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The effect of drug concentration on solvent activity in silicone membranes

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ABSTRACT

The effects of supersaturated formulations on drug permeation through artificial and biological membranes have been reported by a number of research groups. However, little information is known about solvent permeation from these supersaturated formulations, and in particular the effect of high drug concentrations and degree of saturation (DS) on solvent activity. The aim of this study was to determine the effect of the DS of a model drug, oxybutynin, on solvent and drug permeation. Supersaturated residues of oxybutynin in propylene glycol (PG) or (octyl salicylate) OSAL were prepared by the solvent evaporation method. In both formulations a high percentage (25%, v/v) of solvent was used in order to avoid solvent depletion. Permeation of PG and OSAL through silicone was monitored by GC and HPLC, respectively. All OSAL formulations permeated to a higher extent than PG formulations. A decrease in OSAL permeation with 5 DS formulations was observed in comparison with 1 DS or 2 DS formulations, indicating a decrease in solvent activity with drug concentration. In addition, the drug transport from the 5 DS formulation of OSAL was higher than the 1 and 2 DS formulations but lower than predicted. Based on both solvent and drug permeation, this suggests that the low drug permeation observed with 5 DS resulted from a decrease in solvent thermodynamic activity rather than a decrease in solute activity as a result of drug crystallisation. Using PG formulations, the PG permeation remained unaffected with the DS of the formulation, up to 5 DS.

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1. Introduction

Permeation of a compound through the stratum corneum (SC) depends on a number of physicochemical properties such as molecular weight, lipophilicity, polarity, capacity to form hydrogen bonds, solubility and ionisation. Passive permeation enhancement can be achieved by increasing the thermodynamic activity of the drug in the formulation or by co-administration of chemical permeation enhancers. The use of supersaturated formulations to increase drug thermodynamic activity, as a strategy in transdermal drug delivery, was first considered by Higuchi (1960). Supersaturation is a state where the drug is at a higher concentration than the solubility limit and as a consequence the drug flux should increase with increasing degree of saturation (DS). Techniques to produce supersaturated systems include the method of mixed cosolvents (Davis and Hadgraft, 1991), solvent evaporation (Coldman et al., 1969), and heating and cooling (Henmi et al., 1994).

While many workers have used supersaturated systems to enhance drug thermodynamic activity (Davis and Hadgraft, 1991; Pellett et al., 1994, 1997; Raghavan et al., 2000) few reports have shown that solvent/membrane interactions are also strongly dependent on the thermodynamic activity of the solvent. For example, Francoeur et al. (1990) measured the uptake of oleic acid into porcine skin and silastic from a series of ethanol:water vehicles. The uptake of oleic acid (OA) reached its maximum with the vehicle containing 40% ethanol, as the OA was completely solubilised at 40% or higher levels of ethanol. The authors suggested that the uptake of OA by silicone and porcine SC membranes was therefore controlled by OA thermodynamic activity in the applied ethanolic vehicle.

Twist and Zatz (1986) investigated the effects of interactive (vehicles which affect the membrane, e.g. ethanol/water) and non-interactive (vehicles which do not affect the membrane, e.g., water in contact with a silicone membrane) systems on the flux of parabens from saturated aqueous solutions across silicone membranes and observed a higher flux for propylparaben than methylparaben. However, when using mixtures of ethanol:water (interactive solvent), the flux of methylparaben was higher than that of propylparaben (Twist and Zatz, 1988). The authors suggested that the low flux of propylparaben from the ethanol/water mixture resulted from the high solubility of propylparaben in the system, which reduced the alcohol activity. As a result, the amount of alcohol taken up by the membrane decreased leading to a drop in propylparaben uptake and flux relative to that of methylparaben.

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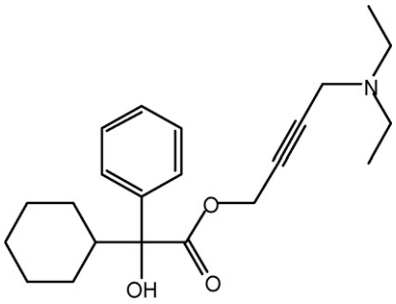


Fig. 1. Chemical structure of oxybutynin.

In another study, the influence of the parabens concentration on the flux through silicone membranes from application of an alcoholic solution was monitored (Twist and Zatz, 1990). This study demonstrated that the flux of paraben increased with paraben concentration, reached a maximum (which did not coincide with the saturated solubility) and then decreased with further increase in paraben concentration. Theoretical models confirmed that the flux of ethanol across the membrane also decreased with solvent activity.

The aim of the present study was to investigate the effect of drug concentration or DS on solvent thermodynamic activity and, consequently, on solvent uptake and drug permeation through silicone. Oxybutynin (Fig. 1) was selected as a model drug as it is a suitable candidate for transdermal drug delivery with a molecular weight of less than 500 Da, a log K_{oct} of 4.12, a melting point of 57 °C (Martindale, 2007; Miyamoto et al., 1995) and it is currently delivered via the transdermal route. Transdermal delivery of oxybutynin has shown comparable efficacy and improved significantly the anticholinergic safety profile compared to oral administration (Davila, 2003).

Propylene glycol (PG) and octyl salicylate (OSAL) were selected as the non-interactive and interactive solvents, respectively (Table 1). PG is widely used as a penetration enhancer in topical dermatological formulations (Bendras et al., 1995). PG readily permeates the skin and may carry the drug with it, as shown by correlations *in vitro* between the permeation of both PG and the drug (Mollgaard and Hoelgaard, 1983; Wotton et al., 1985; Squillante et al., 1998; Trottet et al., 2004). OSAL belongs to a class of skin permeation enhancers classified as GRAS, i.e., Generally Recognised As Safe (Reed et al., 1997; Finnin and Morgan, 1999). OSAL has traditionally been used as a chemical sunscreen and it is regarded as safe in concentrations up to 5% (v/v) (Funk et al., 1995). In transdermal drug delivery, OSAL has been used to enhance the permeation of testosterone, oestradiol and fentanyl through human skin using spray formulations (Morgan et al., 1998a,c; Traversa, 2005). Similar enhancement properties have been observed *in vitro* for testosterone when OSAL was used as a pure solvent or in combination with PG, under occlusive conditions using porcine skin (Nicolazzo et al., 2005).

As noted by other authors there are a number of advantages associated with model membranes, such as silicone, to study membrane transport processes (Ley and Bunge, 2007; Millerioux et al., 2009). Skin is a complex heterogeneous membrane and gaining an understanding of the mechanisms of action is often difficult. Knowledge of how drugs and formulation components permeate silicone membranes will also provide insight from the perspectives of release and controlled drug delivery from polymeric systems (Prokopowicz, 2009) and transport across polymers used for a number of applications, e.g. protective clothing, infusion bags, etc. The extent to which drugs and excipients may permeate such materials is also of importance for prediction of long term storage behaviour in such membranes and from an environmental perspective as silicones are used in protective clothing (Rivin et al., 2005).

2. Materials and methods

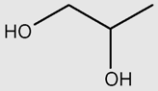
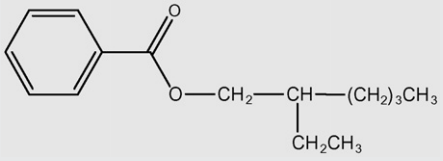
2.1. Materials

Oxybutynin free base was a gift from Acrux, Ltd. (Australia). PG and OSAL were purchased from Sigma (Australia). Phenylboronic acid and 1,2 butanediol, used for GC analysis as derivatisation and internal standard reagents, respectively, were produced by Fluka (Sigma, United Kingdom). Polyethylene glycol 20 oleyl ether (PEG-20-OE), ethanol (99%) and orthophosphoric acid (85%, v/v) were purchased from Sigma (United Kingdom). All HPLC grade solvents were purchased from Fisher (United Kingdom). Silicone membranes with a thickness of 125 μm were used for *in vitro* diffusion studies (Sil-Tec, Technical Products, USA).

2.2. Solubility studies

Saturated solubility values for oxybutynin in PG and OSAL were determined at 32 °C as reported previously (Dias et al., 2007). Using a calibrated micropipette, an aliquot of supernatant (100 μl) was

Table 1
Structure and physicochemical properties of PG and OSAL.

Propylene glycol (PG)	Octyl salicylate (OSAL)
	
MW[a] = 76.1 g/mol Log $K_{oct/wat}$[b] = −0.47 δ[c] = 28.64 MPa$^{1/2}$ Hygroscopic, viscous liquid. Miscible with water, acetone and chloroform. Soluble in ether[a]	MW[a] = 250.3 g/mol Log $K_{oct/wat}$[b] = 5.97 δ[c] = 21.74 MPa$^{1/2}$ Colourless to pale-yellow liquid. Miscible with cosmetic oils, silicone oils. Insoluble in water; freely soluble in absolute ethanol[a]

[a] Compound names, structure, molecular weight (MW), physical state and solubility taken from The Merck Index, 14th Edition, Merck Research Laboratories, 2006.

[b] Octanol:water partition coefficient calculated with Chemdraw® program (Cambridge Soft., UK).

[c] Solubility parameter (δ) estimated using Thermo Chemical Properties Estimation Software: Solubility Parameter Estimation from Fedor's Cohesive Energy (http://www.pirika.com/chem/TCPEE/TCPE.htm). The obtained values were multiplied by 2.0455 to convert from (cal/cm^3)$^{1/2}$ to MPa$^{1/2}$.

Table 2
Solvent uptake by silicone membranes and oxybutynin solubility studies in the respective solvent. Each data point represents the mean ± SD ($n = 3$).

	Oxybutynin solubility (μmol/ml)	Solvent uptake by the membrane	
		Mass uptake (% dry weight)	Molar uptake (μmol/g)
Water	0.6 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
PG	185 ± 8	0.07 ± 0.02	5.3 ± 1.5
OSAL	280 ± 22*	12.8 ± 2.7*	51 ± 11*

* Significantly different from PG ($p < 0.01$).

removed and diluted up to 10 ml with methanol. This solution was further diluted with methanol if necessary and assayed in triplicate using HPLC as described below.

2.3. Solvent uptake

Dry silicone membranes were soaked in the respective solvents and reweighed after 24 h. The solvent taken up by the membrane was calculated using Eq. (1):

$$\%\ \text{uptake} = \frac{(\text{membrane weight after treatment} - \text{dry weight}) \times 100}{\text{dry weight}} \quad (1)$$

2.4. Preparation of formulations

Supersaturated systems were prepared by the solvent evaporation method (Coldman et al., 1969). From the solubility values of oxybutynin in PG and OSAL (Table 2), the amount required to saturate and supersaturate 100 μl of solvent was calculated. This amount was weighed (10 μg precision balance, Mettler AT261, Mettler Toledo, Inc., Switzerland) into a volumetric flask and then 100 μl of respective solvent was added to the volumetric flask and the volume made up, partially, with absolute ethanol. After dissolving the drug by sonication, the solution was left to equilibrate at room temperature for 30 min before completing the volume with ethanol. All solutions were freshly prepared on the day of the permeation studies. Table 3 lists all formulations used in the study. The time taken for the ethanol to evaporate from finite doses applied to silicone samples with a diffusion area of 1 cm^2 was measured at different time intervals to confirm evaporation of ethanol for all formulations.

2.5. Diffusion cell studies

The permeation of oxybutynin and solvent across silicone membranes was investigated at 32 °C using Franz-type diffusion cells, as described previously (Dias et al., 2007). Finite doses of formulations (25 μl/cm^2) were applied across the areas of each piece of membrane using a micropipette. Citrate buffer pH 5.0 with 0.5% (w/v) PEG-20-OE was used as the receptor phase to ensure sink conditions for both drug and solvent throughout the study.

2.6. Analysis

2.6.1. HPLC

The HPLC system consisted of a Hewlett Packard HPLC System series 1050 (HP Scientific, Japan). Data were acquired and analysed using PC/Chrom® software (H&A Scientific, Inc., United States). OSAL and oxybutynin determination was performed using a Waters Symmetryshield® C_{18} column (5 μm particle size, 3.9 mm × 150 mm, Waters Ltd., United Kingdom). A universal Phenomenex® Guard packed with a C_{18} cartridge (Phenomenex, United States) was also used in conjunction with the column. The injection volume was 50 μl. The mobile phase was composed of 30% acetonitrile in water adjusted with orthophosphoric acid to pH 2.5. The flow rate was set to 1 ml/min and the UV detection was performed at 210 nm. The retention time for oxybutynin under these conditions was ~7 min. The mobile phase for elution of OSAL was composed of 90% methanol in water and the wavelength was set at 310 nm. The retention time of OSAL was approximately 8 min. Calibration curves for each assay were constructed using standard solutions at concentrations within the range of 0.003–0.028 μmol/ml. A linear relationship between peak area and concentration was confirmed by the correlation coefficient generated by linear regression (using the least squares method) of the calibration curve. The linearity of each assay was higher than 0.995 and the accuracy ranged from 95 to 105%.

Table 3
Oxybutynin concentration (μmol/μl) in the formulations used in this work. The solvent is expressed in percentage v/v in ethanol.

DS	PG, 25%	OSAL, 25%
1	0.13	0.20
2	0.26	0.39
5	0.65	0.98
7	–	1.37

2.6.2. Gas chromatography

A Chrompack Varian model CP9001 (Chrompack, Netherlands) equipped with a flame ionisation detector (FID) was used for PG quantification. Analyses were performed on a 30 m × 0.32 mm × 1.8 m open column Zebron ZB-624 (Phenomenex, United Kingdom). Helium was used as a carrier gas at a flow rate of 3.5 ml/min. The column was operated according to the following gradient method: initial temperature held at 100 °C for 2 min and then heated to 200 °C at a rate of 20 °C/min, and then stabilised for 2 min (with a total run time of 9 min). The temperature of the injector and detector was 250 °C. The internal standard was 1,2 butanediol in methanol at a concentration of 0.6 μmol/ml. In order to increase the peak detection and the method sensitivity, the internal standard and the PG were derivatised with phenylboronic acid using the protocol described by Porter and Auansakul (1982). Under these conditions, the retention time was 7 and 8 min for the derivatised PG and internal standard, respectively. The method demonstrated linearity of at least 0,99. Standards were prepared with PG concentrations ranging from 0.3 to 6.6 μmol/ml. Precision studies were conducted by performing six repetitive analyses using the concentration extremities of the calibration curve on three different days. The intraday precision for 0.3 and 6.6 μmol/ml samples was 3.9 and 4.0%, respectively, with an accuracy ranging between 95 and 105%.

2.6.3. Statistical analysis and mathematical modelling

Statistical significance was determined using one-way analysis of variance (ANOVA). Post hoc all pair wise multiple comparisons of the means within different groups were performed using the Post hoc Bonferroni test. A probability of $p < 0.05$ was considered statistically significant. All results are presented as mean ± SD, unless otherwise stated. A finite dose model expressed as the Laplace transform (Eq. (2)) was used to analyse the permeation of oxybutynin from the saturated residues produced after application of formulations composed of 25% solvent v/v (OSAL or PG)

$$\overline{Amount} = \frac{AP_1Q_0}{s[V\sqrt{(s/P_2)}\sinh\sqrt{(s/P_2)} + P_1A\cosh\sqrt{(s/P_2)}]} \quad (2)$$

Table 4
Enhancement ratio (ER) and amount of oxybutynin permeated after 35 min (Q_{35}) from saturated and supersaturated spray formulations composed of 25% of PG or 25% OSAL v/v. Each data point represents the mean ± SD ($n = 3$).

DS	Oxybutynin permeation			
	PG		OSAL	
	$Q_{35'}$ (μmol/cm²)	ER	$Q_{35'}$ (μmol/cm²)	ER
1 DS	0.26 ± 0.01	–	0.77 ± 0.054‡	–
2 DS	0.50 ± 0.02*	2.1 ± 0.1	1.37 ± 0.26*,‡	1.8 ± 0.3
5 DS	0.97 ± 0.10**	3.7 ± 0.3	1.41 ± 0.25*,‡	1.8 ± 0.3
7 DS	–	–	1.42 ± 0.17*	1.8 ± 0.2

* Significantly different from 1 DS formulation ($p < 0.05$).
** Significantly different from 1 and 2 DS formulations ($p < 0.05$).
‡ Significantly different from corresponding PG formulation ($p < 0.05$).

where P_1 and P_2, also known as apparent partition and apparent diffusion parameters are defined as follows:

$$P_1 = Kh \tag{3}$$

$$P_2 = \frac{D}{h^2} \tag{4}$$

K and D are the partition and diffusion coefficients, h is the thickness and A is the area of the membrane, V is the volume of donor phase, and Q_0 is the amount applied. Scientist Version 3.0 (Micromath Scientist Software Tool, Inc., USA) was used to fit diffusion equations to experimental data.

3. Results and discussion

3.1. Effect of supersaturation on drug permeation

The uptake and subsequent permeation of both active and solvent is not usually studied and, in the present work, we hypothesised that drug permeation through a membrane will be influenced by the thermodynamic activity of the solvent as well as the active. In order to test this hypothesis, diffusion studies were performed with saturated and supersaturated residues prepared by solvent evaporation, and both drug and solvent permeation through silicone were monitored with an interactive and non-interactive solvent. Using silicone, PG was identified as a non-interactive solvent, as the flux of oxybutynin from saturated PG formulations was statistically the same as from aqueous saturated solutions (data not

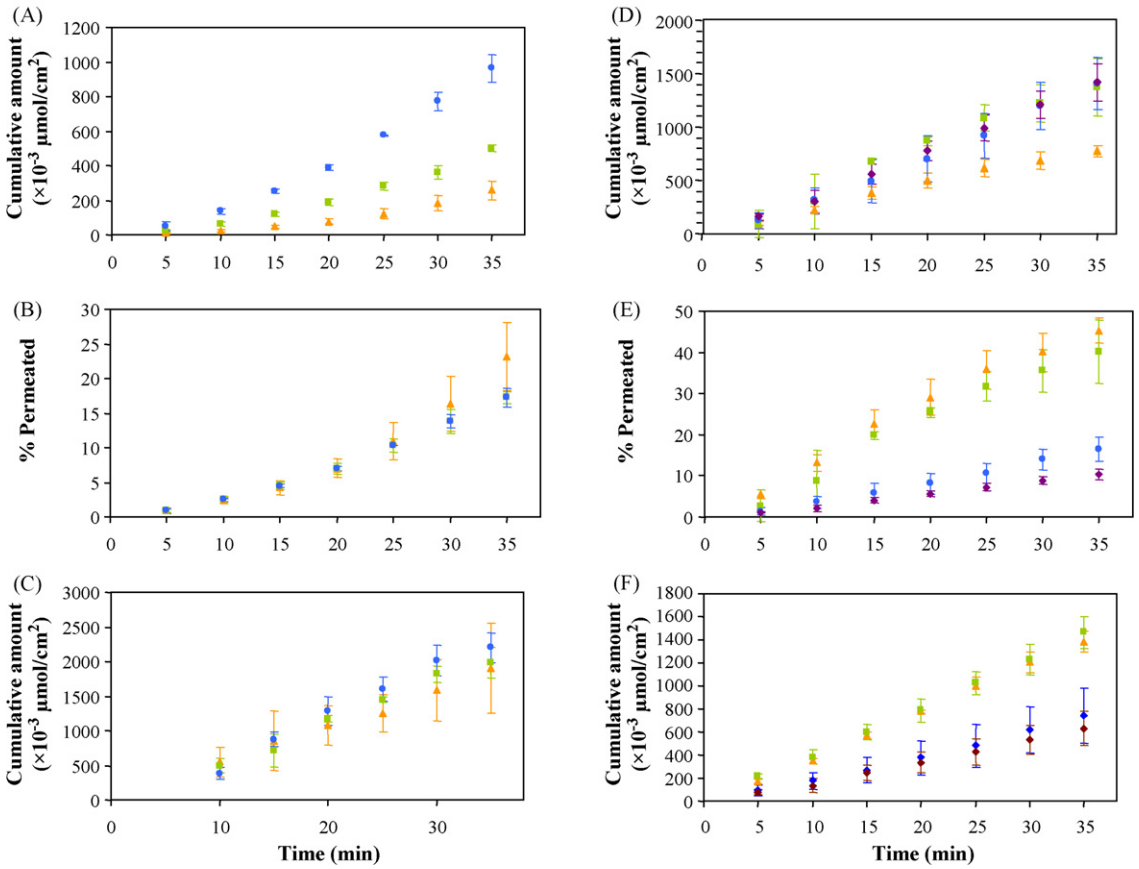


Fig. 2. Cumulative amount of oxybutynin (A), percentage of oxybutynin (B) and PG (C) permeated through silicone membranes from saturated and supersaturated residues prepared with 25% PG and (▲) 1 DS, (■) 2 DS and (●) 5 DS of oxybutynin. Each data point represents the mean ± SD ($n = 3$). Right hand side: Cumulative amount of oxybutynin (D), percentage of oxybutynin (E) and OSAL (F) permeated through silicone membranes from saturated and supersaturated residues prepared with 25% OSAL and (▲) 1 DS, (■) 2 DS, (●) 5 DS and (♦) 7 DS of oxybutynin. Each data point represents the mean ± SD ($n = 3$).

shown). Fig. 2A and B show, respectively, the cumulative amount and the percentage of oxybutynin that permeates through silicone membranes following the application of saturated and supersaturated formulations prepared with 1, 2 and 5 DS, with 25% of PG. The drug permeation increased with the DS of the formulation. The amount permeated after 35 min (Q_{35}) from 1, 2 and 5 DS was 0.26 ± 0.01, 0.50 ± 0.02, and $0.97 \pm 0.10\ \mu mol/cm^2$, respectively, corresponding to an enhancement ratio (ER) of 2.1 ± 0.1 and 3.7 ± 0.3 for 2 and 5 DS formulation, significantly higher than the 1 DS formulation ($p \leq 0.05$) (Table 4) and confirming that the ER was not linearly related to the DS. This observation is in accordance with the literature (Twist and Zatz, 1986). According to the test hypothesis, decreasing PG uptake (as result of a decrease in the PG activity with oxybutynin concentration) will not affect the drug permeation, as the membrane permeability will remain the same. Therefore it was suggested that the low ER observed with the 5 DS formulation results from drug crystallisation either on or in the membrane (although no crystals were evident on the membrane) and not from a decrease in solvent activity.

For the same drug activity, OSAL supersaturated formulations produced higher drug permeation than PG formulations (Fig. 2A and D), confirming that OSAL interacts with the membrane, as the flux of oxybutynin is not independent of the applied solvent (Twist and Zatz, 1986). OSAL has been shown to increase the drug permeation through biological membranes (human, porcine and shed snake skin), but drug permeation enhancement of OSAL through silicone membranes has not been reported before (Morgan et al., 1998a,b,c; Traversa, 2005; Nicolazzo et al., 2005).

Fig. 2D shows the permeation of oxybutynin through silicone membrane after application of saturated and supersaturated formulations prepared with 25% OSAL. As for the PG formulation experiments, drug permeation increases with the DS. However, formulations with 5 and 7 DS show no further improvement in drug permeation compared with the 2 DS formulation. In addition, Fig. 2E represents the percentage of oxybutynin that had permeated through the membrane after 35 min. No differences are seen in the percentage drug permeated between 1 DS and 2 DS formulations suggesting that the 2 DS supersaturated residue is stable. However, the formulations with 5 and 7 DS have lower drug percentages permeated and the same ER (Table 4), which indicates drug crystallisation and/or a decrease in OSAL activity with DS.

In the literature, it has been suggested that the reduced ER observed with supersaturated solutions, results from drug crystallisation because of the high instability of these solutions. However, the drug concentration may indirectly affect its permeation as the solvent activity and consequently the solvent uptake decrease with drug concentration, thus changing the membrane permeability.

The flux of a compound through a membrane depends on both drug and membrane properties. Table 2 shows the solvent uptake by silicone membranes and oxybutynin solubility. OSAL is much more lipophilic than PG (Table 1), as a result the uptake of OSAL by the membrane is higher than for PG, since silicone is also a lipophilic membrane (Cross et al., 2001). In addition, simultaneous changes in the membrane dimensions (swelling and expansion) were noticed with OSAL uptake. As a result, the membrane permeability is expected to be greatly influenced by the solvent uptake.

The diffusion coefficient of oxybutynin across the membrane from 1 DS OSAL formulations, calculated from Eqs. (2)–(4), is significantly greater than that from 1 DS PG formulations, $8.4 \pm 0.8 \times 10^{-6}\ cm^2/min$ and $2.3 \pm 0.7 \times 10^{-6}\ cm^2/min$, respectively ($p \leq 0.01$). These results confirm that the OSAL uptake by the membrane changes the drug diffusivity in silicone membranes to a significant extent.

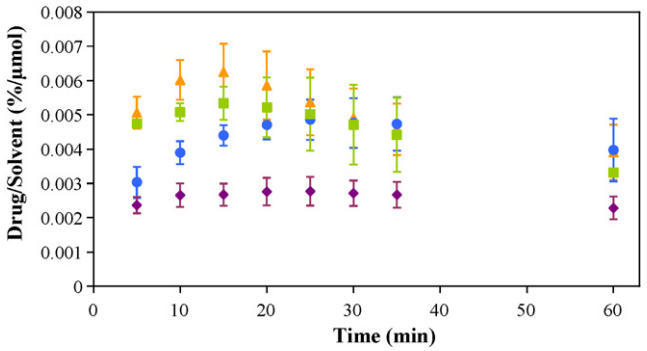


Fig. 3. Relationship between oxybutynin permeated and OSAL permeated from supersaturated residues prepared with 25% OSAL and (▲) 1 DS, (■) 2 DS, (●) 5 DS and (♦) 7 DS of oxybutynin. Each data point represents the mean ± SD ($n = 3$).

3.2. Effect of supersaturation on solvent permeation

OSAL uptake (μmol/g) was significantly higher ($p \leq 0.01$) than PG uptake, as OSAL is more lipophilic than PG, which favours the solvent uptake and hence better permeation of oxybutynin from OSAL across the membrane (Tables 2 and 4). OSAL permeation is lower than PG permeation (Fig. 2C and F) possibly because of the lipophilic nature of OSAL relative to PG and the lower partitioning into the aqueous receptor phase.

The permeation of PG remains the same regardless of the drug DS in the residual phase. It could be argued that the lack of changes in PG permeation with the DS results from drug crystallisation at higher concentrations. However, the oxybutynin permeation increases linearly with DS (Fig. 2A) confirming that the drug concentration in the residual phase is higher than with saturated residues.

Fig. 2F shows the permeation of OSAL through silicone membranes using 1, 2, 5 and 7 DS formulations. Contrary to PG results, the permeation of OSAL is greatly influenced by the drug concentration in the residual phase. Similar OSAL permeation was observed for 1 DS and 2 DS formulations. However, with the 5 DS formulation there is a considerable decrease in solvent permeation, which suggests a reduction in solvent activity with oxybutynin concentration. An additional increase in formulation DS (7 DS) does not result in a decrease in solvent permeation. It is possible that with the 7 DS formulation the drug had crystallised thus resulting in similar solvent thermodynamic activity as the 5 DS formulation.

It was hypothesised that for all supersaturated residues under study, the presence of drug (at different DS) would reduce the solvent activity, thus reducing the solvent permeation. However, as shown in Fig. 2C and F, the behaviour of PG and OSAL in the presence of drug is quite different. It is evident that the OSAL permeation is strongly dependent on drug concentration whereas no differences were seen in PG permeation at different DS. These differences may be related to the drug solubility in the solvent. According to Table 2, the solubility of the oxybutynin in OSAL is 1.5 times higher than the solubility of oxybutynin in PG. Therefore, for the same DS, a greater decrease in OSAL thermodynamic activity is expected, as the mole fraction of the solvent decreases with the greater drug solubility. Similar results and observations were made by Twist and Zatz (1988) for the uptake of a series of alcohols by silicone membranes in the presence of parabens. The authors observed that the alcohol flux decreases with increasing parabens solubility.

Fig. 3 shows the ratio between the percentage drug permeated and the solvent permeation for all OSAL formulations under study. After 20 min, this ratio is the same for saturated and supersaturated solutions with 2 and 5 DS, suggesting that the transport (normalised according to the drug activity) of drug by the solvent is the same for these formulations. This evidence confirms that the decrease

in the oxybutynin permeation with the 5 DS formulation results from a decrease in OSAL uptake and permeation rather than drug crystallisation, assuming that the membrane permeability changes are proportional to the solvent activity/permeation. In addition, the slow decrease in this ratio with time indicates that the drug permeation is also decreasing, possibly caused by the drug and/or solvent depletion, since more than 20% of the drug and solvent had already permeated. Furthermore, formulations with 7 DS show the lowest drug/solvent ratio, indicating that the decrease on drug permeation observed in Fig. 2D is both the result of a decrease on solvent permeation as well as drug crystallisation. Similar solvent permeation observed for formulations prepared with 5 and 7 DS suggests that the solvent thermodynamic activity is also similar.

4. Conclusions

The permeation of oxybutynin from saturated and supersaturated formulations prepared with PG or OSAL, under relevant clinical conditions (i.e., finite dose), was evaluated using silicone membranes. The effect of the solute concentration (i.e. DS) on solvent thermodynamic activity (PG or OSAL) was hypothesised to be a possible reason for the low percentage of drug permeated when using supersaturated formulations. Both solvent and drug permeation were investigated over the time course of the experiments. A decrease in OSAL permeation with 5 DS formulations was observed in comparison with 1 DS or 2 DS formulations, indicating a decrease in solvent activity with drug concentration. In addition, the drug transport from 5 DS formulation was higher than 1 and 2 DS formulations but lower than predicted. Based on both solvent and drug permeation, it was suggested that the low drug permeation observed with 5 DS resulted from a decrease in solvent thermodynamic activity rather than a decrease in solute activity as a result of drug crystallisation. Using PG formulations, the PG permeation remained unaffected with the DS of the formulation, up to 5 DS. The different results obtained with PG and OSAL are because of the differences in the drug solubility between solvents. Oxybutynin is more soluble in OSAL than in PG, therefore for the same DS more drug is required for OSAL formulations, and therefore the effect of DS on the solvent activity is also higher. Future studies will be extended to explore how solvent activity may be affected by drug concentration in skin.

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