2012).

The gravimetric method employed to the study the interaction of the oily vehicles with the membranes, although simple, does lead to yield reliable results on the alteration of membrane barrier properties (Aithal & Aminabhavi, 1990; Dias et al., 2007; McAuley et al., 2010). The membranes were selected to have a range of Hildebrand solubility parameters 17.4-20.8 $(MPa)^{1/2}$, overlapping the calculated and reported values for stratum corneum and skin (20.5 $(MPa)^{1/2}$) (HSPiP software, Dias et al., 2007 Abbott, 2012); whilst the oils, possess solubility parameters in the range of 14.5-17.4 $(MPa)^{1/2}$. The results (Table 3) indicated that the membranes interacted with oils differently depending on the molecular compatibility between both the membrane and oil. The interaction of the oils can be rationalized by considering the process, should it occur, as the occupation of a "hole" within

the membrane matrix (Aminabhavi & Khinnavar, 1993) by an oil molecule. The ability to occupy a hole depends on compatibility of the molar volume, shape and molecular structure of the permeant/vehicle.

The HSP values provide a means to assess the mutual compatibility of molecular structures, and potentially predict an interaction between a vehicle component and the membrane. The Hansen plot for the HDPE membrane and the oils showed a membrane with a small interaction radius (Figure 3), and all oily vehicles located outside the sphere. This is also confirmed by the large HSP distances that exist between the solvents and membrane. PU is a relatively hydrophilic membrane with a solubility parameter of 20.8 $(MPa)^{½}$ and the HSP-distances between the oils and PU were also high. Accordingly the affinity of the oils for HDPE and PU membranes were, perhaps, predictably low with subsequently low uptake. The flux of permeants from the oils, was also generally lower through HDPE and PU membranes than across the silicone membrane (Figure 2). It is important to note the permeant must itself be miscible with the vehicle post-incorporation for partition into and diffusion across the membrane to be facilitated (Cross et al., 2001; Dias et al., 2007; Zhang et al., 2011; Oliveira et al., 2012a; Oliveira et al., 2012b; Lane, 2013). The flux measurements across the various membranes were generally in agreement with the latter concept. Enhancement of the parabens (but not of hydrophilic caffeine) with respect to an aqueous vehicle was observed for oils that were incorporated in the barrier membranes. The latter finding was all-the-more stark given the plasticization of the PU membrane by OA in accordance with OA having the smallest HSP distance of the all the oily vehicles (Table 3).

The affinity of the respective oils for the different membranes (as determined by the swelling, or alternatively the HSP distance between oil and membrane) might be expected to correlate with the normalised flux (Fig. 4). Despite there being no good correlation between flux and either variable, there was a general tendency that when HSP distance was small or the degree of swelling large then the normalised flux of the permeants was increased. When the fluxes of the compounds through the individual membranes are considered (Fig. 5) the scatterplot indicated for silicone membrane that, broadly, as the membrane swelled in the oil then so the normalised fluxes of the compounds increased; particularly those of MP and BP (available for online inspection as "Supplementary Material"). When the effects of the individual oils on normalised fluxes of the compounds were considered in relation to swelling and HSP distance, it was found that IPM and IHD had most effect (Supplementary Material).

However, the relationship between flux and both HSP distance and degree of swelling was complex. For example, IHD was sorbed in the highest amounts by HDPE membrane, whilst IPM was sorbed in the lowest quantity; despite IHD having the largest HSP distance from that of the membrane (Table 4). The HSP distance values between LP and the membranes are similar to those of IPM. However, LP is a viscous mixture of different hydrocarbons; comprising linear and branched alkanes and a small amount of naphthenes and alkyl-substituted cyclo-alkanes (European Food Safety Authority, 2012). The molecular size and viscosity of LP components might hinder the molecular diffusivity into the membranes, when compared to lower molecular weight hydrocarbons. The results showed that although the HSPs indicate a general tendency for solvent-membrane interactions, other molecular

properties may also determine the magnitude with which an interaction actually occurs. The latter is also true of membranes themselves. For example, the absence of branching and high density of chain packing in HDPE membranes provides high stability and chemical resistance to solvent interaction (Harper, 2002; Berins 1991). Silicone membrane, conversely, is cross-linked in structure, and it is likely that the interacting oil is more associated with chain solvation and subsequent membrane swelling interactions rather than polymer dissolution, which can occur with non-cross-linked barriers.

The HSPs of all oils lay within the Hansen sphere for silicone membrane (Fig. 3) and accordingly all the oils behaved as good solvents for this polymer. Therefore since there were differences in the amounts of oil uptake then it may be possible to delineate other molecular properties that can affect the extent and degree of interaction with silicone membrane. IPM and OA possess simlar molecular weights (270 g/mol and 282 g/mol, respectively) and molecular volumes (315 and 319.5 respectively) yet almost three times as much IPM was sorbed to silicone membrane than OA, in agreement with literature reports (Dias et al., 2007). OA contains a *cis*-double bond which provides OA with a 'kinked' structure (Green et al., 1988). The low molecular flexibility within this molecule would require a greater expenditure of energy to penetrate into the membrane. The presence of a carboxylic acid group in OA leads to moderate polarity (Lee et al., 2003) that may also contribute to the lower uptake of this oil by the silicone membrane (Cross et al., 2001). The HSP-distance for IPM from silicone was also lower than for OA. This suggests that both the distance and the molecular nature (e.g. shape, polarity, and molecular flexibility) are also key factors affecting the interactions between the solvent and the membrane.

IHD was taken up in greatest quantity by silicone membrane in amounts that were significantly higher in comparison to other oils studied. The HSP distance for IHD was larger than that of HD, a molecule with the same molecular formula and weight as the linear hydrocarbon IHD. Accordingly it was anticipated that HD would be taken up in greater quantities than IHD due to the equivalent molecular mass. Since this was not the case, it was hypothesized that the branched structure of IHD compared with HD contributed in some way to its preferential sorption by membranes. Molecules with straight chains contain larger surface area, and thus greater dispersion forces, than branched-chain molecules of the same molecular weight. Despite both oils having the same molecular size, the molecular shape of IHD is almost spherical, while the shape generated by HD is oval. Although both oils are predicted to be good solvents from their HSP values, the branched structure of IHD along with its compact spherical shape could enable a greater partitioning of the oil into the space between the branched cross-linked membrane structure. If this occurs in stratified membranes composed of non-covalently linked molecules (e.g. the lipid matrix of the stratum corneum) then this would be expected to affect the packing of those membranes.

5. Conclusion

This study has shown that application of model permeants as solutions in pharmaceutically relevant oils vehicles is associated with non-ideal permeation behaviour across synthetic barrier membrane models. Application of saturated solutions of three model permeants in various (non-evaporating) oils led to different permeation fluxes depending on the oily vehicle employed for permeant dissolution. The use of Hansen solubility parameters

indicated that the dependency of the flux on the vehicle derived from preferential vehicle-membrane interactions. However, studying the HSP distances between vehicles and membranes, while providing an indication of compatibility between vehicles and membranes, requires a more in-depth physicochemical profiling of parameters such as molecular flexibility, molecular shape and molecular packing properties. It was shown that a series of different oils were sorbed to differing degrees by membranes with the effect of altering model permeant transport across the membranes. Nevertheless no simple correlation was found to exist between the Hansen solubility parameters of the oils or swelling of the membrane and the change in the normalised fluxes of the three compounds investigated. The findings of this study employing simple barrier membranes raises the potential for the common pharmaceutical and cosmetic formulation aids examined in this study to alter the delivery of co-formulated excipient (e.g. paraben preservatives as shown above) or even active pharmaceutical ingredients. It would appear that more sophisticated modelling perhaps incorporating tools such as principal component analysis might need to be employed to identify and measure the key factors that might influence the effects of oily vehicles on the diffusion of compounds through membranes, after topical application.

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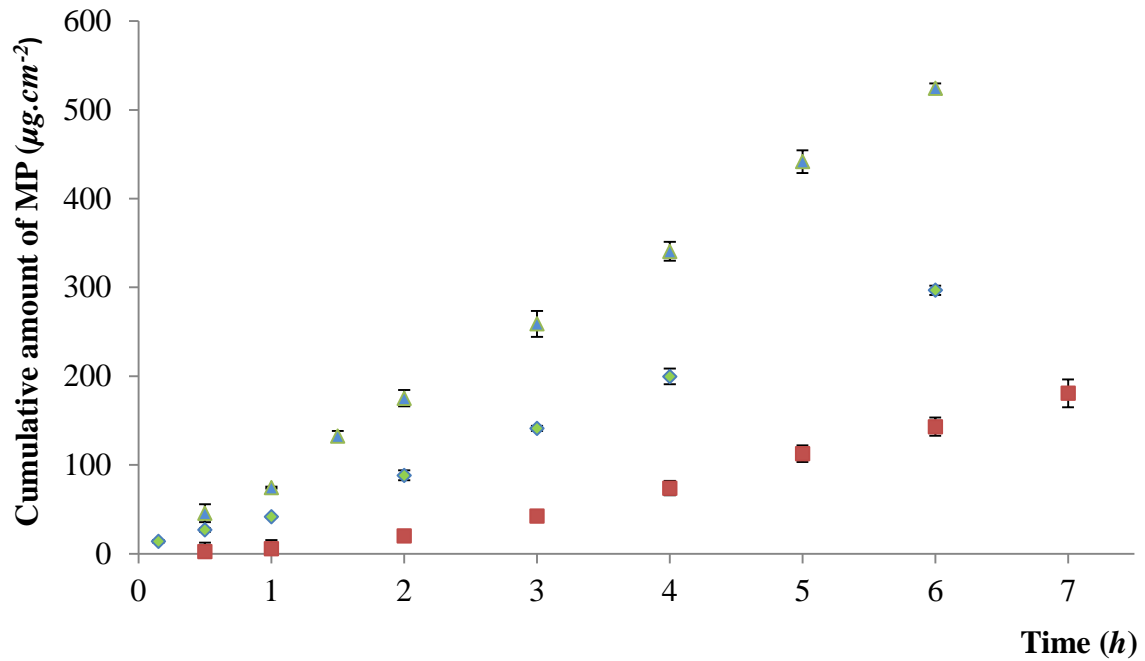
Figure 1. An example of the cumulative amount of methyl paraben (MP) permeated across ▲ silicone, ▇ high density polyethylene and ◆ polyurethane membranes versus time when applied in isohexadecane (IHD). Data represent mean ± sd (n=3-5). Several error bars lie within the symbols.
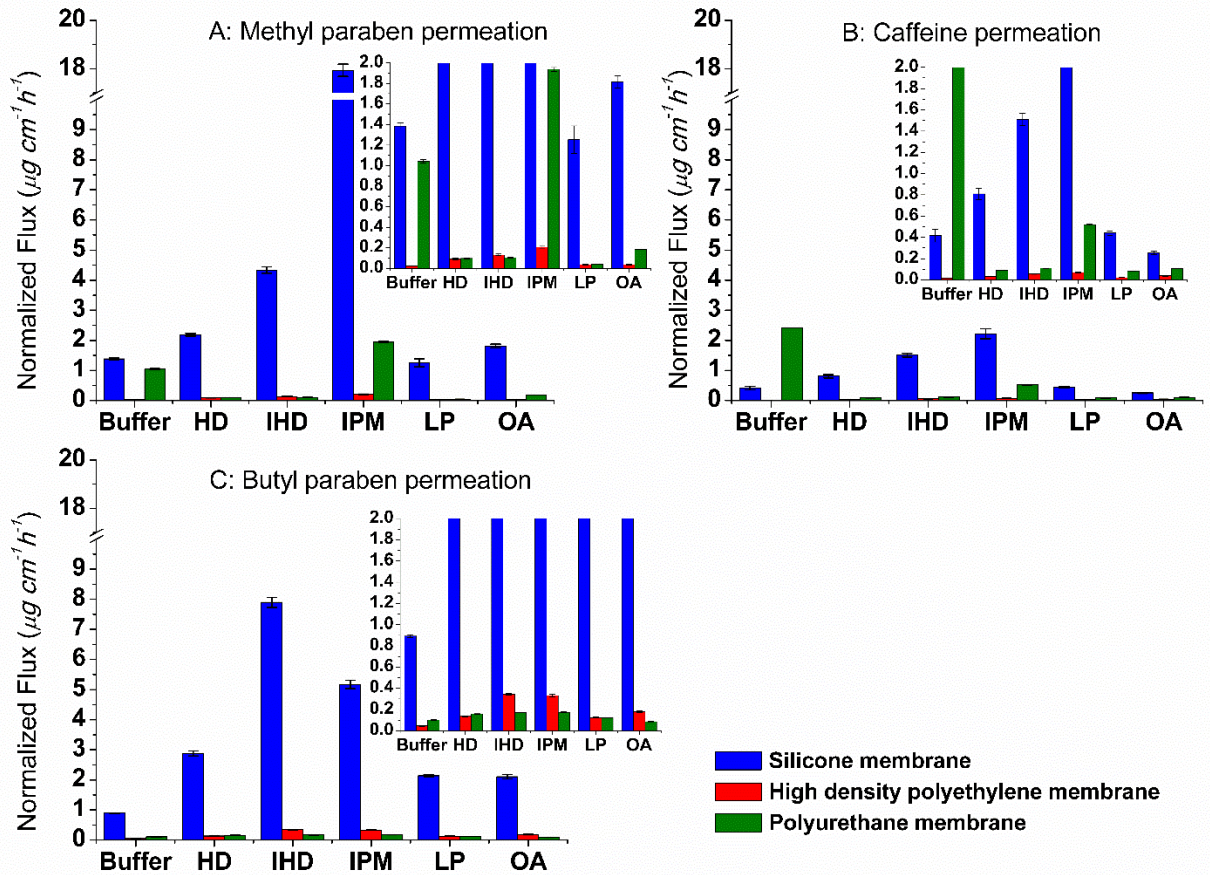
Figure 2. Normalized flux data (in $\mu g.cm^{-1}h^{-1}$) for (A) methyl paraben (B) caffeine (C) butyl paraben across ■ silicone, ■ high density polyethylene and ■ polyurethane membranes when applied in different oils and phosphate buffer. Data represent mean ± sd (n=3-5).The inset figures are an enlargement of the region from 0 - 2 $\mu g.cm^{-1}h^{-1}$.
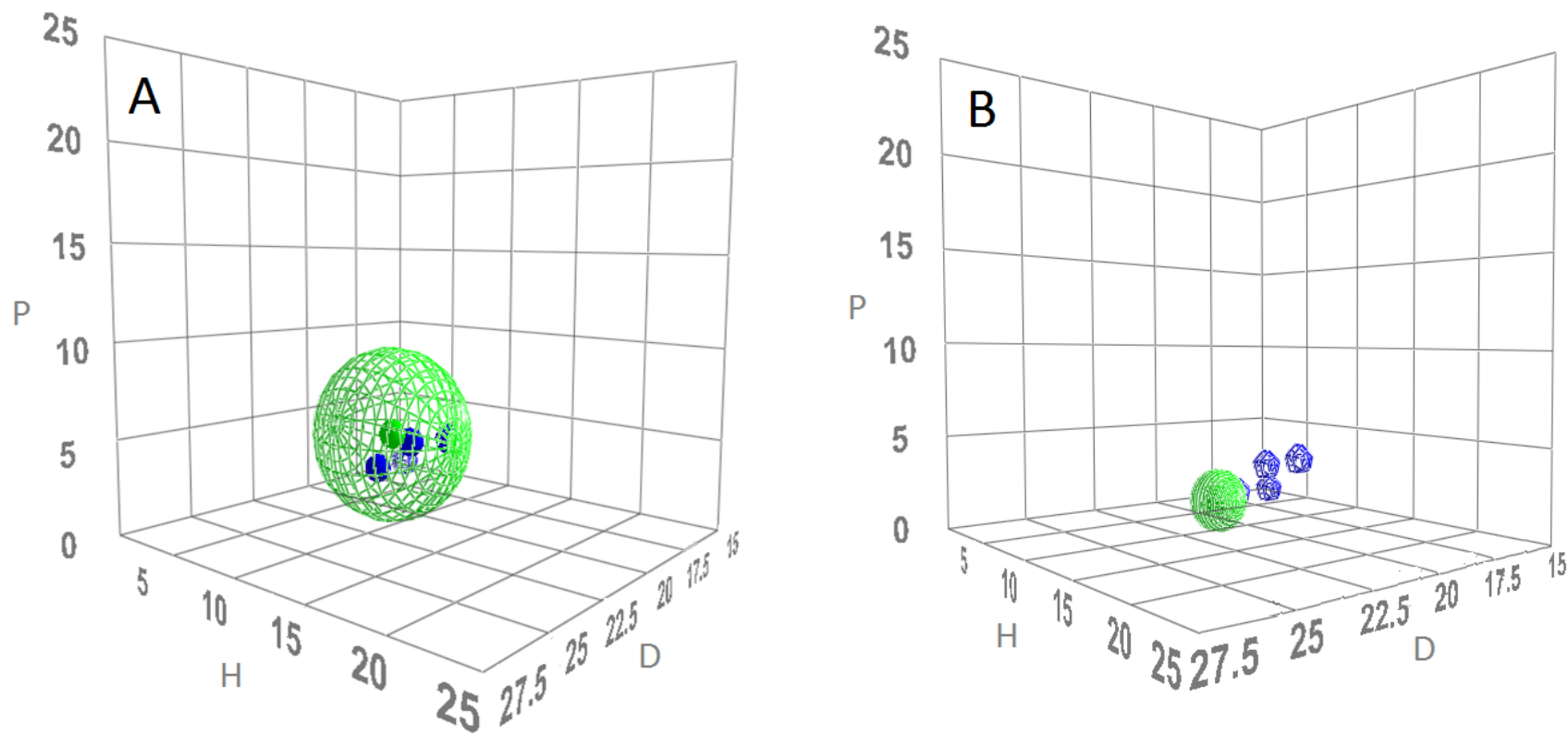
Figure 3. Example Hansen solubility spheres (HSP) for (A) silicone and (B) high density polyethylene (HDPE) membranes. Each axis is one of the three component Hansen solubility parameters (HSPs), δ_D, δ_H, or δ_P (representing the magnitude of the dispersive or van der Waals forces, the hydrogen bonding, and the polar bonding, respectively). The centre of the sphere (green symbol) represents the three-dimensional solubility parameter for the membrane. The blue symbols are the HSPs of oils used in this investigation. The radius of the sphere is 5.7 MPa$^{1/2}$ for silicone and 2 MPa$^{1/2}$ for HDPE.
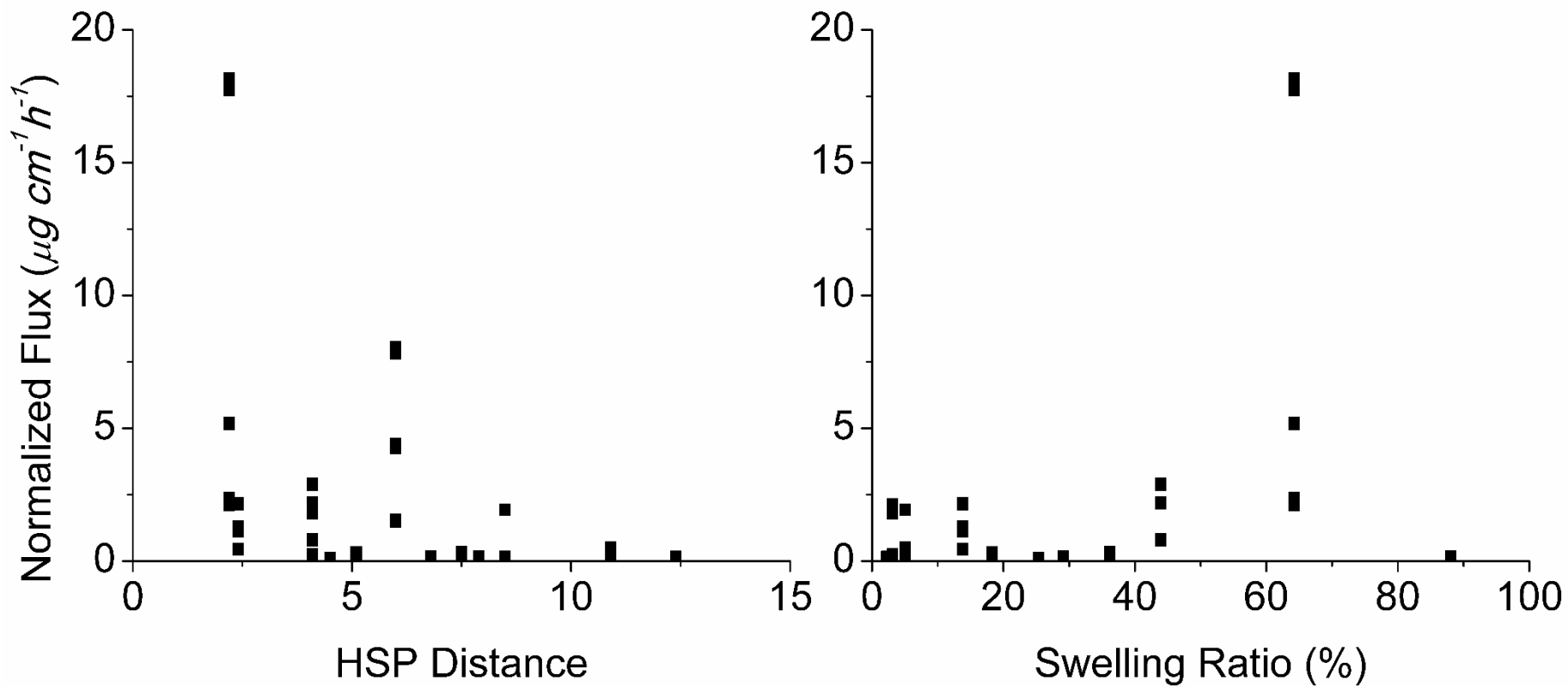
Figure 4　　Scatter plot of normalized flux data for three permeants (methyl paraben, caffeine and butyl paraben) across three membranes (silicone, high density polyethylene and polyurethane) when applied in five different oily vehicles (hexadecane; isohexadecane; isopropyl myristate, liquid paraffin, and oleic acid). Data represent all original data points from the study (n = 189). A poor correlation was observed for both Hansen solubility parameter (HSP) Distance and membrane swelling ratio as predictors of normalized flux (regression coefficient 0.186).
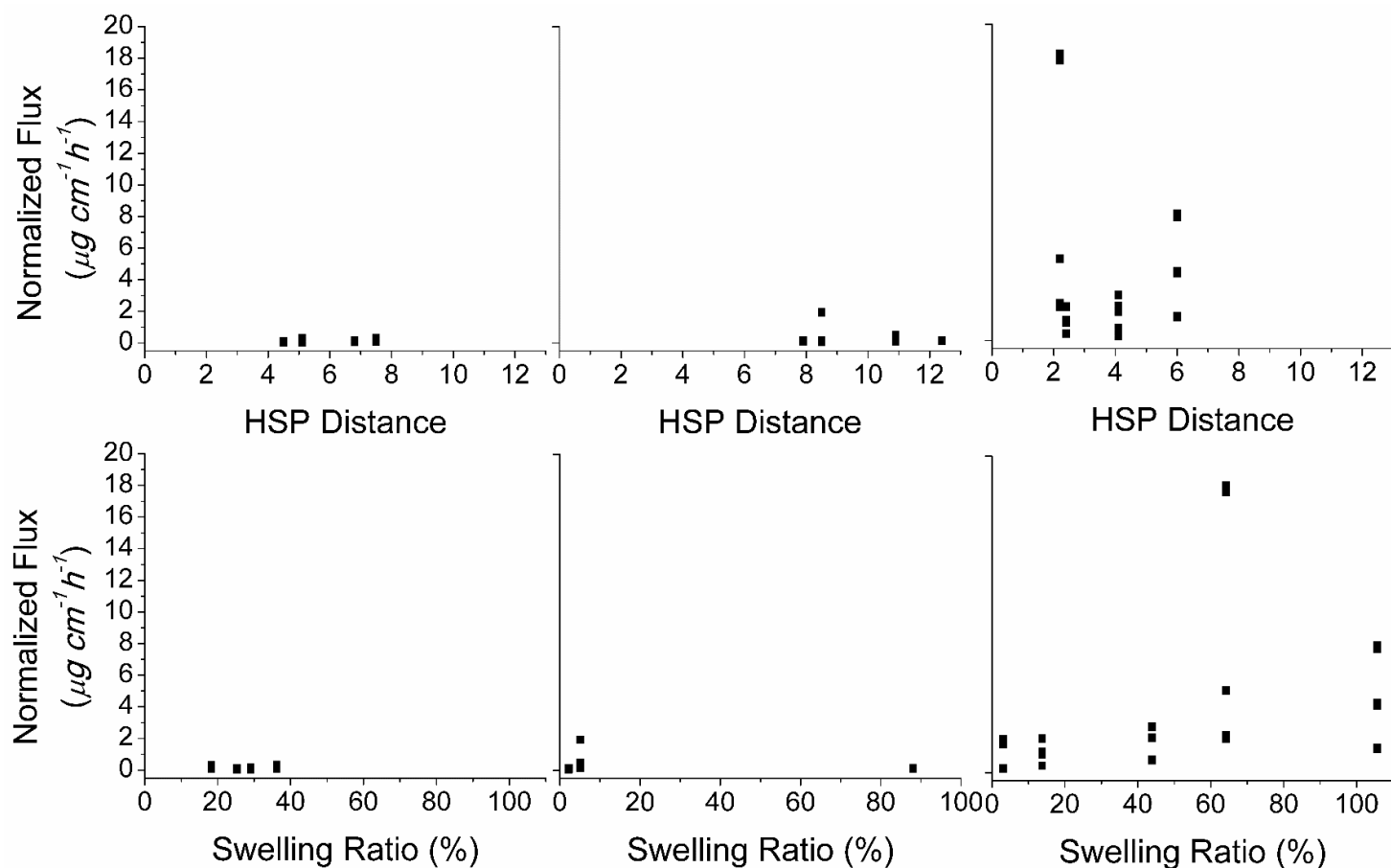
Figure 5. Scatter plot of normalized flux data as a function of Hansen solubility parameter (HSP) Distance or swelling ratio for three permeants (methyl paraben, caffeine and butyl paraben) when applied in five different oily vehicles (hexadecane; isohexadecane; isopropyl myristate, liquid paraffin, and oleic acid) across each of silicone, high density polyethylene (HDPE) and polyurethane(PU) membranes, respectively. Data represent all original data points for HDPE (n = 69); PU (n = 75) and Silicone (n = 45).

Table 1. Properties of the oils, membranes and permeants used in this investigation: isopropyl myristate (IPM), oleic acid (OA), hexadecane (HD), isohexadecane (IHD), liquid paraffin (LP), silicone membrane, high density polyethylene membrane (HDPE), polyurethane membrane (PU), caffeine (CF), methyl paraben (MP) and butyl paraben (BP)

Name	Molecular formula	MW	$MVol^*$	$\delta_D{}^*$	$\delta_P{}^*$	$\delta_H{}^*$	$Radius^*$
IPM	$C_{17}H_{34}O_2$	270.4	315	16.0	2.7	2.7	
OA	$C_{18}H_{34}O_2$	282.5	319.7	16.0	2.8	6.2	
HD	$C_{16}H_{34}$	226.4	294.2	16.3	0	0	
IHD	$C_{16}H_{34}$	226.4	295.3	14.7	0	0	
LP	C_nH_{2n+2}	340.0	424.1	16.1	1.8	3.7	
Silicone	$[Si(CH_3)_2O]_n$			17	2.9	2.6	5.7
HDPE	$(CH_2\text{-}CH_2)_n$			18	0	2	2
PU	$(-R-O-C-NH-R2-NH-C-O-)_n{}^*$			18.1	9.3	4.5	8
CF	$C_8H_{10}N_4O_2$	194.2	151.7	19.5	10.1	13.0	
MP	$C_8H_8O_3$	152.1	128.7	17.9	5.9	13.5	
BP	$C_{11}H_{14}O_3$	194.2	180.6	17.3	4.9	10.4	

*data determined by Hansen Solubility Parameters in Practice (HSPiP) software version 4.0.04 Copyright 2013 (www.Hansen-Solubility.com).

Table 2 Properties and solubility of the permeants in vehicles (solubility values represent mean ± SD, of n ≥5 determinations). Abbreviations: methyl paraben (MP), butyl paraben (BP), caffeine (CF), molecular weight (MW), partition coefficient (LogP), isopropyl myristate (IPM), oleic acid (OA), hexadecane (HD), isohexadecane (IHD), liquid paraffin (LP), deionized water (DIW).

Property	MP	BP	CF
MW	152.2	194.2	194.2
Log P	1.96	3.57	-0.07
Solubility in vehicles (mg.mL^{-1}			
IPM	35.04 ± 1.15	120.80 ± 2.60	0.83 ± 0.02
OA	6.58 ± 0.11	60.58 ± 1.16	5.08 ± 0.20
IHD	0.09 ± 0.01	1.32 ± 0.01	0.07 ± 0.00*
HD	0.08 ± 0.01	1.23 ± 0.01	0.07 ± 0.00*
LP	0.07± 0.01	1.21 ± 0.02	0.08 ± 0.00*
Phosphate buffer (pH=7.0)	2.39 ± 0.07	0.25 ± 0.01	25.72 ± 0.63
DIW	2.01 ± 0.04	0.26 ± 0.01	26.40 ± 0.32

Table 3 Amount (mg oil/g membrane) of oil in different membranes (m_{upt}) and the percentage difference in weight of membranes ($\%\Delta W$) after being soaked in different vehicles for approximately 17 h at 32°C. Data represent mean ± sd (n≥4). Abbreviations: isopropyl myristate (IPM), oleic acid (OA), hexadecane (HD), isohexadecane (IHD), liquid paraffin (LP), deionized water (DIW), high density polyethylene (HDPE) and polyurethane (PU).

Membrane		IHD	IPM	HD	OA	LP
Silicone	m_{upt}	1048.6 ± 17.6	662.1 ± 19.8	464.6 ± 9.2	31.2 ± 1.3	137.5 ± 5.2
	$\%\Delta W$	105.6 ± 1.1	64.2 ± 1.4	43.9 ±0.7	3.1 ± 0.1	13.8 ± 1.8
HDPE	m_{upt}	364.0 ± 24.1	188.7 ± 11.7	262.7 ± 9.6	297.0 ± 19.5	300.7 ± 17.2
	$\%\Delta W$	36.2 ± 2.0	18.3 ± 2.1	25.3 ± 3.1	29.1 ± 2.2	29.1 ± 2.9
PU	m_{upt}	22.4 ± 1.1	51.7 ± 1.9	20.4 ± 1.0	885.8 ± 27.2	23.4 ± 1.0
	$\%\Delta W$	2.3 ± 0.2	5.1 ± 0.4	2.2 ± 0.1	88.1 ± 5.1	2.2 ± 0.2

Table 4 Hansen solubility parameter (HSP) distance determined using Equation 2 between the HSP of the oils and different membranes MPa$^{1/2}$. Abbreviations: isopropyl myristate (IPM), oleic acid (OA), hexadecane (HD), isohexadecane (IHD), liquid paraffin (LP), deionized water (DIW), high density polyethylene membrane (HDPE) and polyurethane (PU).

Oil	OA	IPM	HD	IHD	LP
Silicone	4.1	2.2	4.1	6.0	2.4
HDPE	6.8	5.1	4.5	7.5	5.1
PU	7.9	8.5	10.9	12.4	8.5