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Development and Evaluation of an Intracutaneous Depot Formulation of Corticosteroids Using Transcutol as a Cosolvent: In-vitro, Ex-vivo and In-vivo rat Studies

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Abstract—A topical delivery system has been developed using 50% Transcutol (diethylene glycol monoethyl ether) to decrease the body burden of topically administered dexamethasone and hydrocortisone. The delivery system was evaluated in-vitro using a dissolution apparatus to measure the release of steroid from the gel. In 10 h, 29·6 ± 0·39% dexamethasone and 45·5 ± 0·84% hydrocortisone was released from the formulation compared with 23·0 ± 0·48 and 39·9 ± 0·77%, respectively, from control formulations without Transcutol. Ex-vivo evaluation was made using rat whole skin in a diffusion cell; the amount of steroid reaching the acceptor cell was significantly less from the formulation containing Transcutol compared with controls. There was also a 2-fold increase in the retention of dexamethasone and a 3-fold increase in the retention of hydrocortisone in the skin at the end of the permeation experiments compared with control experiments. In-vivo studies were made using a formulation containing [^{3}H]hydrocortisone applied to rat skin, followed by measurement of total radioactivity in the blood. For the Transcutol formulation the area under the blood concentration-time curve (0–96 h) was 6·06 ± 1·27 compared with 2·52 ± 0·43 × 10^6 d min^{-1} mL^{-1} h for the control formulation, indicating a 58% reduction in body burden.

The major barrier for the absorption of drugs through the skin is the stratum corneum. Once a drug reaches the dermis there is no further hindrance for absorption into the systemic circulation, but this is not always desirable. Drugs applied topically may not cross the stratum corneum efficiently or may permeate across the skin and enter the systemic circulation. For topically applied drugs in dermatological conditions, the ideal situation would be that the drugs penetrate the stratum corneum but do not enter the systemic circulation, remaining in the skin for a prolonged period. Drugs that are capable of binding to skin proteins or are lipophilic will have affinity for skin. Local delivery is more advantageous over the systemic application as it reduces the systemic body burden (Ritschel 1988). Transcutol (diethylene glycol monoethyl ether) is a hygroscopic liquid, freely miscible with polar and non-polar solvents. Recently, Ritschel & Hussain (1988) reported that Transcutol is a solvent for delivery of griseofulvin to all layers of the skin. It has also been used as cosolvent in topical and parenteral products. Transcutol is non-irritating and non-toxic (Product Information, Gatteffossé Co.), and has an oral LD50 of 8·69 g kg^{-1} in rat (Budavari 1989).

The purpose of this investigation was to study the usefulness of Transcutol in the development of an intracutaneous depot for drugs. Dexamethasone and hydrocortisone were chosen as model compounds for the development of an intracutaneous depot in rat.

Materials and Methods

Analytical methods

All the samples from solubility and drug release studies were analysed by UV spectrophotometry (λ_{max} for dexamethasone, 240 nm (Cohen 1973); λ_{max} for hydrocortisone, 242 nm (Florey 1983)) in methanol. For solubility determination of both drugs in Labrafil, chloroform was used as a solvent. For drug release studies from topical delivery systems, distilled water/propylene glycol (1:1) was used as dissolution medium. Standard calibration curves were prepared from solutions of known concentrations of both drugs in methanol, chloroform, and dissolution medium ranging from 2–10 $\mu g\ mL^{-1}$ (r = 0·9920–0·9998).

[^{3}H]Dexamethasone and [^{3}H]hydocortisone (radiochemical purity, 97·5%, New England Nuclear, Boston MA) were used for all other studies. Radiolabelled drug (1–2 μCi) was added to drug solutions and the specific activity determined by liquid scintillation counting.

Skin and blood samples

A known weight of skin (approx. 10–15 mg) was solubilized with 1 mL of NCN tissue solubilizer at 50°C in a water bath; scintillation fluid was added, and the samples were counted using an external standard (^{137}Cs) for quench correction. Blood samples were digested with 1 mL of NCN tissue solubilizer and decolourized by adding 0·5 mL benzoyl peroxide (0·2 g mL^{-1} in toluene) and counted after addition of scintillation fluid.

Solubility and apparent partition coefficient (APC)

The solubility of dexamethasone and hydrocortisone was determined at 37°C in distilled water, propylene glycol, Labrafil, and Transcutol. The apparent partition coefficient of dexamethasone and hydrocortisone was determined in the following systems (Ritschel & Barkhaus 1988a): (i) mineral oil and distilled water; (ii) isopropyl myristate and buffer pH 7·4 and (iii) n-octanol and buffer pH 7·4.

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Skin permeation

The permeation of model drugs was studied using whole rat skin (Hussain 1986) and the Thomas diffusion cell (Ritschel & Barkhaus 1987). Phosphate buffer (pH 7·4) (Diem & Lentner 1970) was used as a receptor medium and contained 1000 units mL^{-1} potassium penicillin G to retard microbial growth. The drug solution (200 μL) was applied to the stratum corneum side in each of the donor compartments. Samples (200 μL) were withdrawn periodically from the receptor compartment over 144 h and analysed for drug content. At the end of the experiment, the amount of drug present in the skin was determined.

Skin penetration

The distribution of model drugs in the skin from all four solvents was determined at presumed steady state. The same procedure described in skin permeation was followed but no sampling of the receptor phase was attempted. The experiment was stopped at 72 h and the drug distribution in the skin was determined as described previously (Ritschel et al 1989).

Optimization of Transcutol concentration

Saturated dexamethasone and hydrocortisone solutions were prepared in solvent mixtures (distilled water and Transcutol) containing 0, 5, 10, 15, 25, 50, 75, or 100% of Transcutol. The permeation experiments were conducted as described before but no sample was withdrawn from the receptor compartment. The experiments were stopped at presumed steady state and the amount of dexamethasone and hydrocortisone present in the skin was determined.

Preparation of topical formulation

In a preliminary study, gel formulations were prepared with different percentages (6, 8, 10, 12 and 15%) of Cab-O-Sil. Physical stability of the gel was observed for two weeks. A gel containing 10% Cab-O-Sil was chosen for the final formulation of the following composition: dexamethasone or hydrocortisone, 0·09%; propylene glycol, 12·00%; Transcutol, 50·00%; Cab-O-Sil, 10·00% and triethanolamine buffer pH 8·00 to make up to 100·00%.

The procedure for gel preparation was as follows: the drug was added to the mixture of propylene glycol, Transcutol, and triethanolamine buffer (Diem & Lentner 1970). A weighed quantity of Cab-O-Sil was added slowly with constant stirring to obtain a uniform mix. A control gel was prepared by the same procedure without Transcutol. Gels for ex-vivo and in-vivo evaluation were prepared with the addition of tritiated drug (2 μCi per g gel).

In-vitro evaluation of topical formulation

The release of dexamethasone and hydrocortisone from both control and treatment gels was monitored at 37°C by modification of the method of Turakka et al (1984). A dissolution apparatus was used (USP method I) with the basket replaced with a plastic cylinder (i.d. = 3·00 cm; o.d. = 3·20 cm; height = 4·5 cm) containing the gel and separated from the receptor phase by a semipermeable membrane (cut-off mol. wt 500). Distilled water/propylene glycol was the receptor phase (250 mL) to ensure solubility of the drugs. Samples (5 mL) were withdrawn periodically and analysed for drug content.

Ex-vivo evaluation of topical formulation

The gel formulations were evaluated ex-vivo using the Thomas diffusion cells, using a weighed quantity of gel (500 mg) as the donor phase. At the end of the permeation studies the amount of drug remaining in the skin was determined.

In-vivo evaluation of topical formulation

For in-vivo evaluation hydrocortisone only was studied. Four rats were used in each group and were kept in climatized animal quarters (r.h. 35%, 22 ± 1°C), with a 12 h light-dark cycle. The animals were kept on standard pelletized food. All in-vivo studies were performed on rats fasted overnight with free access to water. Feeding was resumed 3 h after dosing.

The day before the experiment the hair on the dorsal side of the rat was clipped. After anaesthetizing by ether inhalation, a flexible teflon ring (i.d. = 2·7 cm; o.d. = 3·3 cm; height = 3·0 mm) was fixed to the skin using a medical adhesive. A weighed amount of gel (1 g) was applied evenly on the area (4·24 cm^2) enclosed by the ring. The area was covered by a polyethylene membrane and an elastic bandage was wrapped around the body. After 6 h, the gel was removed and the area was cleaned (3 times) with a cotton swab moistened with ethanol. The amount of drug recovered was determined by extracting the drug from the gel and the cotton swabs, and subtracted from the dose administered. Blood samples (75 μL) were collected retro-orbitally by using heparinized capillary tubes and the amount of radioactivity present in the whole blood was determined.

Statistical methods

The data was analysed by Tukey's multiple range test (when comparing more than 2 sets of data) or by unpaired *t*-test. $P < 0.05$ indicated a significant difference.

Results and Discussion

Solubilities of dexamethasone and hydrocortisone

Solubilities of dexamethasone and hydrocortisone in distilled water, propylene glycol, Labrafil, and Transcutol are listed in Table 1.

Apparent partition coefficients (APC)

Various solvent systems have been used to relate partition coefficients to percutaneous absorption, including mineral oil, n-octanol, and isopropyl myristate (IPM), which reflect the partitioning of drugs into the dead stratum corneum cells, intercellular spaces, and cells, respectively. Barry (1983) recommends IPM for work related to percutaneous absorption, since its polar and non-polar nature mimics the complex nature of the skin. Table 2 lists the APC values of the model drugs in different systems. A high value in buffer/n-octanol for both drugs is a good indication that the drugs partition very well into intercellular spaces. Very low values for partitioning into mineral oil indicate that the drugs may not partition into the dead stratum corneum cells. An APC value of one or greater in IPM is generally required for optimal penetration (Blank & Gould 1961); these results are in agreement with those of Blank & Gould (1961) and indicate that IMP is an appropriate solvent for APC studies (Barry 1983).

Table 1. Solubility of dexamethasone and hydrocortisone in distilled water, propylene glycol, Labrafil, and Transcutol.

	Solubility (mg mL^{-1}) (mean ± s.d., n = 5)	
Solvent	Dexamethasone	Hydrocortisone
Distilled water	0·445 ± 0·148	0·247 ± 0·077
Propylene glycol	13·60 ± 1·588	15·23 ± 2·758
Labrafil	3·445 ± 1·537	14·38 ± 1·447
Transcutol	72·91 ± 6·423	34·31 ± 3·150

Table 2. Apparent partition coefficient of dexamethasone and hydrocortisone between mineral oil/distilled water, buffer pH 7·4/n-octanol, and buffer pH 7·4/isopropyl myristate (IPM).

	Apparent partition coefficient (mean ± s.d., n = 3)	
Solvent system	Dexamethasone	Hydrocortisone
Mineral oil/ dist. water	0·104 ± 0·027	0·034 ± 0·004
Buffer/n-octanol	27·35 ± 3·48	25·85 ± 3·20
Buffer/IPM	1·810 ± 0·410	0·742 ± 0·082

Permeation parameters

The effect of propylene glycol, Labrafil, and Transcutol on the lag time and permeation of both dexamethasone and hydrocortisone was studied, and compared with the control (saturated drug solutions in distilled water). The permeation parameters were calculated by the procedure described by Ritschel et al (1989). Tables 3 and 4 list the permeation parameters of dexamethasone and hydrocortisone, respectively. There is no significant effect of propylene glycol and Transcutol on the lag time of dexamethasone when compared with the control ($P > 0·05$), whereas in the presence of Labrafil the lag time was significantly decreased ($P < 0·05$). In the case of hydrocortisone the lag time was significantly decreased ($P < 0·05$) in the presence of Labrafil and significantly increased in the presence of Transcutol ($P < 0·05$). The permeation of dexamethasone was significantly decreased in the presence of propylene glycol and Transcutol ($P < 0·05$). Labrafil has no effect on the permeation ($P > 0·05$). The permeation of hydrocortisone in presence of Transcutol was significantly different from distilled water ($P < 0·05$). There is no difference between Labrafil and distilled water ($P > 0·05$); however, the permeation decreased in the presence of propylene glycol ($P < 0·05$).

Amount of drug in the skin

Tables 3 and 4 list the amount of dexamethasone and hydrocortisone present in the skin at the end of the permeation studies. For dexamethasone the amount in the skin differed by at least an order of magnitude for the three co-solvents when compared with distilled water. In contrast hydrocortisone retention was decreased by propylene glycol. In the presence of Labrafil or Transcutol the skin retention capacity of hydrocortisone was increased by at least an order of magnitude.

Drug distribution in the skin

The penetration of model drugs into the skin as a function of skin depth was studied from saturated drug solutions of all three solvents. The distribution of dexamethasone and hydrocortisone as a function of skin depth at steady state is shown in Figs 1 and 2, respectively.

Optimization of Transcutol concentration

The skin retention of the model drugs as a function of Transcutol concentration was determined at steady state. The amounts of dexamethasone and hydrocortisone present in the skin as a function of concentration of Transcutol are shown in Fig. 3. The amount of dexamethasone and hydrocortisone retained in the skin increased as a function of Transcutol concentration. The amount of drug remaining in the skin reached a plateau with 50% of Transcutol, with no further increase in skin retention of the model drugs by further increase in Transcutol concentration, indicating that

Table 3. Permeation parameters and amount of dexamethasone present in the skin from ex-vivo studies using different solvents. (Mean ± s.d.)

Solvent (n)	Lag time (h)	Permeability (cm h^{-1})	Amount ($\mu g\ mg^{-1}$)
Distilled water (5)	38·0 ± 8·07	$1·044 \times 10^{-3} \pm 2·500 \times 10^{-4}$	0·0635 (n = 2)
Propylene glycol (6)	31·3 ± 7·46	$9·498 \times 10^{-5} \pm 5·600 \times 10^{-5}$	1·254 ± 0·398
Labrafil (6)	21·0 ± 5·79*	$2·760 \times 10^{-4} \pm 7·560 \times 10^{-5}$	0·303 ± 0·166
Transcutol (6)	31·2 ± 11·68	$4·400 \times 10^{-5} \pm 1·180 \times 10^{-5}$	1·227 ± 0·203

* $P < 0·05$ compared with control value.

Table 4. Permeation parameters and amount of hydrocortisone present in the skin from ex-vivo studies using different solvents. (Mean ± s.d.)

Solvent (n)	Lag time (h)	Permeability (cm h^{-1})	Amount ($\mu g\ mg^{-1}$)
Distilled water (5)	32·8 ± 2·97	$1·114 \times 10^{-3} \pm 4·737 \times 10^{-4}$	0·0545 (n = 2)
Propylene glycol (4)	38·5 ± 8·26	$4·095 \times 10^{-4} \pm 3·710 \times 10^{-4}$*	0·0275 (n = 2)
Labrafil (6)	10·1 ± 3·19*	$1·430 \times 10^{-4} \pm 1·780 \times 10^{-5}$	0·673 ± 0·098
Transcutol (6)	66·1 ± 21·35*	$9·270 \times 10^{-5} \pm 3·570 \times 10^{-5}$*	4·745 ± 0·345

* $P < 0·05$ compared with control values.

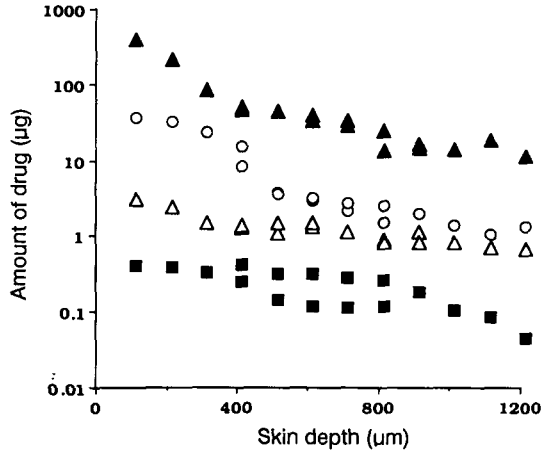

FIG. 1. Distribution (mean) of dexamethasone in skin as a function of skin depth in the presence of various solvents. Distilled water (■), propylene glycol (○), Labrafil (△) and Transcutol (▲). (n = 3).

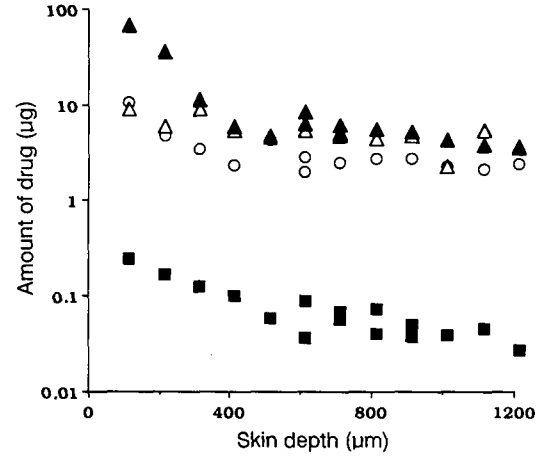

FIG. 2. Distribution (mean) of hydrocortisone in skin as a function of skin depth in the presence of various solvents. Distilled water (■), propylene glycol (○), Labrafil (△) and Transcutol (▲). (n = 3).

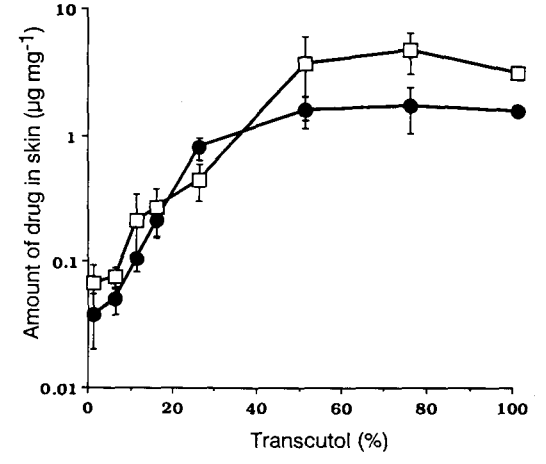

FIG. 3. Mean ± s.d. amount of dexamethasone (●) and hydrocortisone (□) present in skin as a function of Transcutol concentration. (n = 3).

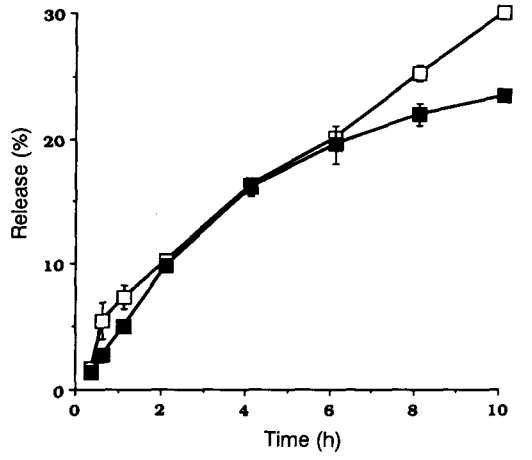

FIG. 4. Percent of dexamethasone released from gel with (■) and without (□) Transcutol. (Mean ± s.d., n = 3).

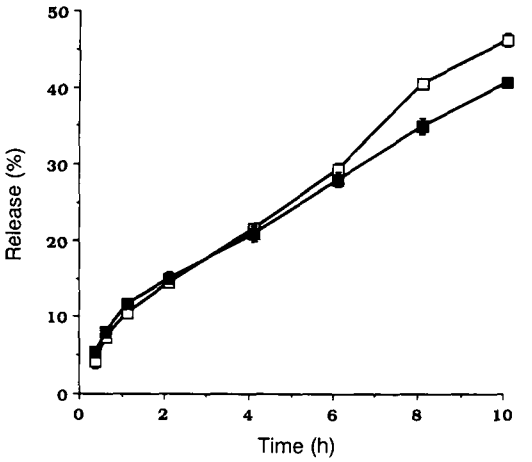

FIG. 5. Percent of hydrocortisone released from gel with (■) and without (□) Transcutol. (Mean ± s.d., n = 3).

the penetration of dexamethasone and hydrocortisone was saturated (skin capacity) and any further increase in Transcutol may not result in the improvement in the penetration of model drugs. Therefore, 50% Transcutol was chosen as an optimum concentration, and was used in all further studies.

In-vitro drug release from topical formulation

The selected gel formulation was physically stable for two weeks. The drug release from the gel was studied from control (without Transcutol) and treatment (with 50% Transcutol) formulations. The percent of dexamethasone released in 10 h was 29·6 ± 0·39 and 23·0 ± 0·48% from control and treatment gel, respectively. In the case of hydrocortisone 45·5 ± 0·84 and 39·9 ± 0·77% of the initial concentration was released from control and treatment gel, respectively. The mean percentages of dexamethasone and hydrocortisone released from gel with and without Transcutol are shown in Figs 4 and 5, respectively, showing no significant difference in drug release from the gels. These results indicate that Transcutol does not effect the drug

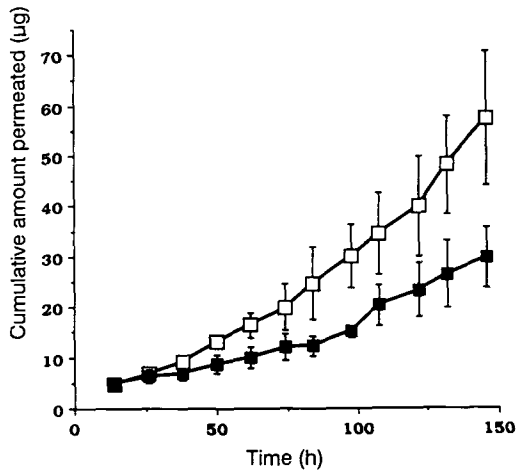

FIG. 6. Cumulative amount of dexamethasone permeating across rat skin from gel with (■) and without (□) Transcutol. (Mean ± s.d., n = 4).

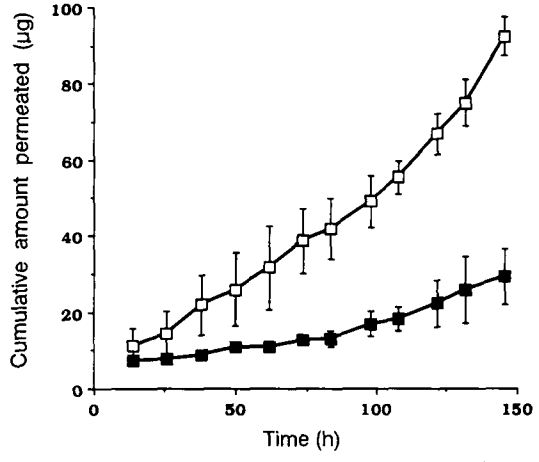

FIG. 7. Cumulative amount of hydrocortisone permeating across rat skin from gel with (■) and without (□) Transcutol. (Mean ± s.d., n = 4).

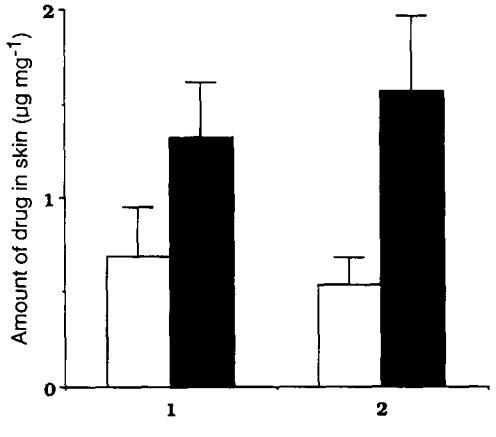

FIG. 8. Mean ± s.d. amount of dexamethasone (1) and hydrocortisone (2) in skin at the end of ex-vivo permeation studies. Gel with (■) and without (□) Transcutol. (n = 4).

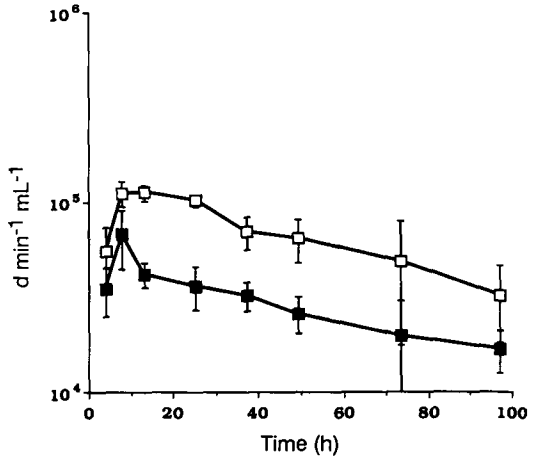

FIG. 9. Amount of radioactivity present in 1 mL of whole blood as a function of time after single dose administration of hydrocortisone gel with (■) and without (□) Transcutol. (Mean ± s.d., n = 4).

release from the topical formulation and are also in agreement with previous results from our laboratories (Ritschel & Barkhaus 1988a, b).

Ex-vivo permeation studies

The cumulative amounts of dexamethasone and hydrocortisone permeated from the two gels (control and treatment) are shown in Figs 6 and 7, respectively. The amount of dexamethasone and hydrocortisone reaching the receptor compartment is always less from the gel containing Transcutol when compared with the control gel. In the presence of Transcutol the amount of dexamethasone and hydrocortisone permeated was significantly decreased ($P < 0.05$) when compared with control. At the end of the permeation studies the amount of dexamethasone and hydrocortisone present in the skin was determined (Fig. 8). There is a 2-fold increase in the skin retention of dexamethasone in the presence of Transcutol and a 3-fold increase for hydrocortisone. These results indicate that Transcutol decreased the permeation of dexamethasone and hydrocortisone across the skin and increased the penetration into the skin.

In-vivo permeation studies

For all in-vivo studies, the radioactivity present in whole blood was determined (Fig. 9). The areas under the curve (AUC) for both control and treatment gel after topical

Table 5. Area under the curves (0–96 h) after topical application of hydrocortisone gel with (treatment) and without (control) Transcutol.

	Area under the curve (10^6 d min^{-1} mL^{-1} h)	
	Control	Treatment
Rat 1	6·23	2·34
Rat 2	5·37	2·81
Rat 3	7·76	2·02
Rat 4	4·87	2·96
Mean ± s.d.	6·06 ± 1·27	2·52 ± 0·43

Reduction in body burden due to Transcutol = 58·22% ($P < 0.05$)

administration for each rat are listed in Table 5. The radioactivity present in whole blood is significantly lower after topical administration of the gel containing Transcutol when compared with the control gel. The reduction in systemic body burden was calculated by comparing the AUC values of the control and treatment group. The systemic body burden of the drug was reduced by 58% in the presence of Transcutol ($P < 0.05$).

Proposed mechanism for an intracutaneous depot

The stratum corneum is a heterogeneous structure (Brody 1966) and can be considered morphologically and functionally as a two-compartment system consisting of protein bricks and lipid mortar (Elias 1983). The composition of lipids in epidermis differs markedly starting from the basal layer, stratum germinativum, to the outermost, stratum corneum (Gray & Yardley 1975; Elias et al 1979; Grayson & Elias 1982; Lampe et al 1983; Imokawa et al 1989). The intercellular space volume is relatively small (1–10% of the total) and may be a major pathway for permeation but at the same time the intercellular lipids are important in controlling the percutaneous absorption (Elias 1981; William & Elias 1989). We believe that in the presence of Transcutol, the intercellular lipids are swollen without altering the multiple bilayer structure. These swollen lipids appear to hold the model drugs and thereby form an intracutaneous depot for model drugs in the presence of Transcutol. In the presence of Transcutol higher drug levels were also seen in further epidermal layers and in the dermis. Transcutol may also be acting on the intracellular lipids of the other epidermal layers and the ground substance of the dermis, due to its dual solubility in polar and non-polar materials. The drug levels in epidermis and dermis are lower than those of stratum corneum, which indicates that the barrier nature of stratum corneum was not altered in the presence of Transcutol, as would also be expected from the permeation parameters shown in Tables 1 and 2. The swollen lipids may be important factors in the development of an intracutaneous depot in the presence of Transcutol.

Conclusion

Ex-vivo, in-vivo and drug distribution studies strongly suggest that Transcutol increases the penetration of model drugs into the skin and decreases the permeation across the skin.

Acknowledgement

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