Journal of Pharmaceutical Analysis xxx (2017) xxx-xxx

Contents lists available at ScienceDirect

Journal of Pharmaceutical Analysis

journal homepage: www.elsevier.com

Original article

Effect of plasma surface treatment of poly(dimethylsiloxane) on the permeation of pharmaceutical compounds

Laura J. Waters[a, *], Catherine V. Finch[a], A.K.M. Mehedi H. Bhuiyan[a], Karl Hemming[a], John C. Mitchell[b]

[a] *Department of Pharmacy, School of Applied Science, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, UK*
[b] *Medway Centre for Pharmaceutical Sciences, University of Greenwich, Chatham, Kent ME4 4TB, UK*

ARTICLE INFO

Keywords:
Permeation
PDMS
Silicone
Plasma
Flux
Hydrophobicity

ABSTRACT

This paper addresses the modification of poly(dimethylsiloxane), *i.e.* PDMS, using plasma surface treatment and a novel application of the membrane created. A set of model compounds were analysed to determine their permeation through PDMS both with, and without, plasma treatment. It was found that plasma treatment reduced permeation for the majority of compounds yet had little effect for some compounds, such as caffeine, with results indicating that polarity plays an important role in permeation, as is seen in human skin. Most importantly, a direct correlation was observed between plasma-modified permeation data and literature data through calculation of membrane permeability (K_p) values implying plasma-modified silicone membrane (PMSM) could be considered a suitable *in vivo* replacement to predict clinical skin permeation.

1. Introduction

Poly(dimethylsiloxane), also known as PDMS, is a commonly used polymer based on its favourable properties including transparency, gas permeability and general high level of stability [1]. The basic structure of the polymer is composed of –O–Si$(CH_3)_2$ – units which can be manufactured to a variety of specific requirements depending upon the constraints of the application, *i.e.* several types are available with specific functions [2]. The extensive range of uses of PDMS includes air separation [3,4], environmental control [5], separation of liquid mixtures [6], wound dressings and medical applications [7,8], microfluidics [9–11] and biochemical sensing [12]. As a result of such a diverse, and extensive, breadth of functionalities a substantial amount of literature can be found on the properties of PDMS (see previous references) or, for example, the dependence of gas permeability on membrane thickness (thus requiring reliable preparation techniques) [13].

As expected, researchers have attempted to modify the surface of PDMS to enhance its suitability, particularly in the field of microfluidics. This is because biological samples easily and strongly interact with PDMS surfaces because of the inherent hydrophobicity of the material which has led to numerous applications of modified PDMS surfaces in biological assays, such as biomolecule separation, immunoassay [14], cell culture and DNA hybridisation [15].

One particularly interesting modification to standard PDMS that has been the subject of investigation in recent years is modification of the surface using plasma treatment. It is generally accepted that PDMS (upon exposure to plasma) develops silanol groups (–OH) at the expense of methyl groups ($–CH_3$) [16,17] as a result of oxidation of the surface layer [18]. This creates a more highly hydrophilic surface which can be observed through a reduction in the contact angle of water [19] and may cause a wrinkling effect under certain conditions [20]. As a consequence of this transformation, the properties of the membrane are trans-

Peer review under responsibility of Xi'an Jiaotong University.
* Corresponding author.
Email address: l.waters@hud.ac.uk (L.J. Waters)

http://dx.doi.org/10.1016/j.jpha.2017.05.003
Received 2 February 2017; Received in revised form 15 May 2017; Accepted 15 May 2017
Available online xxx

formed. For example, it has been reported that freshly oxidised PDMS showed a significantly smaller gas diffusion coefficient compared with untreated membrane [21]. In some studies the process of plasma surface treatment is the first step in a series of procedures to modify the surface, *i.e.* to create a variety of more complex products that have different properties to the original PDMS or to avoid certain disadvantages. For example, following plasma treatment it is possible to immerse the membrane in acrylic acid, then immobilise with chitosan and gelatin and finally culture fibroblast cells onto the surface to enhance cell growth [22]. Other compounds have also been incorporated onto the surface of plasma treated PDMS, for example self-assembled amphipathic film, to address nonspecific protein adsorption issues thus broadening the potential uses of PDMS-based microfluidic chips in complex biological analysis [23].

There is one area of analytical research that utilises PDMS yet has not previously considered plasma treated surface modification, namely the use of PDMS to determine the permeation of pharmaceutical compounds for the prediction of skin permeability [24]. Traditionally, such permeation studies utilise human or, more frequently animal, skin whereby the amount of a compound is monitored over a period of time as it permeates across the skin layer from a donor to receiver phase [25]. This data is essential for a large variety of chemicals where there is the likelihood they will, at some point, come into contact with human skin, such as cosmetics, pharmaceuticals and household products. In recent years PDMS has been proposed as an ethical, economic and reliable alternative for the determination of compound permeation along with several other techniques [26]. For example, when permeation of different vehicles was considered, a trend between flux values for the model membrane and skin was evident suggesting that silicone membrane may provide information on qualitative trends [27]. This is particularly useful for compounds intended for use in cosmetic products where the use of animal testing within the EU and several other countries is no longer an option. However, it has been found that the data generated does not always directly relate to *in vivo* data and can be affected by a variety of factors, such as the presence of surfactants [28,29]. In the current work we consider the impact on permeation for a set of model compounds following transformation of the hydrophobic surface of PDMS using plasma surface treatment with the intention to create a more hydrophilic (*i.e.* more skin-like [30]), and therefore potentially more suitable, *in vitro* model.

2. Experimental

2.1. Plasma surface treatment method

Polydimethylsiloxane (PDMS) sheets (Silatos™) were used as purchased from ATOS, Sweden (150 × 200 × 0.13 mm). Disks were cut with a diameter of 14 mm and placed in a benchtop laboratory plasma unit (Henniker Scientific) under low pressure on full power (40 kHz, 100 W), this was then repeated on the alternate surface under identical conditions with both surfaces exposed for 90 s each (based on the knowledge that a more prolonged exposure time can result in cracking [31]). Contact angle analysis and permeation studies were performed immediately (within one hour) after plasma treatment to avoid storage stability issues. To examine the stability of the plasma-treated PDMS membrane, permeation analysis of a model compound (lidocaine) was performed through freshly treated and aged membrane. Results implied the membrane retained its hydrophilic surface even after eight weeks of storage (data not shown), implying stability was not an issue in this study. Furthermore, polar solvents, such as those used in this study, are known to enhance the stability of plasma-treated membranes thus ensuring stability was not an issue in this work.

2.2. Contact angle analysis

The static contact angle of the untreated and treated PDMS samples was measured by the sessile drop method using an optical goniometer with attached precision syringe (FTA1000, Surface Science Instruments, USA). A drop of deionised water was dispensed from the syringe onto the freshly treated PDMS surface below. A minimum of three measurements were taken for each sample from different locations on the surface to determine an average value.

2.3. Permeation studies

Sixteen model compounds were analysed using a Franz-type, bespoke, diffusion cell system with a diffusional area of 0.64 cm^2: aminopyrine (Fisher Scientific, Loughborough, UK, ≥ 97%), benzoic acid (Sigma Aldrich, Dorset, UK, ≥ 99.5%), caffeine (Sigma Aldrich, Dorset, UK, ≥ 99%), ethyl 4-hydroxybenzoate (Sigma Aldrich, Dorset, UK, ≥ 99%), ethyl 4-aminobenzoate (Sigma Aldrich, Dorset, UK, > 98%), ibuprofen (BASF, ≥ 99%), lidocaine (Sigma Aldrich, Dorset, UK, ≥ 98%), methyl 4-hydroxybenzoate (Sigma Aldrich, Dorset, UK, ≥ 98%), methyl 4-aminobenzoate (Sigma Aldrich, Dorset, UK, ≥98%), propyl 4-hydroxybenzoate (Sigma Aldrich, Dorset, UK, ≥ 99%), propyl 4-aminobenzoate (Alfa Aesar, Lancashire, UK, 98%), Flurbiprofen (Tokyo Chemical Industry Ltd, > 98%), Diclofenac (Tokyo Chemical Industry Ltd, > 98%), Ketoprofen (Tokyo Chemicals Industry Ltd, > 98%) acetyl salicylic acid (Sigma Aldrich, Dorset, UK, ≥ 99%) and salicylic acid (Sigma Aldrich, Dorset, UK, ≥ 99.5%), all as saturated solutions placed in the donor phase. In all cases samples were analysed using a UV spectrophotometer (Agilent Technologies, UK) to determine concentrations at a suitable wavelength for each drug.

Donor and receiver phases consisted of sonicated 0.05 M pH 7.4 phosphate buffered saline (K_2HPO_4, Sigma Aldrich, Dorset, UK, KH_2PO_4, Sigma Aldrich, Dorset, UK and NaCl, Fisher Scientific Ltd., Loughborough, UK) and an experimental temperature of 32 °C. Cells were stirred and left to equilibrate for 30 min, *i.e.* the equilibration period receptor phase remained as the starting experimental receptor phase solution. 0.6 mL samples were extracted from the 1.5 mL receptor phase every 45 min and replaced with fresh buffer for a total of 6 h. K_p values were then calculated using all data points for all compounds from t = 0 except in the case of caffeine where an initial lag period of 60 min was discarded from calculation as a result of the comparatively low extent of permeation. Upon addition of compound to the donor phase the buffer was unable to maintain the original pH and so the pH was measured for each resultant solution to allow calculation of the distribution coefficient (log D).

Solubility data required for analysis is presented in Table S1 (Supplementary information).

3. Results and discussion

3.1. Surface hydrophobicity

PDMS is renowned for its hydrophobic nature with typical static water contact angle (WCA) measurements in the region of ≥ 100° [19]. Water contact angles were measured for PDMS as received and then again after plasma treatment. Prior to treatment the average WCA was found to be 112.3° (± 0.9) whereas after plasma treatment the contact angle had reduced to an average of 60.7° (± 5.1). This result confirms that the plasma treatment process had significantly reduced the hydrophobicity of the surface, as expected based on previous literature [32].

3.2. Permeation analysis

3.2.1. Effect of surface treatment on permeation

As can be seen in Fig. 1, pre-treatment of the silicone membrane used in the permeation analysis results in a significant reduction in cumulative amount permeated over a 6 h period for benzoic acid. This confirms that even though it is only the surface of the silicone that has been modified through the plasma treatment, the effect on the overall properties of the membrane is significant. This result presents the first reported evidence that plasma treatment on silicone membrane can affect the permeation of pharmaceutical compounds which is an important finding based on the fact that permeation studies are often used when analysing pharmaceutical compounds.

Interestingly, across the range of compounds analysed, the degree to which plasma treatment altered the permeability profile varied somewhat. As previously mentioned, the cumulative amount of benzoic acid permeated was dramatically reduced by replacing standard membrane with plasma treated membrane. This considerable effect was also observed for several other compounds, for example, ibuprofen, lidocaine and aminopyrine. In contrast, several compounds did not exhibit a dramatic reduction in permeation using membrane pre-treated with plasma, as exemplified in Fig. 2 with caffeine. Other compounds for which permeation was not dramatically reduced by replacement with plasma treated membrane included ethyl 4-aminobenzoate and diclofenac.

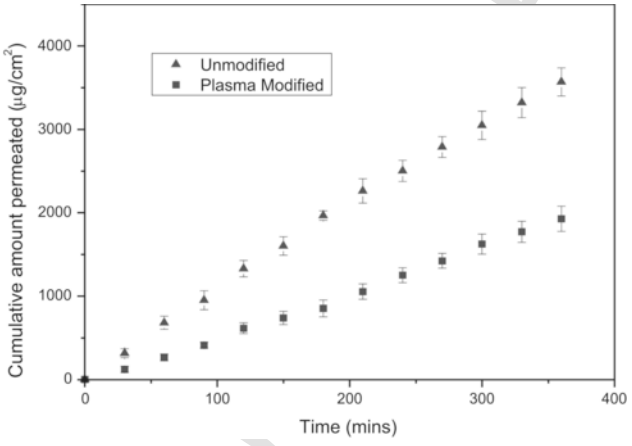

Fig. 1. Cumulative amount permeated for benzoic acid using (▲) unmodified silicone membrane and (■) plasma surface treated silicone membrane. $n = 3$, ± = SD.

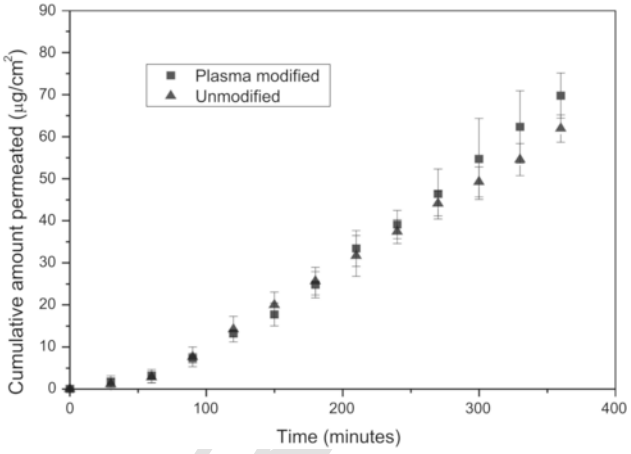

Fig. 2. Cumulative amount permeated for caffeine using (▲) unmodified silicone membrane and (■) plasma surface treated silicone membrane. $n = 3$, ± = SD.

As it was found experimentally that different compounds resulted in different total amounts permeated, both with standard, unmodified membrane and plasma treated membrane, the data was simplified to allow a clearer interpretation to be made. This was achieved by considering the total cumulative amount permeated using plasma treated membrane as a percentage of the total cumulative amount permeated using standard, unmodified membrane. A summary of the values (after a total experimental time of six hours) can be seen in Table 1.

Based on the data in Table 1 it can be seen that the most significant reduction in permeation was generally observed for compounds with the lower polar surface areas. These findings indicate that polarity plays an important role in permeation, as is seen in biological systems such as intestinal absorption [33], blood-brain barrier permeation [34] and human skin permeation. Based on previous work, transdermal penetration has been linked with structural predictors, such as polar surface area whereby the usefulness of such parameters has been assessed [35]. It would appear that our plasma treated membrane findings fit well with published literature [36], as illustrated in Fig. 3, and that treatment has an impact on the permeation of a set of compounds to varying extents which can be linked to polar surface area ($R^2 = -0.73$, values for PSA derived using Chemspider (www.chemspider.com)).

Assuming that the surface of the membrane has a negative charge overall, the more water soluble compounds (which may have a dipolar effect) were removed from the dataset and the linearity reconsidered. It was found that there was no change in the linearity of the data after the removal of the more hydrophilic compounds. Furthermore, analysis was undertaken to consider if logD, molecular weight or hydrogen bonding were related to the reduction in permeation and no significant relationships were observed (data not shown). In addition, Table 1 shows that polar surface area is not directly related to the amount permeated, either unmodified or plasma treated, confirming it is the *change* in permeation that is related to polar surface area rather than the specific permeation values.

Table 1
Total cumulative amount of compound permeated after 6 h through unmodified and plasma treated membrane, also expressed as a percentage reduction (%). Polar surface area (PSA) values were calculated using Chemspider (www.chemspider.com).

Compound	Amount permeated (μg/cm^2)			
	Unmodified	Plasma treated	Reduction (%)	PSA (Å^2)
Acetyl salicylic acid	561.1	432.1	23.00	64
Aminopyrine	3360.5	1727.7	48.59	27
Benzoic acid	3507.5	1893.8	46.01	37
Caffeine	58.92	66.73	−13.27	58
Diclofenac	41.11	38.50	6.351	49
Ethyl 4-aminobenzoate	1519.56	1543.58	−1.581	52
Ethyl 4-hydroxybenzoate	782.8	631.8	19.29	47
Flurbiprofen	345.0	279.7	18.93	37
Ibuprofen	1916.6	868.0	54.71	37
Ketoprofen	118.1	96.03	18.93	54
Lidocaine	4911.4	2819.24	42.60	36
Methyl 4-aminobenzoate	2346.51	1760.04	24.99	52
Methyl 4-hydroxybenzoate	818.76	601.5	26.53	47
Propyl 4-aminobenzoate	1495.01	1473.85	1.415	52
Propyl 4-hydroxybenzoate	679.76	425.15	37.46	47
Salicylic acid	1841.8	1437.4	21.96	58
Butyl 4-aminobenzoate	901.1	714.1	20.75	52
Butyl 4-hydroxybenzoate	782.4	652.1	16.66	47

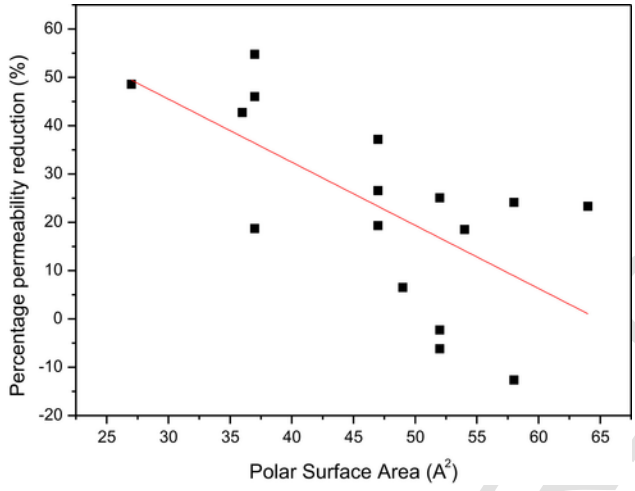

Fig. 3. Reduction in the cumulative amount permeated using silicone membrane to highlight the importance of polar surface area (PSA).

3.2.2. *Suitability of plasma treated silicone to predict in vivo skin membrane permeability*

Membrane permeability (K_p) is frequently considered when investigating the behaviour of compounds through skin for inter-laboratory studies, although it should be noted that maximum flux is sometimes considered for individual studies [37]. Skin permeability may be characterised by both steady state flux and permeability coefficient, and whilst steady state flux appears more practical from a clinical perspective as it can be used readily to evaluate the use of delivery devices, it does not allow for the normalisation of concentration and therefore hinders inter-penetrant comparisons. Furthermore, significant quantities of permeability data have been published in the form of permeability coefficients, for example the large collection of skin permeability data published by Flynn [38] which allows for comparative analysis such as this work to be undertaken. Researchers have attempted to simplify the prediction of K_p to aid in the development of formulations using a variety of *in vitro* systems (for example [39] and [40]), mainly with the aims of either avoiding the use of animal testing or for economic reasons [26]. An ideal skin mimic system will result in K_p values that correlate well with literature. Permeability data acquired during this study is presented in Table 2 for both standard PDMS membrane and plasma-treated membrane for a set of compounds. These are presented along with literature values [41–45] which were selected based on their similarity to the experimental conditions used during this study.

Membrane permeability values using standard membrane (for comparison) and then using plasma pre-treated membrane were calculated and compared with literature data (Figs. 4 and 5). Using standard PDMS membrane produced a partially linear relationship between experimental and literature data ($R^2 = 0.77$). Although this will allow some prediction of permeability, it cannot be considered a close enough fit to be confident in predicting data for compounds beyond those considered in this study. However, if the PDMS membrane is firstly plasma treated and then used for analysis with the same set of compounds, the linearity increases significantly with an $R^2 = 0.88$. This method offers an improved system using plasma-treated membrane for permeability analysis and would provide an enhanced experimental *in vitro* system for predictive purposes.

Membrane permeability (K_p) is constant for a particular compound and is a reflection of the ability to cross the membrane, normalised by concentration. In an ideal situation, a compound should always provide an identical value, regardless of vehicle formulation based on the assumption that the compound does not interact with the formulation components. In this case, a slightly different scenario is presented in that different K_p values were observed for a compound with identical formulations yet different membrane properties. This finding implies there must be an interaction between the membrane itself and the compound to result in the difference in K_p values observed for the majority of the compounds analysed.

Table 2
Experimental membrane permeability (K_p) values ($\times 10^{-4}$) for both standard PDMS membrane and plasma-treated membrane, presented alongside literature permeability data [41–45]. All results are expressed as the mean ± S.D. ($n = 3$).

Chemical	Membrane permeability (Kp) $\times 10^{-4}$ (cm/min)		
	Standard PDMS	Plasma-treated PDMS	Literature
Acetyl salicylic acid	1.255 ± 0.051	0.9821 ± 0.0709	0.085 [41]
Aminopyrine	2.01 ± 0.11	1.075 ± 0.139	0.198 [42]
Benzoic Acid	11.38 ± 0.40	6.236 ± 0.428	2.94 [43]
Caffeine	0.08840 ± 0.00440	0.1026 ± 0.0120	0.108 [42]
Diclofenac	0.6099 ± 0.0316	0.5618 ± 0.0272	0.167 [44]
Ethyl 4-aminobenzoate	47.83 ± 1.56	49.35 ± 0.98	121 [42].
Ethyl 4-hydroxybenzoate	18.40 ± 0.47	15.00 ± 1.03	2.32 [42]
Flurbiprofen	2.169 ± 0.063	1.767 ± 0.126	0.379 [43]
Ibuprofen	11.91 ± 0.54	5.432 ± 0.514	0.56 [43]
Ketoprofen	0.3557 ± 0.0193	0.2944 ± 0.0126	1.17 [43]
Lidocaine	36.11 ± 1.54	22.98 ± 1.09	4.209 [45]
Methyl 4-aminobenzoate	36.45 ± 2.54	27.80 ± 2.31	11.04 [42]
Methyl 4-hydroxybenzoate	7.092 ± 0.363	5.698 ± 0.359	1.49 [42]
Propyl 4-hydroxybenzoate	39.43 ± 0.62	26.17 ± 1.65	2.18 [42]
Propyl 4-aminobenzoate	55.04 ± 1.75	55.31 ± 2.27	134 [42].
Salicylic Acid	6.560 ± 0.359	5.158 ± 0.142	2.30 [44]
Butyl 4-aminobenzoate	109.9 ± 5.8	89.21 ± 7.61	121 [38].
Butyl 4-hydroxybenzoate	71.21 ± 3.28	60.94 ± 3.91	16.62 [38]

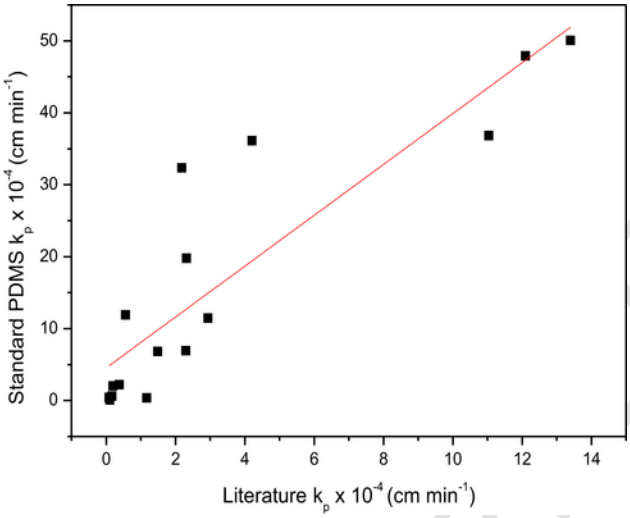

Fig. 4. Relationship between experimental K_p values (standard membrane) and literature K_p values ($R^2 = 0.77$).

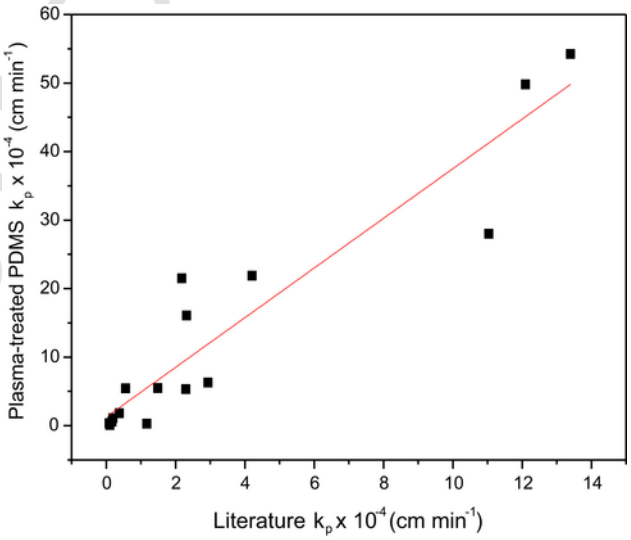

Fig. 5. Relationship between experimental K_p values (plasma-treated membrane) and literature K_p values ($R^2 = 0.88$).

4. Conclusions

In summary, this study presents the first attempt to modify PDMS membrane using plasma treatment to determine the subsequent effect on permeability analysis. It can be seen that it is possible to modify the permeability of compounds through the membrane and the extent of the effect is dependent upon the polar surface area of the permeating molecule. Furthermore, plasma-treated membrane is a more suitable system for the *in vitro* analysis of compounds as it has been found to correlate more closely with literature data compared with standard PDMS membrane.

5. Summary

Predicting the permeation of compounds through skin is currently one of the biggest obstacles in replacing the use of animals in pharmaceutical analysis. Although PDMS has shown some promise as a skin mimic, the results did not match literature data closely enough for it to be deemed a suitable alternative. This paper considers modification of the membrane using plasma treatment which was then tested with a set of compounds and found to closely match literature data from established *in vivo* systems. Thus, proving that modified PDMS is a suitable skin mimic for the pharmaceutical industry to adopt to replace current systems.

Acknowledgments

The authors wish to thank Henniker Ltd for supporting this study.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpha.2017.05.003.

References

[1] I. Klammer, M.C. Hofmann, A. Buchenauer, et al., Long-term stability of PDMS-based microfluidic systems used for biocatalytic reactions, J. Micromech. Microeng. 16 (2006) 2425–2428.

[2] S. Deguchi, J. Hotta, S. Yokoyama, et al., Viscoelastic and optical properties of four different PDMS polymers, J. Micromech. Microeng. 25 (9) (2015) 097002.

[3] S. Koter, A. Kujawska, W. Kujawski, Modeling of transport and separation in a thermopervaporation process, J. Membr. Sci. 480 (2015) 129–138.

[4] P. Li, H.Z. Chen, T.S. Chung, The effects of substrate characteristics and pre-wetting agents on PAN-PDMS composite hollow fiber membranes for CO_2/N2 and O2/N2 separation, J. Membr. Sci. 434 (2013) 18–25.

[5] J.S. Turner, Y.L. Cheng, Heterogeneous polyelectrolyte gels as stimuli-responsive membranes, J. Membr. Sci. 148 (1998) 207–222.

[6] Z. Dong, G. Liu, S. Liu, et al., High performance ceramic hollow fiber supported PDMS composite pervaporation membrane for bio-butanol recovery, J. Membr. Sci. 450 (2014) 38–47.

[7] A. Agarwal, T.B. Nelson, P.R. Kierski, et al., Polymeric multilayers that localize the release of chlorhexidine from biologic wound dressings, Biomaterials 33 (2012) 6783–6792.

[8] J.A. Juárez-Moreno, A. Ávila-Ortega, A.I. Oliva, et al., Effect of wettability and surface roughness on the adhesion properties of collagen on PDMS films treated by capacitively coupled oxygen plasma, Appl. Surf. Sci. 349 (2015) 763–773.

[9] X. Fan, C. Jia, J. Yang, et al., A microfluidic chip integrated with a high-density PDMS-based microfiltration membrane for rapid isolation and detection of circulating tumor cells, Biosens. Bioelectron. 71 (2015) 380–386.

[10] I.T. Martin, B. Dressen, M. Boggs, et al., Plasma modification of PDMS microfluidic devices for control of electroosmotic flow, Plasma Process. Polym. 4 (2007) 414–424.

[11] M.E. Vlachopoulou, G. Kokkoris, C. Cardinaud, et al., Plasma etching of poly(dimethylsiloxane): roughness formation, mechanism, control, and application in the fabrication of microfluidic structures, Plasma Process. Polym. 10 (2013) 29–40.

[12] S. Gu, Y. Lu, Y. Ding, et al., Droplet-based microfluidics for dose-response assay of enzyme inhibitors by electrochemical method, Anal. Chim. Acta 796 (2013) 68–74.

[13] G. Firpo, E. Angeli, L. Repetto, et al., Permeability thickness dependence of polydimethylsiloxane (PDMS) membranes, J. Membr. Sci. 481 (2015) 1–8.

[14] Y.J. Ko, J.H. Maeng, Y. Ahn, et al., Real-time immunoassay with a PDMS-glass hybrid microfilter electro-immunosensing chip using nanogold particles and silver enhancement, Sens. Actuators B-Chem. 132 (2008) 327–333.

[15] Y.M. Hsu, C.C. Chang, The portable fluorescence detection system matched with PDMS microfluidic biochip for DNA hybridization detection, Optik 126 (20) (2015) 2600–2605.

[16] S. Bhattacharya, A. Datta, J.M. Berg, et al., Studies on surface wettability of poly(dimethyl) siloxane (PDMS) and glass under oxygen-plasma treatment and correlation with bond strength, J. Microelectromech. Syst. 14 (2005) 590–597.

[17] V. Danilov, H.E. Wagner, J. Meichsner, The distribution of CH3 over the film thickness and shrinkage of H2 plasma-modified PDMS films, Plasma Process. Polym. 10 (2013) 320–327.

[18] M.K. Chaudhury, G.M. Whitesides, Correlation between surface free energy and surface constitution, Science 255 (1992) 1230–1232.

[19] K.S. Deshpande, S. Kuddannaya, J. Staginus, et al., Biofunctionalization and self-interaction chromatography in PDMS microchannels, Biochem. Eng. J. 67 (2012) 111–119.

[20] F.A. Bayley, J.L. Liao, P.N. Stavrinou, et al., Wavefront kinetics of plasma oxidation of polydimethylsiloxane: limits for sub-μm wrinkling, Soft Matter 10 (2014) 1155–1166.

[21] D.A. Markov, E.M. Lillie, S.P. Garbett, et al., Variation in diffusion of gases through PDMS due to plasma surface treatment and storage conditions, Biomed. Microdevices 16 (2014) 91–96.

[22] A. Salati, H. Keshvari, A. Karkhaneh, et al., Design and fabrication of artificial skin: chitosan and gelatin immobilization on silicone by poly acrylic acid graft using a plasma surface modification method, J. Macromol. Sci. Phys. 50 (2011) 1972–1982.

[23] X. Yu, J. Xiao, F. Dang, Surface modification of poly(dimethylsiloxane) using ionic complementary peptides to minimize nonspecific protein adsorption, Langmuir 31 (2015) 5891–5898.

[24] K.B. Sloan, J. Synovec, H. Ketha, A surrogate for topical delivery in human skin: silicone membranes, Ther. Deliv. 4 (2013) 203–224.

[25] H. Benson, A. Watkinson, Topical and Transdermal Drug Delivery, Wiley, Hoboken, USA, 2012.

[26] L.J. Waters, Recent developments in skin mimic systems to predict transdermal permeation, Curr. Pharm. Des. 21 (2015) 2725–2732.

[27] R.M. Watkinson, R.H. Guy, G. Oliveira, et al., Optimisation of cosolvent concentration for topical drug delivery III - Influence of lipophilic vehicles on ibuprofen permeation, Skin Pharmacol. Phys. 24 (2010) 22–26.

[28] L. Waters, L. Dennis, A. Bibi, et al., Surfactant and temperature effects on paraben transport through silicone membranes, Colloids Surf. B 108 (2013) 23–28.

[29] Y. Shahzad, L.J. Waters, C. Barber, Solvent selection effects on the transport of compounds through silicone membrane, Colloids Surf. A 458 (2014) 96–100.

[30] H. Trommer, R.H.H. Neubert, Overcoming the stratum corneum: the modulation of skin penetration, Skin Pharmacol. Phys. 19 (2006) 106–121.

[31] S.H. Tan, N.T. Nguyen, Y.C. Chua, et al., Oxygen plasma treatment for reducing hydrophobicity of a sealed polydimethylsiloxane microchannel, Biomicrofluidics 4 (3) (2010) 032204.

[32] D. Bodas, J.Y. Rauch, C. Khan-Malek, Surface modification and aging studies of addition-curing silicone rubbers by oxygen plasma, Eur. Polym. J. 44 (2008) 2130–2139.

[33] P. Ertl, B. Rohde, P. Selzer, Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties, J. Med. Chem. 43 (2000) 3714–3717.

[34] J. Kelder, P.D.J. Grootenhuis, D.M. Bayada, et al., Polar molecular surface as a dominating determinant for oral absorption and brain penetration of drugs, Pharm. Res. 16 (1999) 1514–1519.

[35] J.E. Grice, S.E. Cross, C. Brownlie, et al., The application of molecular structural predictors of intestinal absorption to screening of compounds for transdermal penetration, J. Pharm. Pharmacol. 62 (2010) 750–755.

[36] A. Pranitha, P.K. Lakshmi, Towards a correlation between polar surface area of drugs with ex-vivo transdermal flux variability, Iran. J. Pharm. Sci. 10 (2014) 47–60.

[37] P.S. Mertz, K.B. Sloan, The flux of select NSAIDs through silicone membranes from mineral oil, Pharmaceutics 6 (2014) 354–365.
[38] G.L. Flynn, Physicochemical determinants of skin absorption, in: T.R.G.C.J. Henry (Ed.), Principles of Route-to-Route Extrapolation for Risk Assessment, ed., Elsevier, New York, 1990, pp. 93–127.
[39] P.A. Lehman, A simplified approach for estimating skin permeation parameters from in vitro finite dose absorption studies, J. Pharm. Sci. 103 (2014) 4048–4057.
[40] J. Shen, L. Kromidas, T. Schultz, et al., An in silico skin absorption model for fragrance materials, Food Chem. Toxicol. 74 (2014) 164–176.
[41] M. Walker, T.A. Hulme, M.G. Rippon, et al., In vitro model(s) for the percutaneous delivery of active tissue repair agents, J. Pharm. Sci. 86 (1997) 1379–1384.
[42] T. Uchida, W.R. Kadhum, S. Kanai, et al., Prediction of skin permeation by chemical compounds using the artificial membrane, Strat-M™, Eur. J. Pharm. Sci. 67 (2015) 113–118.
[43] K. Zhang, M. Chen, G.K.E. Scriba, et al., Human skin permeation of neutral species and ionic species: extended linear free-energy relationship analyses, J. Pharm. Sci. 101 (2012) 2034–2044.
[44] I.T. Degim, W.J. Pugh, J. Hadgraft, Skin permeability data: anomalous results, Int. J. Pharm. 170 (1998) 129–133.
[45] R. Miki, Y. Ichitsuka, T. Yamada, et al., Development of a membrane impregnated with a poly(dimethylsiloxane)/poly(ethylene glycol) copolymer for a high-throughput screening of the permeability of drugs, cosmetics, and other chemicals across the human skin, Eur. J. Pharm. Sci. 66 (2014) 41–49.