International Journal of Pharmaceutics 384 (2010) 67–72

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Oxybutynin permeation in skin: The influence of drug and solvent activity

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ARTICLE INFO

Article history:
Received 20 August 2009
Accepted 22 September 2009
Available online 30 September 2009

Keywords:
Octyl salicylate
Propylene glycol
Oxybutynin
Skin
Permeation
Supersaturation

ABSTRACT

The influence of degree of saturation (DS) of oxybutynin on permeation from octyl salicylate (OSAL) or propylene glycol (PG) vehicles was investigated, *in vitro*, in human skin. The permeation of OSAL and PG was also evaluated and the quantity of drug and solvent in the skin at the end of the diffusion study was measured. For OSAL the permeation of oxybutynin increased linearly with DS of drug for both 25 and 50% OSAL formulations. However, no differences were seen in oxybutynin permeation for formulations with the same DS but with different OSAL amounts, although the drug permeation was always slightly higher for 50% OSAL formulations. There was a decrease in the amount of OSAL extracted from skin with drug concentration (up to 5 DS). There was also a good correlation between the DS calculated from the amount of oxybutynin and OSAL extracted from the skin, and the actual DS of the formulation. In contrast oxbutynin DS did not affect PG permeation and there were no significant differences in oxybutynin permeation for the formulations with different DS. The lack of permeation enhancement for PG formulations appears to be related to PG depletion from the skin. The findings emphasise the importance of maintaining the drug in solution in order to achieve effective permeation from dermal and transdermal formulations.

1. Introduction

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 its solubility limit and as a consequence of its higher thermodynamic activity, the flux should increase proportionally. The manipulation of drug thermodynamic activity, via supersaturation, to enhance drug permeation has been reported by a number of workers but few reports have investigated the influence of solvent/vehicle thermodynamic activity on drug permeation. This is surprising as the solvent/vehicle has been shown to dictate the extent and residence time of drug permeation *in vitro* (Francoeur et al., 1990; Trottet et al., 2004).

We have recently investigated the effect of the degree of drug saturation (DS) for the model drug, oxybutynin, on solvent and drug permeation in silicone membrane (Santos et al., 2009). Supersaturated residual phases of oxybutynin in octyl salicylate (OSAL) or propylene glycol (PG) were prepared by the method of solvent evaporation (Coldman et al., 1969). A decrease in OSAL permeation with the 5 DS formulation was observed in comparison with the 1 DS and 2 DS formulations, indicating a decrease in solvent activity with drug concentration. In addition, the drug transport from the 5 DS formulation was higher than from the 1 and 2 DS formulations but lower than predicted. Based on both solvent and drug permeation, this 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. For PG formulations, the PG permeation remained unaffected with increasing DS of the formulation, up to 5 DS.

In this paper we have extended the previous studies with OSAL and PG in silicone to human skin. The objectives were, firstly, to investigate the effect of drug concentration on OSAL thermodynamic activity, *in vitro*, in human skin and secondly, to compare the results for OSAL and PG with the data from the previous silicone studies. In order to achieve this, the permeation of OSAL in the absence and presence of drug was evaluated. Additionally, the quantity of drug and solvent (OSAL or PG) in the skin at the end of the diffusion study was evaluated using mass balance studies.

2. Materials and methods

2.1. Materials

Oxybutynin free base was a gift from Acrux, Ltd (Australia). OSAL and PG 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,

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doi:10.1016/j.ijpharm.2009.09.043

Table 1
Oxybutynin concentrations (μmol/μl) in the 25% PG and OSAL formulations.

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

United Kingdom). Polyethylene glycol 20 oleyl ether (PEG-20-OE) and orthophosphoric acid (85%, v/v) were purchased from Sigma (United Kingdom). All HPLC grade solvents were purchased from Fisher (United Kingdom).

2.2. Methods

2.2.1. 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 (Santos et al., 2009) 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 1 lists all formulations used in the study.

2.2.2. Diffusion studies

Female abdominal tissue obtained from a single donor, with appropriate patient consent and institutional ethical approval, was stored at −20 °C until required. The permeation of oxybutynin, OSAL and PG across heat separated epidermis (Kligman and Christophers, 1963) was investigated using stainless steel flow-through diffusion cells (Hamilton Engineering, Australia) with an area available for drug diffusion of 1 cm^2. The receptor phase selected was 0.5% w/v PEG-20-OE in PBS pH 7.4 as no changes in the membrane permeability were observed compared with the buffer solution (PBS, pH 7.4) without surfactant (data not shown). The skin was mounted in the diffusion cells and equilibrated with the receptor solution 1 h prior to starting the study. To ensure sink conditions were maintained during the diffusion study, the receptor solution was pumped through the receptor compartment at a flow rate of 1 ml/h with a peristaltic pump (Watson Marlow, Stauff Corporation, Australia). At this flow rate, the receptor solution residing within the receptor compartment was replaced approximately 20 times/h (Traversa, 2005). A finite dose (3.6 μl/cm^2) of formulation was applied to the skin surface using a micropipette. At selected intervals, 0.2 ml samples were collected from the receptor compartment (Retriever II Fraction collector, Foss Pacific, Australia). Each experiment was conducted a minimum of four times. Prior to the start of the diffusion experiments, skin integrity was measured by impedance (Woo et al., 1992).

2.2.3. Mass balance studies

At the end of the permeation studies, the SC surface still mounted in the Franz cells was washed six times with 1 ml of an aqueous solution of 6% PEG-20-OE w/v. After washing (6× 1 ml), the membrane was blotted with filter paper. The membrane was then carefully stretched and the surface was swabbed with a cotton bud (dipped in the washing solution) in the parallel and perpendicular directions, in order to remove the excess liquid on the skin surface. The washing fractions were collected into the same vial, together with the cotton bud and the filter paper, and analysed by HPLC, after dilution with methanol. The membranes were then weighed, placed in an Eppendorf® vial and the drug was extracted twice with ethanol (2× 1 ml). Following application of 3.6 μl/cm^2 of a formulation of 50% OSAL v/v the OSAL recovery was 91 ± 4%. An aqueous 6% PEG-20-OE solution was chosen because of its solubilising capacity for drug (0.01 mmol/ml) and solvent (Walters et al., 1997).

2.2.4. HPLC and GC analysis

OSAL and oxybutynin were analysed by HPLC and PG was analysed by GC using the instrumentation and methodology previously reported (Santos et al., 2009).

2.2.5. Data analysis

Linear regression was used to assess the interval of skin permeation data (μg/cm^2) between 16 and 24 h and the slope estimated, giving a mean flux ($\bar{J}_{16-24\,h}$). Drug permeation from saturated residues was analysed using a finite dose model expressed as a Laplace transform as described previously (Santos et al., 2009). This allows the determination of P_1 and P_2, also known as the apparent partition and apparent diffusion parameters which are defined as follows:

$$P_1 = Kh \tag{1}$$

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

The lag time t_{lag} and permeability coefficient k_p are further defined as

$$t_{lag} = \frac{1}{6P_2} \tag{3}$$

and

$$k_p = P_1 \times P_2 \tag{4}$$

Statistical significance was determined using one-way analysis of variance (ANOVA). Post hoc all pair wise multiple comparison of the means within different groups was performed using the Post hoc Bonferroni test. A probability of $p < 0.05$ was considered statistically significant. All results are presented as the mean ± SD, unless otherwise stated.

3. Results and discussion

3.1. Permeation of oxybutynin and OSAL from saturated and supersaturated residues

Permeation of oxybutynin and OSAL after the application of finite dose formulations with 25 or 50% OSAL v/v and with different DS were studied over 24 h. At the end of the experiment the skin surface was washed and the drug and solvent inside the skin was quantified, after extraction with ethanol.

3.1.1. Oxybutynin permeation: effect of drug and OSAL concentration

Fig. 1 shows the effect of DS and OSAL dose on the mean flux ($\bar{J}_{16-24\,h}$) of oxybutynin through human skin, following application of 3.6 μl/cm^2 of the formulations prepared with 25 and 50% OSAL at different DS. Table 2 gives the permeation enhancement ratio (ER_{per}) for each formulation which is the ratio between the mean flux of the formulation under study and the mean flux from the reference (saturated) formulation. A good correlation was found between the $\bar{J}_{16-24\,h}$ and the DS ($r^2 > 0.994$) for both formulations, but the ER_{per} obtained was slightly lower than predicted for the 25% OSAL formulation.

Table 2
Oxybutynin amount permeated ($Q_{24\,h}$), extracted from the skin, recovered from washing and total recovery after 24 h diffusion studies (n = 4–9).

Oxybutynin studies	Permeation ($Q_{24\,h}$)		Extraction		Washing, %	Total recovery, %
	μmol/cm²	ER_{per}	μmol/cm²	ER_{ext}		
25% OSAL						
1 DS	0.019 ± 0.002	–	0.016 ± 0.004	–	76 ± 11	89 ± 11
2 DS	0.028 ± 0.007*	1.5	0.038 ± 0.008*	2.4	87 ± 9	100 ± 9
5 DS	0.082 ± 0.012*,‡	4.3‡	0.083 ± 0.027*,‡	5.3‡	84 ± 7	98 ± 6
7 DS	0.042 ± 0.003*,‡,†	2.2†	0.032 ± 0.013†	2.1†	79 ± 22	86 ± 27
50% OSAL						
1 DS	0.026 ± 0.009	–	0.023 ± 0.005	–	92 ± 13	102 ± 13
2 DS	0.050 ± 0.012*	1.9	0.061 ± 0.006*	2.6	88 ± 15	99 ± 14
5 DS	0.093 ± 0.021*,‡	3.5‡	0.111 ± 0.030*,‡	4.7‡	92 ± 10	96 ± 9

* Significantly different from 1 DS ($p < 0.05$).
† Signficantly different from 5 DS ($p < 0.05$).
‡ Signficantly different from 2 DS ($p < 0.05$).

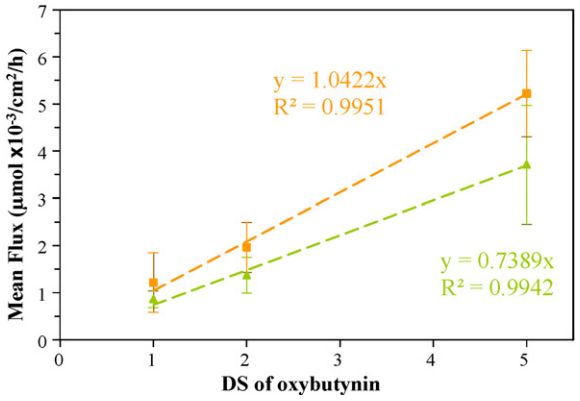

Fig. 1. Correlation between the mean flux of oxybutynin and the DS of the formulation, following application of 3.6 μl/cm² ( ) 25% and ( ) 50% OSAL v/v formulations. Each data point represents the mean ± SD (n = 4–9). (For interpretation of the references to color in this artwork, the reader is referred to the web version of the article.)

The amount of oxybutynin delivered across the skin at 24 h ($Q_{24\,h}$) and the amount extracted from the skin at 24 h is also shown in Table 2. These data are plotted in Fig. 2. There is an excellent correlation between the amounts permeating and the amount extracted from the skin. For 7 DS (25% OSAL) less oxybutynin enters the skin and permeates through it indicating that as soon as the ethanol evaporates it leaves a residual phase that is unstable and the drug is unavailable to permeate the skin, possibly because of crystallisation. (It was not possible to formulate 7 DS with 50% OSAL because of the unstable nature of the system and the rapid crystallisation of drug.) It is effectively as efficient as the 2 DS formulation. In general the amounts permeated and extracted from the 50% OSAL are higher than the 25% OSAL at any given DS. The largest amount of oxybutynin was found in the wash at the end of the experiment (>86%) underlining the problems of transdermal delivery even from formulations in which the activity state of the drug is high.

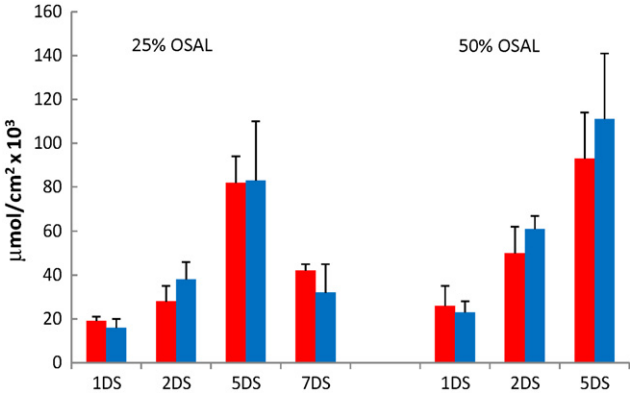

Fig. 2. Amount of oxybutynin delivered across the skin after 24 h – Q_{24} ( ) and extracted amounts ( ) of oxybutynin from 25% OSAL (left) and 50% OSAL (right) at different degrees of saturation. (For interpretation of the references to color in this artwork, the reader is referred to the web version of the article.)

Permeation from the saturated residue with 1 DS was further analysed using a finite dose diffusion model and the values of the permeation parameters (P_1, P_2, t_{lag}, $\bar{J}_{16-24\,h}$ and k_p) are listed in Table 3. No statistical differences ($p < 0.05$) were detected between the different OSAL concentrations, although the P_1 and thus k_p values are slightly higher with the 50% OSAL formulation.

After 24 h, the percentage of oxybutynin permeated with 25% OSAL (v/v) formulations prepared with 1, 2 and 5 DS was 7.6 ± 0.7, 5.7 ± 1.4 and 6.5 ± 0.9%, respectively. The percentage drug permeated for 50% OSAL formulations was even lower, between 5.2 ± 1.8% (1 DS), 4.9 ± 1.2% (2 DS) and 3.7 ± 0.8% (5 DS), confirming that increasing the OSAL volume (50% v/v) did not further improve the efficiency of drug permeation.

3.1.2. OSAL permeation: effect of drug and OSAL concentration

Fig. 3 shows the permeation of OSAL from formulations prepared with and without oxybutynin at different DS from 25 and 50% OSAL formulations. There are no differences in the OSAL permeation with increasing drug concentration in contrast to the results obtained with silicone as a model membrane (Santos et al., 2009). This may reflect the additional hydrophilic barrier posed by the viable epidermis. OSAL is a highly lipophilic enhancer with a log $K_{oct/wat}$ = 5.77 (Santos et al., 2009) for that reason the hydrophilic nature of the viable epidermis is likely to contribute significant resistance to its permeation across the skin. Therefore, significant amounts of OSAL are not expected to partition readily out of the SC. ATR-FTIR and tape stripping studies have previously

Table 3
Skin permeation parameters of oxybutynin: effect of OSAL concentration. P_1, P_2 and k_p were determined by fitting a finite dose model to the drug permeation profile from saturated spray formulations composed of 25 or 50% OSAL v/v. Each value represents the mean ± SD (n = 4).

Oxybutynin	OSAL (v/v)	
	25%	50%
Permeation parameters		
P_1 (×10⁻⁵ cm)	6.6 ± 1.8	10.0 ± 5.6
P_2 (h⁻¹)	0.04 ± 0.01	0.04 ± 0.02
t_{lag} (h)	4.3 ± 1.8	5.1 ± 2.3
$\bar{J}_{16-24\,h}$ (μmol ×10⁻³/cm²/h)	0.8 ± 0.3	1.1 ± 0.6
k_p (×10⁻⁶ cm/h)	2.5 ± 1.0	3.6 ± 1.2

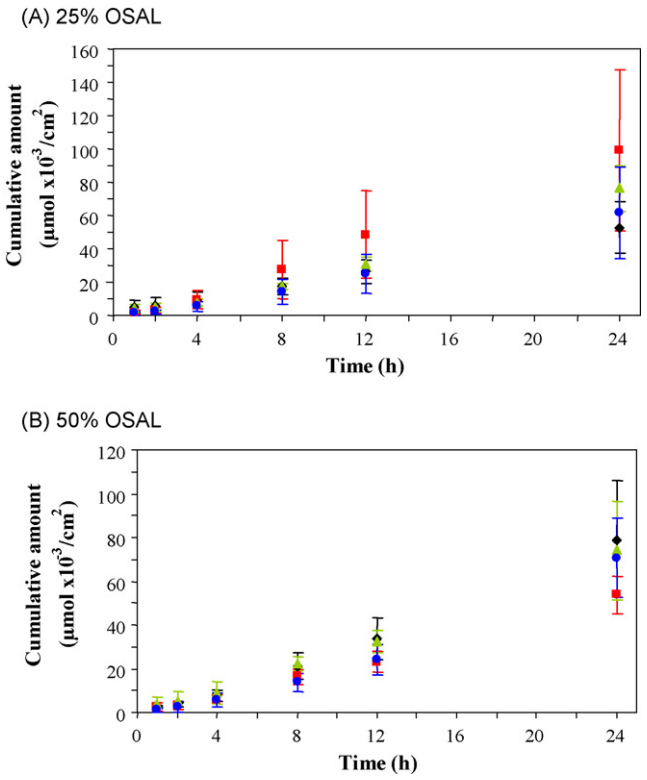

Fig. 3. (A) Permeation of OSAL across skin after application of 3.6 μl/cm² formulations composed of 25% OSAL (●) without drug or with (■) 1 DS, (▲) 2 DS and (♦) 5 DS of oxybutynin. Each data point represents the mean ± SD (n = 4–5). (B) Permeation of OSAL following application of 3.6 μl/cm² of 50% OSAL (●) without drug or with (■) 1 DS, (▲) 2 DS and (♦) 5 DS of oxybutynin. Each data point represents the mean ± SD (n = 4–5). (For interpretation of the references to color in this artwork, the reader is referred to the web version of the article.)

confirmed that OSAL accumulates in the lower regions of the SC (Traversa, 2005).

The permeation of OSAL across the skin after 24 h following application of 3.6 μl/cm² of formulations composed of 25 or 50% of OSAL (without drug) was $56 \pm 16 \times 10^3$ and $76 \pm 24 \times 10^3$ nmol/cm², respectively (Table 4, ANOVA, $p < 0.05$). It is interesting to note that the total recovery of the OSAL was rather low which may reflect evaporation of this solvent to the atmosphere as previously suggested by Traversa (2005). The amount from the wash suggests that there is an excess of material on the surface and therefore the activity state of the OSAL should be the same.

The permeation of OSAL after administration of finite doses of formulations without drug was also analysed to separate partition and diffusion processes. The data are presented in Table 5. No statistical differences were seen in the permeability parameters (P_1, P_2, $\bar{J}_{16-24\,h}$, k_p and t_{lag}) with an increase in the quantity of OSAL applied (ANOVA, $p > 0.05$).

Table 5
Skin permeation parameters of OSAL: effect of OSAL concentration. P_1, P_2 and k_p were determined by fitting a finite dose model to the OSAL permeation profile from spray formulations composed of 25 or 50% OSAL v/v, without drug. Each value represents the mean ± SD (n = 4–5).

OSAL	OSAL v/v	
	25%	50%
Permeation parameters		
P_1 ($\times 10^{-6}$ cm)	10.3 ± 3.3	14.2 ± 5.4
P_2 (h^{-1})	0.06 ± 0.01	0.06 ± 0.02
t_{lag} (h)	2.6 ± 0.2	2.8 ± 0.7
$\bar{J}_{16-24\,h}$ (μmol $\times 10^{-3}$/cm²/h)	2.8 ± 0.8	3.2 ± 0.8
k_p ($\times 10^{-7}$ cm/h)	6.6 ± 2.0	8.1 ± 1.9

Table 4 shows that there is a decreasing trend in the permeation of OSAL with increased DS of oxybutynin (25%) and little effect for the 50% formulation. There was a more marked effect when the same experiments were conducted on silicone membranes (Santos et al., 2009).

The results from finite dose diffusion studies confirm that the permeation of OSAL across human skin is very low. This also contrasts with the silicone experiments in which permeation was much faster. According to the present study, the mean flux of OSAL across heat separated epidermis is ~3 nmol/h/cm², which is in agreement with previous studies (Walters et al., 1997; Jiang et al., 1999).

3.2. Mass balance studies

Measurements of both drug and solvent were performed in receptor phase, membrane and donor compartments after 24 h diffusion.

3.2.1. Oxybutynin

Table 2 shows the amount of oxybutynin extracted from the skin per area of exposure (μmol/cm²), post diffusion studies. Differences were observed in the amount of drug extracted with different DS (ANOVA, $p < 0.001$) from formulations prepared with the same solvent dose. For each formulation, the enhancement ratio of the drug extracted from the skin (ER_{ext}) may be obtained as the ratio between the mean amount extracted for the formulation under study and the mean amount extracted from the reference (saturated) formulation. For the 2 DS and 5 DS formulations, the ER_{ext} was close to the DS of the formulation, but not in agreement with the enhancement ratio ER_{per} observed from the permeation studies In the case of 7 DS there was no correlation with ER_{ext} and DS because of the instability of the formulation and premature crystallisation.

Table 4
OSAL amount permeated ($Q_{24\,h}$), extracted from the skin, recovered from washing and total OSAL recovery after 24 h diffusion studies (n = 4–9).

OSAL studies	Permeation ($Q_{24\,h}$), μmol/cm²	Extraction, μmol/cm²	Washing, %	Total recovery, %
25% OSAL				
No drug	0.056 ± 0.016	0.416 ± 0.136	50 ± 25	61 ± 21
1 DS	0.100 ± 0.048	0.392 ± 0.184	31 ± 2	46 ± 3
2 DS	0.076 ± 0.016	0.368 ± 0.136	32 ± 8	46 ± 7
5 DS	0.064 ± 0.028	0.248 ± 0.080*	40 ± 9	50 ± 3
7 DS	0.068 ± 0.004	0.344 ± 0.084	45 ± 17	55 ± 18
50% OSAL				
No drug	0.076 ± 0.024	0.523 ± 0.152	42 ± 16	50 ± 17
1 DS	0.052 ± 0.008	0.519 ± 0.196	40 ± 14	53 ± 19
2 DS	0.076 ± 0.024	0.427 ± 0.108	41 ± 21	48 ± 18
5 DS	0.072 ± 0.020	0.332 ± 0.096**	42 ± 13	47 ± 6

*, ** Significantly different from formulations with no drug ($p < 0.05$).

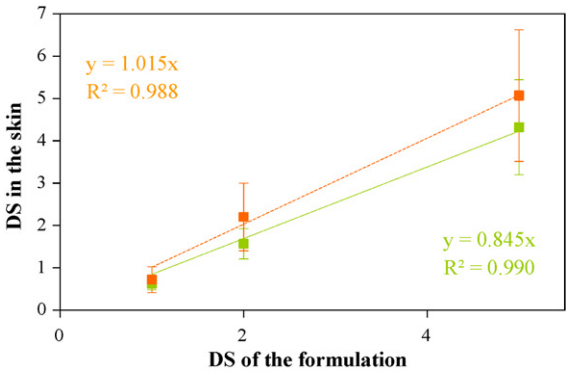

Fig. 4. Correlation between the DS of the formulation and the experimental DS in the skin 24 h after application of 3.6 μl/cm^2 of formulation for (■) 25% and (■) 50% OSAL formulations. (For interpretation of the references to color in this artwork, the reader is referred to the web version of the article.)

Based on these findings, it was hypothesised that the decrease in the oxybutynin permeation ER_{per} (Table 2) resulted from a decrease in the solvent activity and a decrease in solvent uptake by the membrane, as the ER_{ext} is in agreement with the DS of the formulation. In addition, these results suggest that the drug is in a stable and supersaturated state in the skin, when supersaturated formulations up to 5 DS are applied.

Table 2 also shows the amount of drug recovered from the residual phase on the skin. As expected, the drug recovery increases with the concentration applied. Drug recovery percentages from the washing vary between 79 and 92%, which reflects the poor permeation achieved by these formulations, even when a high dose of solvent is used. Finally, the total values of oxybutynin recovered for all formulations are very high (ranging from 89 to 102%), confirming the efficacy of the mass balance studies.

3.2.2. OSAL

Table 4 lists the amounts of OSAL that had permeated after 24 h. The amount of OSAL recovered inside and on the skin as well as the total amount of OSAL recovered following the application of 3.6 μl/cm^2 of formulation (25 and 50% OSAL v/v) with or without drug at different DS are also reported. No differences were seen in the OSAL permeated or extracted with the dose of OSAL (ANOVA, $p > 0.05$).

The total recovery of OSAL was less than 60% of the total dose applied. This loss is in line with previous findings (Treffel and Gabard, 1996; Walters et al., 1997; Traversa, 2005). The OSAL recovery after the application of 2.5 mg/cm^2 of an emulsion gel or petroleum jelly with 3% OSAL concentration to human skin *in vitro*, was 68 ± 8 and 54 ± 1% of the applied OSAL dose, respectively, after a 6 h exposure time (Treffel and Gabard, 1996). Under infinite (100 μl/cm^2) and finite dose (5 μl/cm^2) conditions, the total recovery of OSAL (applied in a hydroalcoholic vehicle with 5% w/w OSAL) was ~83 and ~70% after 48 h, respectively (Walters et al., 1997). More recently, the application of 5 μl/cm^2 of an ethanolic solution of 5% OSAL resulted in net losses varying from 19 to 58% of the total dose applied, after 16 h (Traversa, 2005). Protein binding, metabolism, and loss of the product applied during washing and OSAL evaporation to the atmosphere were discussed as possible reasons for the low recovery.

3.2.3. Correlation between amount of OSAL and oxybutynin extracted

Knowing the amount of drug and solvent extracted from the skin (Tables 2 and 4) it is possible to determine the actual drug DS in the skin. Fig. 4 shows the correlation between the DS calculated from the amount of drug and solvent extracted from the skin and the DS of the formulation. There is a very good correlation ($r^2 = 0.99$) between both up to the 5 DS, which is in agreement with the extraction ER_{ext} results reported in Table 2. This suggests that the main determinant of the DS of the drug in the skin is the relative amounts of drug and solvent in the skin.

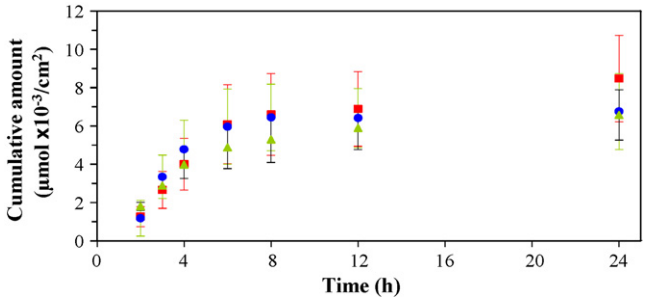

Fig. 5. Permeation of oxybutynin through heat separated human epidermis from the application of 3.6 μl/cm^2 of PG formulations (25% PG) with (■) 1 DS, (●) 2 DS, and (▲) 5 DS. Each data point represents the mean ± SD (n = 4–5). (For interpretation of the references to color in this artwork, the reader is referred to the web version of the article.)

However, when higher concentrations (7 DS, 25% OSAL formulations) were used, the experimental drug DS measured in the skin is only 1.7 ± 0.3, which is lower than for the 5 DS formulations. In addition, the oxybutynin permeation from 7 DS was lower than that from a 5 DS formulation. These results suggest that the chemical potential of oxybutynin in the skin for the 7 DS formulation decreased because of drug crystallisation in the residual phase. As a result the amount of drug extracted from the skin decreased and is similar to the amount extracted from the 2 DS formulation.

3.3. Permeation of oxybutynin and PG from supersaturated residues

Fig. 5 shows the oxybutynin permeation following the application of 25% PG formulations with 1, 2 and 5 DS. No significant differences were found in the amount permeated between the different DS, indicating that permeation enhancement is not achieved using supersaturated PG formulations. Furthermore, the permeation of oxybutynin follows the same profile as the PG (Fig. 6) and it decreases when PG flux ceases, i.e., after 8–12 h.

The effect of the oxybutynin concentration on PG permeation through skin was also investigated following application of PG formulations at different DS. Fig. 6 shows the cumulative amount of PG permeation through human skin *in vitro*, after the application of 3.6 μl/cm^2 of the formulations. The drug concentration in the formulation does not affect PG permeation. In addition, the amount of

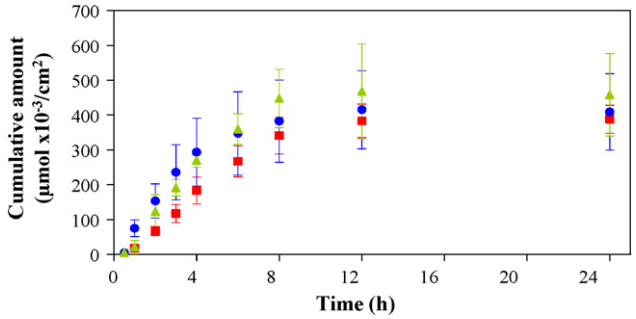

Fig. 6. Permeation of PG through heat separated human epidermis after application of finite doses of 3.6 μl/cm^2 of PG formulations (25% PG) with (■) 1 DS, (▲) 2 DS, and (●) 5 DS of oxybutynin. Each data point represents the mean ± SD (n = 5). (For interpretation of the references to color in this artwork, the reader is referred to the web version of the article.)

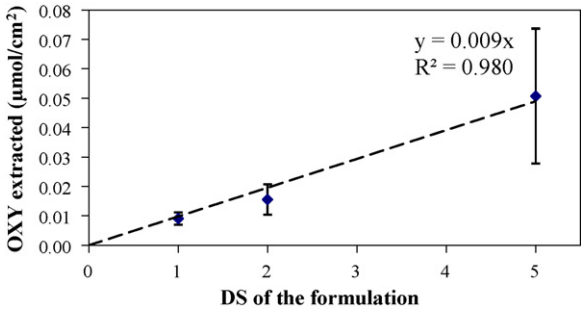

Fig. 7. Correlation between the amount of oxybutynin extracted from the skin and the DS of the formulation applied (25% PG v/v). Each data point represents the mean ± SD (n = 4–5).

PG permeating across the skin decreases after 6–8 h and stops completely after 12 h of diffusion. The total PG permeated after 24 h was approximately 300 μg/cm^2, which represents 30% of the total solvent applied. Finally, no PG was recovered from the washes and extractions after the 24 h period, suggesting that the PG was probably lost by solvent evaporation. This will be evaluated in future studies.

Based on these findings, it was concluded that the lack of oxybutynin permeation enhancement with increasing DS from PG formulations is caused by the rapid depletion of the solvent from the skin. In the literature, PG was also found to permeate the skin together with metronidazole (Wotton et al., 1985). Moreover, the permeation of metronidazole only occurred when the drug was dissolved in the vehicle and stopped after PG depleted from the skin. Trottet et al. (2004) also demonstrated the significance of PG in the permeation of loperamide.

Fig. 7 shows the amount of drug recovered from the skin after the permeation studies. Surprisingly, the drug extracted from the skin increased proportionally with the DS of the formulation, which is not in agreement with the lack of drug permeation enhancement with DS. These findings suggest that following an initial period of high drug uptake, which is proportional to the DS of the drug in residual phase, the drug in the skin may start to crystallise as a result of solvent depletion. Consequently, the drug permeation decreases and almost stops, as the drug is no longer in solution.

4. Conclusions

Previous work in silicone membranes confirmed that there was a decrease in OSAL permeation with 5 DS formulations compared with 1 DS or 2 DS formulations. 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 in silicone remained unaffected with the DS of the formulation, up to 5 DS. The present work sought to investigate if the solute concentration (i.e. DS) had similar effects on solvent thermodynamic activity (PG or OSAL) and drug transport in skin.

For OSAL formulations, an enhancement in drug permeation through skin was observed with increasing DS. Furthermore, the permeation of OSAL remained unaffected by the DS of the formulation. However, a decrease in the amount of OSAL extracted from the skin with increasing DS was observed suggesting that the thermodynamic activity of OSAL in the residual phase decreased with drug concentration. Using mass balance studies, the DS of the drug in the solvent extracted from the skin was similar to the DS of the formulation, up to 5 DS. The low drug permeation ER observed with the 5 DS formulation is related to the decrease in OSAL uptake (solvent activity) as a result of the high drug concentration in the residual phase. This conclusion was further confirmed by increasing the drug concentration (7 DS), which increased the OSAL uptake in the membrane as a result of a decrease in drug activity in the residual phase (drug crystallisation). These data also suggest that for OSAL formulations, the decrease in the percentage drug permeation could be a result of the decrease in both drug and solvent activity with DS.

For PG formulations, drug permeation through the skin stopped at the same time as the exhaustion of PG from the skin, indicating that the presence of drug in solution is critical for drug permeation. The results for both solvents underline the importance of the presence of solvent in order to maintain the drug in a supersaturated state in the skin.

Acknowledgements

We gratefully acknowledge Acrux Ltd. Australia who provided the funding for this work.

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