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An In-vitro Study of the Effect of Hydrocolloid Patch Occlusion on the Penetration of Triamcinolone Acetonide through Skin in Man

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Abstract

The aim of this study was to evaluate the effect of occlusion using hydrocolloid-containing patches on in-vitro triamcinolone acetonide (TACA) penetration of the epidermis while monitoring the uptake of water by the patches as a result of transepidermal water loss.

The hydrocolloid patches were a laminate of a pressure-sensitive hydrophobic adhesive (containing a dispersion of 39% of either pectin or carmellose sodium) and a polyethylene film. The diffusion of a representative corticosteroid (TACA) through isolated epidermal sheet was shown to depend on the site from which the skin was removed. The two patch-types exhibited markedly different hydration rates when applied to the membranes. For example, after 96 h the carmellose sodium patch showed ten times the weight increase of the pectin patch. Epidermal diffusion rates were, however, similar, both showing a 3-4-fold enhancement over unoccluded conditions.

The increase in TACA diffusion with the patches can be explained by the increase in skin hydration that occurs during occlusion. Despite the large differences in transepidermal water transfer through the epidermal membranes with the two types of hydrocolloid patch, however, this level of stratum corneum hydration was apparently similar. As the rate of diffusion was also independent of hydrocolloid patch component, it seems possible that the hydrophobic component of the patch matrix may also influence the level of skin hydration and consequent drug diffusion.

The state of hydration of the stratum corneum is known to influence the permeability of the skin to most topically applied substances and consequently it is believed that there is a positive relationship between the extent of hydration of the stratum corneum and the percutaneous absorption rate of both lipophilic and hydrophilic compounds (Boddé et al 1990). Vehicles that promote the hydration of the stratum corneum act by reducing the normal diffusion of water vapour from the skin, or transepidermal water loss (TEWL), resulting in retention of water within this horny layer (Sarkany & Hadgraft 1969) and are termed occlusive vehicles. Such vehicles include many types of impermeable and semipermeable covering (Barry et al 1984) and various lipophilic dosage forms (Roberts & Walker 1993). Occlusion itself is defined as the complete impairment of passive TEWL at the application site resulting in hydration of the stratum corneum (Bucks et al 1989). TEWL has frequently been used to assess the barrier function of skin in in-vitro and in-vivo studies (Abrams et al 1993; Bucks et al 1993; Nangia et al 1993).

Hydrocolloid-containing patches were originally developed for stoma care and the treatment of exuding wounds (Hollingsbee & Timmins 1990); more recently they have been employed in dermatological therapy. They comprise a powder mixture of hydrocolloids dispersed in a hydrophobic adhesive matrix; the adhesive matrix provides the primary structure of the patch, enabling adhesion to the skin, whereas the hydrocolloids absorb water and water vapour from intact skin as well as exudate from wound cavities. Although these patches are unmedicated they can be used in conjunction with topically applied drugs. The occlusive effect of Actiderm, for example, has been studied on the percutaneous penetration of a number of drugs including corticosteroids (Queen et al 1988; David & Lowe 1989; Juhlin 1989; Martin & Marriott 1989; Wilkinson & Ohayon 1990; Hollingsbee et al 1991). It was found to be effective in controlling and sustaining the localized delivery of the steroid into the skin and enhancing the healing of psoriatic plaques. Occlusion has been shown to enhance the percutaneous absorption of a variety of topically applied drugs in-vivo, including nicotinates (Ryatt et al 1988), local analgesics (Villada et al 1990) and corticosteroids (Lavker et al 1992; Volden 1992), and triamcinolone acetonide (TACA), which is used in the topical and systematic treatment of a variety of inflammatory conditions (Groel 1968; Burdick 1974; Barry & Woodford 1975). Although occlusion enhances the pharmacological response produced by these drugs in-vivo, little work has been performed to quantify the extent by which occlusion enhances percutaneous penetration in-vitro. Kadir et al (1990) investigated the effect of occlusion with Actiderm on the penetration of topically applied TACA in-vitro, but did not correlate the enhanced drug diffusion with the water-vapour-uptake characteristics of the applied covering.

The aim of this study was to evaluate the effect of occlusion, using hydrocolloid-containing patches, on TACA penetration of the epidermis in-vitro while monitoring the uptake of water by the patches as a result of TEWL.

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Materials and Methods

Materials

TACA was donated by E. R. Squibb and Son, Moreton, UK (now Bristol-Myers Squibb); [1,2,4(n)-^{3}H] TACA (60·8 mCi mg^{-1}) was supplied by Amersham International, Bucks, UK. Sorenson's buffer (pH 7·4) was prepared from sodium dihydrogen phosphate (2·1 mg mL^{-1}), disodium hydrogen phosphate (19·1 mg mL^{-1}) and sodium chloride (4·4 mg mL^{-1}) all of which were AnalaR grade from BDH, Poole, Dorset, UK. All solvents were HPLC grade from Aldrich Chemical Co., Dorset, UK.

For the patch preparation, the adhesive premix was supplied by ConvaTec, Deeside, Clwyd, UK and comprised a mixture of hydrophobic synthetic and semisynthetic elastomers, tackifying resins and mineral oil. Propylene glycol was purchased from Eastman Kodak, Rochester, NY, USA. The Actiderm dermatological patches were supplied by ConvaTec, Princeton, NJ, USA; carmellose sodium (71/35XF) was obtained from Aqualon Co., Wilmington, USA; and Pectin (HM) was from A/S Kobenhavns Pektinfabrik, Lille Kensved, Denmark.

Skin preparation

Fresh, surgically excised samples of skin were obtained from abdominoplasties and mammoplasties. The age of donors, all female, ranged from 20–60 years. Skin was stored at 4°C for a maximum of 24 h after surgical excision before removal of the epidermal membranes.

The skin sample with the fat layer removed was immersed in distilled water at 60°C for 30 s, removed and placed dermal-side-down on a cork dissection board. The epidermis was gently teased off the dermis, using forceps, and floated over cold distilled water. The epidermal sheet was then collected on to aluminium foil and excess water allowed to drain and stored at −20°C until required (Kligman & Christophers 1963).

Patch manufacture

Hydrocolloid adhesive mixes were prepared by addition of the hydrocolloid powders (either pectin or carmellose sodium to the heated adhesive premix (comprising the hydrophobic components) in a Sigma blade mixer (S330C, Brabender OHG, Germany) to produce a homogeneous dispersion. After cooling the hydrocolloid premix was extruded (measuring extruder 10DW, Brabender) using a ribbon die adjusted to give an adhesive sheet of uniform thickness (0·425 mm). This was then laminated between a sheet of polyethylene film and a silicone release paper (which was removed before use).

Measurement of patch hydration controlled by epidermal membranes

In-vitro hydration of patch material using isolated epidermal membranes was performed using Franz-cell-type diffusion cells. The receptor compartment was filled with sonicated, iso-osmotic Sorenson's buffer (0·1 M, pH 7·4), the volume was 12 mL and the area of exposed skin 2·6 cm^2. The donor compartment was secured to the receptor compartment by means of springs. The epidermal membrane was clamped, stratum corneum uppermost, between the ground glass surfaces of the two chambers to produce an adequate seal. The diffusion cells were then placed in a Perspex holder mounted on a 15-place stirring plate (Camlab Ltd, Cambridge, UK) in a water bath maintained at 32°C.

After an equilibration period of 1 h, the epidermal membranes were gently wiped to remove surface moisture and pre-weighed discs of patch material (radius 0·75 cm) containing either 39% w/w carmellose sodium or 39% w/w pectin were gently placed on the skin surface. Any air bubbles that might have accumulated beneath the epidermal membrane surface were removed via the sampling port. The diffusion cells were then left for 24 h, after which time the patch material was removed and re-weighed. This procedure was repeated at intervals of 48, 72 and 96 h.

In-vitro drug penetration studies

Epidermal membranes were prepared and placed within the diffusion cells as mentioned previously. To ensure complete mixing in the receptor chamber, however, Teflon-coated followers were used with a 15-place stirring plate.

Donor solutions containing tritiated TACA were prepared by dissolving the steroid in acetone and, where appropriate, unlabelled TACA was added. Donor solution (100 μL) containing either 1 or 10 μCi of TACA was pipetted on to the surface of the epidermal membranes and the acetone was left to evaporate. This solution covered the whole of the exposed epidermal membrane. After 30 min, discs of patch material (radius 0·5 cm) containing either 39% w/w carmellose sodium or 39% w/w pectin were placed carefully on the stratum corneum. Samples (1 mL) were removed from the receptor compartment via the sampling port using 1-mL syringes which had each been modified by attachment of a 6-cm length of Portex tubing (Hythe, Kent, UK) in order to enable samples to be removed from the centre of the receptor chamber. The 1-mL sample removed was replaced immediately with the same volume of receptor medium. For each experiment diffusion of the TACA through an occluded skin sample was always compared with diffusion of drug through a non-occluded sample of skin taken from the same source of dissected skin.

The enhancement in permeation of TACA can be expressed in terms of an enhancement ratio (ER) calculated as shown in equation 1.

$$ER = \text{Total amount penetrated (Occluded)/Total amount penetrated (Unoccluded)} \quad (1)$$

The apparatus described above was also used to evaluate the effect of the anatomic source of the skin on TACA penetration using samples removed from the breast and from the abdomen (n = 6). TACA with an activity of 1 μCi (2·2 × 10^6 dpm), which represented a dose of 1·65 × 10^{-5} mg, was applied to 2·6 cm^2 of skin. All replicates employed epidermal membranes from the same piece of skin.

Throughout the duration of the experiments the level of buffer in the side-arm was maintained at the same level as the skin to ensure constant contact between receptor medium and skin sample. In all completed experiments the integrity of the epidermal membranes was challenged by placing three drops of methylene blue solution on the stratum corneum surface. Immediate appearance of the blue dye in the receptor phase was taken as an indication of skin damage and the results for that particular cell were ignored.

Analytical procedures

Cutaneous metabolism of corticosteroids is thought to occur via oxidation of the hydroxyl group on position 11 to form a ketone (Noonan & Wester 1989) and by formation of the C_{21} carboxylic acid (Sieh 1982). As the viability of the skin was not maintained in the present studies, however, it seems reasonable to assume that the tritium labels on positions 1, 2 and 4 remained attached to the steroid nucleus. Monitoring of the tritium content of the receptor compartment was, therefore, representative of the total amount of TACA that had penetrated the epidermal membrane. This assumption was previously confirmed by HPLC analysis (Ladenheim 1991).

Samples removed from the receptor compartments were placed in scintillation vials, the scintillant Cocktail T (BDH, Dorset, UK; 3 mL) was added, and the vials shaken. After a 10-min equilibration period, to enable any chemiluminescence to subside, the activity in each sample was measured using a Rackbeta liquid scintillation counter (LKB, Turku, Finland). Correction was made for background radiation and quenching effects by an external channels ratio method using quench-correction curves for ^3H isotopes.

Statistical analysis of the data was performed using a two-tailed Mann–Whitney U-test (Siegel 1956).

Results

Patch hydration studies

The data in Fig. 1 show the weight increase of patches (mg cm^{-2}) over 96 h when placed on epidermal membranes; this was taken to be indicative of patch hydration over the time-period studied. The results show that the mean weight increase of patches containing 39% w/w pectin was 2·1 mg cm^{-2} after 24 h rising to 2·3 mg cm^{-2} after 96 h. Mean weight increases for patches containing 39% w/w carmellose sodium were, however, 4·4 mg cm^{-2} after 24 h, rising to 24·7 mg cm^{-2} after 96 h. The patches containing 39% w/w carmellose sodium showed a linear weight increase over 96 h with a correlation coefficient of 0·951. The increases in weight of patches containing 39% w/w pectin after 24 h were found not to be significantly different from the increase after 96 h ($P < 0·05$).

Percutaneous absorption studies

The effect of skin source on TACA penetration through epidermal membranes is shown in Fig. 2. Two sources of both abdominal and breast skin were studied. The percentage amount of applied TACA that had penetrated through the epidermal membranes after 96 h was found to be 0·17 ±0·03 and 0·27 ±0·07 units for abdominal sections and 0·73 ±0·19 and 0·71 ±0·16 units for breast sections.

These data suggest that the source of skin has an influence on the penetration characteristics of TACA. Statistical analysis showed, however, that there was no significant difference in TACA penetration through epidermal membranes obtained from the same anatomic region ($P < 0·005$). For each comparative experiment, therefore, epidermal membranes from the same skin sample were used for all replicates.

The effect of covering applications of TACA with dermatological patches containing 39% w/w carmellose sodium is shown in Fig. 3. The cumulative amount of TACA which had penetrated after 96 h, expressed as a percentage of the applied dose, was 0·71% for control experiments. Covering the application with patches containing 39% w/w carmellose sodium enhanced the penetration of TACA through epidermal membranes to 2·11% of the applied dose, a three-fold enhancement in TACA penetration. Similar trends were found

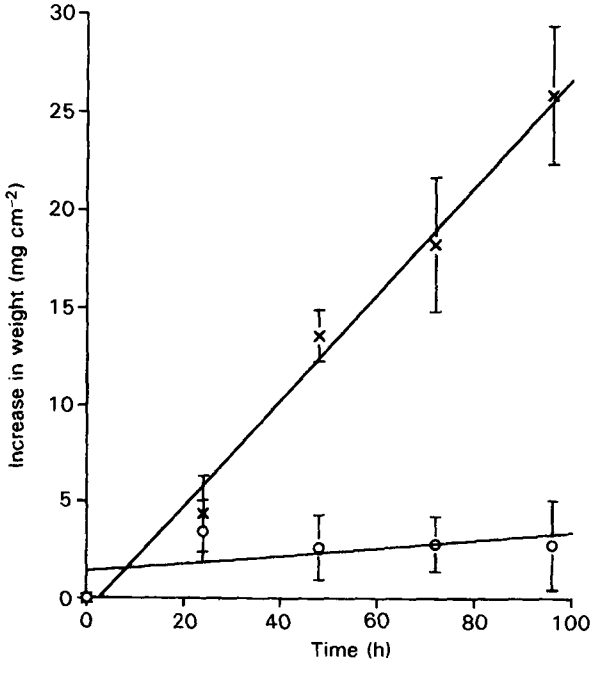

FIG. 1. Increase in weight of patch material containing 39% w/w pectin (○) and 39% w/w carmellose sodium (×) when placed on isolated epidermal membranes (n = 4, mean ± s.d.).

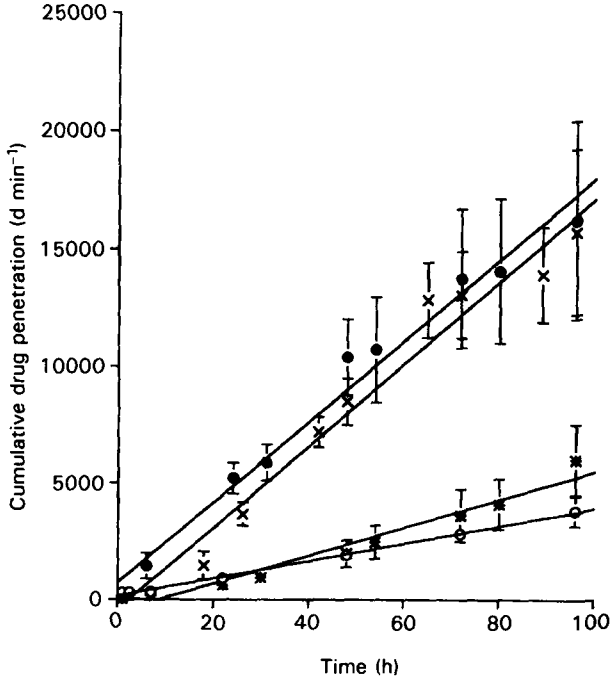

FIG. 2. Penetration of triamcinolone acetonide through epidermal membranes using two different abdominal (○ and *) and two different breast (● and ×) skin samples (n = 6, mean ± s.d.).

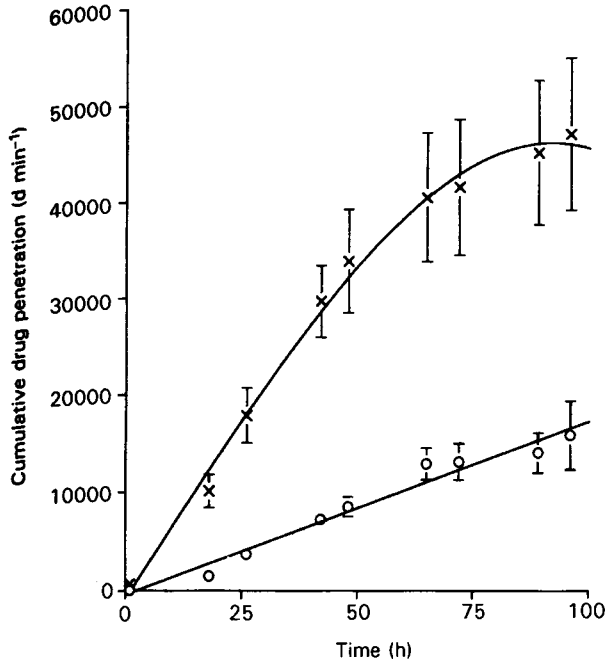

FIG. 3. Comparison of the penetration of triamcinolone acetonide through epidermal membranes with (×) and without (○) patches containing 39% w/w carmellose sodium (n = 7, mean ± s.d.).

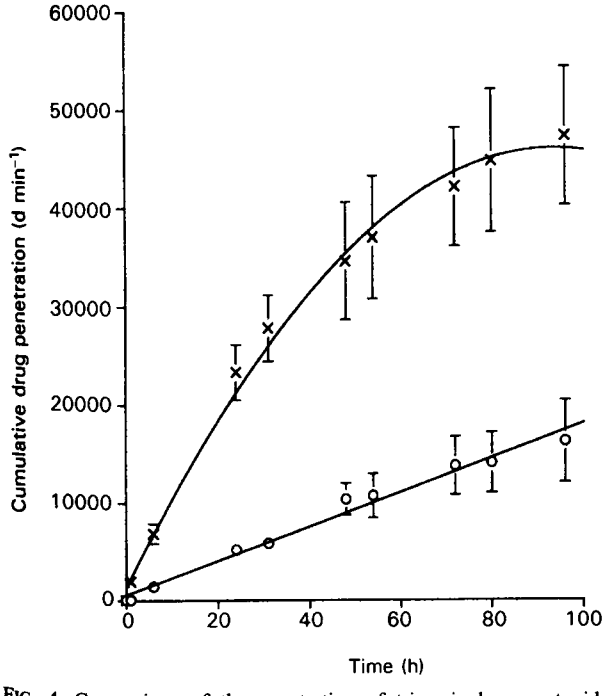

FIG. 4. Comparison of the penetration of triamcinolone acetonide through epidermal membranes with (× , n = 6) and without (○, n = 7) patches containing 39% w/w pectin (mean ± s.d.).

for patches containing 39% w/w pectin with a different skin source (Fig. 4). The total percentage of TACA which had penetrated over 96 h was enhanced from 0·73% to 2·15% of the applied dose when covered with patch material.

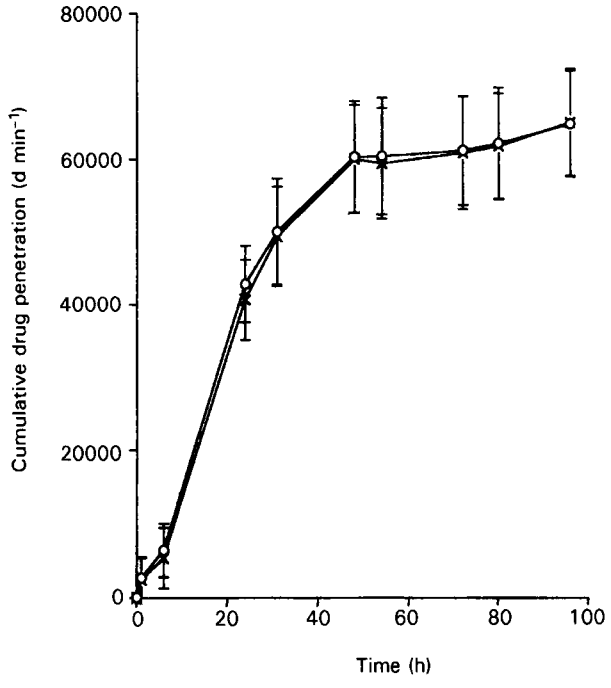

FIG. 5. Comparison of the penetration of triamcinolone acetonide (1 μCi) when covered with patches containing either 39% w/w pectin (○) or 39% w/w carmellose sodium (×) (n = 7, mean ± s.d.).

Table 1. Effect of applied dose and patch composition on penetration of TACA through epidermal membranes.

Applied dose (μCi)	Hydrocolloid composition of patch	Dose penetrated (% ± s.d.)
1	Carmellose sodium	2·93 (±0·33)
1	Pectin	2·92 (±0·33)
10	Carmellose sodium	3·25 (±0·32)
10	Pectin	3·22 (±0·34)

Fig. 5 shows a comparison of TACA penetration after application of 1 μCi of TACA, through epidermal membranes from the same source of skin, when covered with patches containing either 39% pectin or 39% carmellose sodium. Similar data were obtained for an application of 10 μCi of steroid, although the amount of steroid diffusing was higher by a factor of ten (data not shown). In both instances, patch composition did not affect either the rate or extent of TACA permeation through epidermal membranes. The cumulative amounts of TACA that had penetrated after 96 h are shown in Table 1.

Discussion

Application of patches to the surface of the skin produces retention of water in the stratum corneum which reduces the concentration gradient of water through the skin. As this is the driving force responsible for water vapour transmission, TEWL will drop as the tissue becomes hydrated (Aly 1982; Faergemann et al 1983). In this study, the gain in weight of patches when placed on epidermal membranes was primarily a

Table 2. Estimated TEWL values for abdominal skin in-vitro from patch-weight increase data.

Duration of application (h)	Estimated TEWL ($g\ m^{-2}\ h^{-1}$)	
	Carmellose sodium patch	Pectin patch
24	1·82	1·04
48	2·62	0·55
72	2·42	0·39
96	2·57	0·24

result of the absorption of water vapour that had been transmitted through the skin. Measurement of patch weight increases can, therefore, give an indication of TEWL values beneath the patch covering. Assuming that the patch material used in this study absorbed and retained all the water vapour transmitted through the skin, and knowing the area and duration of application, the TEWL of abdominal skin beneath each patch type can be estimated (Table 2).

Comparison of the data shown in Table 2 with documented TEWL values of 4·40 $g\ m^{-2}\ h^{-1}$ for in-vivo abdominal skin (Rougier et al 1989) suggests that the application of patches to the skin caused a decrease in TEWL because of the retention of water within the stratum corneum. This effect appears to be more pronounced on application of patches containing pectin compared with patches containing carmellose sodium. It has been shown that patches containing carmellose sodium have a greater affinity for water vapour (Ladenheim et al 1991). It is, therefore, possible that although these patches do induce some water retention within the stratum corneum, flux of water vapour through the skin can occur as a result of the presence of the hygroscopic hydrocolloid in the patch. Any water absorbed by the patch is more tightly bound to carmellose sodium than to pectin, thus ensuring that a steeper diffusion gradient is established and maintained. Conversely, patches containing pectin have a relatively low water vapour uptake capacity (Ladenheim et al 1991) thus reducing TEWL to a greater extent and possibly inducing higher levels of stratum corneum hydration. Both patches employed in this study enhanced the total amount of TACA penetrating the skin over 96 h. The proposed mechanisms for this effect are explained by the increase in skin hydration that occurs during occlusion.

The enhancement ratio (ER; equation 1) produced by patches containing carmellose sodium and pectin were found to be 2·97 and 2·94, respectively, suggesting that the two patch types enhanced the penetration of TACA to a similar extent. This is corroborated by the data shown in Fig. 5, which demonstrated that application of either of the two types of patch produced identical TACA flux profiles.

Figs 3 to 5 show that the flux of TACA under covered conditions was not linear over 96 h, decreasing after longer times. This was unlikely to be a result of the lack of sink conditions because the amount of TACA penetrating the receptor compartment was considerably less than both the saturation solubility of TACA in water and sink conditions (10% of permeant in receptor medium). The reduction in diffusion could be because of the formation of a reservoir of TACA within the epidermal membrane; this effect has been demonstrated in-vivo by Vickers (1963). Similar TACA diffusion profiles were obtained in some instances when tinctures containing the drug were applied in-vitro to the epidermal membrane in man and occluded with a different hydrocolloid patch (Kadir et al 1990). The reduced slope of the cumulative penetration curve over 24–48 h was attributed by these workers to the amount of penetrant partitioning into the skin before the total evaporation of the vehicle determining the resultant flux.

Alternatively, the reduced diffusion could be a result of the removal of the TACA from the skin surface into the patch by the diffusion of water. This would ultimately result in a reduction in the amount of TACA available for epidermal penetration. This effect may be of only minor importance, however, because the rate of TACA diffusion was independent of patch-type even though the water uptake by the patches was markedly different (Fig. 1). It is possible that the reduction in steroid diffusion rate observed at times longer than 24 h (Fig. 5) is a result of partition of the steroid into the hydrophobic compartment of the patch matrix.

Because the two patch types exhibited different water vapour uptake properties it was thought possible that this would result in different levels of skin hydration beneath the patches. It was hypothesized that such a difference in induced skin hydration would produce altered skin penetration profiles of TACA. The results reported in these studies show this not to occur. These findings confirm those obtained in-vivo by Hollingsbee et al (1990) who showed that percutaneous absorption of betamethasone valerate beneath a range of semipermeable films was not markedly affected by water vapour transmission rate.

The data in Table 2 suggest that both types of patch prevent the normal passage of water vapour from the skin, albeit by different amounts. Despite the ability of the patches to prevent water vapour escaping into the environment, it is, however, unclear where the water accumulates. It is possible that the stratum corneum has limited retention capacity for water and that once this capacity has been exceeded, no more hydration of the stratum corneum can be induced other than at rates controlled by uptake of water by the two patches. The level of hydration induced in the stratum corneum beneath the two types of patch might, therefore, be the same, which explains why the percutaneous absorption of TACA beneath the two types of patch was identical.

Evaluation of the composition of the two types of patch shows that although 39% w/w is hydrocolloid, the majority of the patch (61% w/w) is composed of a hydrophobic adhesive matrix. It seems likely, therefore, that the hydrophobic component has a greater influence on the level of skin hydration than the hydrocolloid component. As the hydrophobic component is identical in the two formulations, it seems reasonable that alteration of the hydrocolloid has a marginal effect on both skin hydration beneath the patch and drug permeation. It is, however, possible that increasing the proportion of the hydrocolloid component as a percentage of the total mass would alter the hydration levels of the underlying stratum corneum.

Conclusions

The diffusion of a representative corticosteroid (TACA) through isolated stratum corneum has been shown to be dependent upon the site from which the skin was removed.

TEWL through isolated epidermal membrane would appear to be dependent upon the composition of the hydrocolloid patch. In contrast, the water content of the underlying stratum corneum did not appear to be dependent upon the type of hydrocolloid contained in the patch, because the diffusion of TACA was not altered when either carmellose sodium or pectin was incorporated within a defined hydrophobic matrix. The flux of the applied corticosteroid was increased between 3–4 times when occluded by either hydrocolloid patch in comparison with that obtained when the drug was applied unoccluded. Consequently it was believed possible that the hydrophobic component of the patch matrix may play a role in the hydration of the skin and therefore drug diffusion.

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