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In vitro percutaneous absorption of metronidazole and glucose: comparison of o/w, w/o/w and w/o systems

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Abstract

The percutaneous absorption of model hydrophilic drugs with intermediate and high polarity, metronidazole and glucose, respectively, from three emulsion types (o/w, w/o/w and w/o) has been studied. All the emulsions were prepared with exactly the same composition in order to avoid the influence of the formulation and to study the role of the emulsion type alone. The yield of the w/o/w emulsion containing glucose was high (95.8%), while that of the w/o/w emulsion containing metronidazole was lower (77.6%), although the multiple character of the emulsion was not in question. Absorption of metronidazole across hairless rat skin over 24 h ranged from 55 to 69% of the applied dose and was similar for the three emulsions studied. Absorption of glucose ranged from 1 to 4% and was found to be greater from the o/w emulsion than that observed from the w/o/w or w/o emulsions. The amount of glucose found in the dermis seems to be dependent on the emulsion type: o/w > w/o/w ≅ w/o. The differences between the emulsions cannot be attributed only to the evaporation rate of water alone. X-ray diffraction patterns obtained after treatment of the stratum corneum with the three emulsions did not display any difference, but were somewhat different from that observed with untreated stratum corneum.

Keywords: w/o/w emulsion; o/w emulsion; w/o emulsion; Percutaneous absorption; Metronidazole; Glucose; X-ray diffraction

1. Introduction

The stratum corneum (SC) constitutes the principal barrier for cutaneous penetration and allows only limited absorption of the majority of the drugs. However, absorption can be increased by changing the permeability of the SC or the thermodynamic activity of the drug. In this respect, various investigations are being carried out using vehicles containing penetration enhancers (Williams and Barry, 1992), as well as novel carrier systems such as liposomes (Egbaria and Weiner, 1990), but few studies have been performed on the role of conventional dosage forms.

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Among these, Nastruzzi et al. (1993) showed that normalized fluxes (J_n) of methyl nicotinate were higher from a w/o emulsion than from an o/w emulsion, while Youenang Piemi et al. (1994) observed that methyl nicotinate seemed to penetrate equally readily from an w/o or o/w emulsion. Kundu et al. (1993) demonstrated that the release rate of retinoic acid, which is lipophilic, from w/o cream decreased 2.5-fold when compared to the o/w cream. These conflicting results can be explained, at least partly, by the fact that different emulsion types were obtained by changing the formulation.

In our previous studies, the role of the emulsion type was studied and in order to avoid any influence of the formulation the emulsions were prepared with exactly the same composition. There is increased interest in drug administration with a novel system, the multiple emulsion, which has already shown advantages for controlled release in vitro (Fukushima et al., 1987) and in vivo after oral administration (Mishra and Pandit, 1990; Omotosho et al., 1990) as well as after parenteral administration (Miyakama et al., 1993). However, few studies have been performed on topical administration. In our experiments, the release and percutaneous absorption of metronidazole (Ferreira et al., 1994a) and glucose (Ferreira et al., 1994b) from an w/o/w emulsion was found to be intermediate between o/w and w/o emulsions following application at an infinite dose.

The aim of this work was to study the percutaneous absorption of model hydrophilic drugs with intermediate and high polarity, metronidazole and glucose, respectively, from o/w, w/o/w and w/o emulsions applied at a finite dose. A consequence of this mode of application is that, immediately after application, the physicochemical and thermodynamic conditions change radically from those of the freshly applied formulation (Shah et al., 1989). As in our previous studies, all the emulsions were prepared according to the same formula. In order to determine the origin of the differences between the emulsions, the rate of water loss from the emulsions, as well as the structure of the residual film, as determined by X-ray diffraction, has been studied.

2. Materials and methods

2.1. Materials

Metronidazole was purchased from Sigma Chimie S.a.r.l. (France). D-[1-^{3}H]Glucose (spec. act. 2.9 Ci/mmol) was obtained from Amersham Life Science. The following chemicals were used in formulation of the emulsions: lipophilic surfactant (Hypermer A60: a modified polyester) and hydrophilic surfactant (Synperonic PE/F127: a block copolymer of ethylene oxide and propylene oxide) were obtained from ICI Surfactants (Clamart, France) and paraffin oil was obtained from Coopération Pharmaceutique (Paris, France). All other chemicals used for analysis were analytical reagent grade or HPLC grade.

2.2. Preparation of emulsions

The emulsions containing metronidazole were prepared as described previously (Ferreira et al., 1994a). Briefly, a w/o/w multiple emulsion and two (o/w and w/o) simple emulsions were prepared according to the same formula. This was 20% paraffin oil, 3.2% Hypermer A60, 0.8% Synperonic PE/F127, 0.5% $MgSO_4.7H_2O$, 0.5% metronidazole and 75.0% distilled water, by weight. The w/o/w multiple emulsion was prepared in two steps: in the first step the w/o primary emulsion was formed and in the second 20% w/w of an aqueous solution of the hydrophilic emulsifier was added to 80% w/w of the w/o primary emulsion. The mixture was then homogenized at 700 rpm for 40 min. The simple emulsions (o/w or w/o) were made by adding aqueous phase containing $MgSO_4 \cdot 7H_2O$ and metronidazole to the oil phase.

The emulsions containing glucose (0.5% w/w) were prepared according to the formula described previously (Ferreira et al., 1994b). In this formula, the volume fraction of the w/o primary and w/o/w multiple emulsions was decreased in comparison with those emulsions containing metronidazole. In previous experiments, it was found that the low viscosity of these emulsions facilitated their fabrication in small batches using an Ultra Turrax T-25 type Ika agitator for to

prepare the primary emulsion and a magnetic stirring bar for preparation of the w/o/w emulsion.

2.3. Assays of the emulsions

Microscopic observations were made with an optical microscope (Laboval 4, Bioblock, France) at 1000 × magnification after dilution in the appropriate external phase. Conductivity was measured directly on the emulsions with Conductivity Meter CDM3 (Copenhagen) in order to determine the emulsion type.

2.4. Determination of yield of the w / o / w multiple emulsion

The yield of the w/o/w emulsion containing glucose was determined by centrifugation (1000 rpm for 1 min) after dilution, which was necessary for separation of the external aqueous phase. Considering that the paraffin oil/water partition coefficient of glucose was found to be very small, the diffusion of glucose across multiple droplets after dilution would be negligible. The w/o/w emulsion was diluted 10-fold with an aqueous solution of glucose at the same osmolarity as that of the internal aqueous phase. After centrifugation, the lower layer (aqueous solution) was then filtered with a Millipore filter (0.45 μm in pore size) and the radioactivity analyzed. In previous experiments, it was found that the radioactivity of an aqueous solution of glucose was almost the same before and after filtration on a Millipore filter as described above.

The yield of the w/o/w emulsion containing metronidazole cannot be determined by dilution. Preliminary determinations showed that the oil/water partition coefficient of metronidazole in the presence and absence of the lipophilic surfactant was not negligible. Consequently, dilution, which was also necessary for separation of the external aqueous phase, induced the diffusion of metronidazole from the internal aqueous phase to the external diluting phase. Thus, the yield was determined as follows: about 20 ml of the fresh w/o/w emulsion, which has been withdrawn 20 min after addition of the external aqueous phase to the w/o primary emulsion, was centrifuged (1000 rpm for 5 min). In this step, the mean diameters of the multiple droplets are large and, consequently, the viscosity of the w/o/w emulsion is low. This facilitated the separation of the external aqueous phase. After centrifugation, the aqueous phase (the lower layer) was then filtered with a Millipore filter (0.45 μm pore size) and the content of metronidazole analyzed by HPLC. Measurements of the conductivity before and after the centrifugation/filtration procedure were performed in order to estimate the breakdown of the multiple droplets during this step. In this study, experiments were conducted in triplicate.

2.5. Evaporation of water

The rate of dehydration of the emulsions was studied as described previously (Wepierre and Adrangui, 1982). The emulsions were applied at a dose of 6 mg/cm^2 on a sheet of aluminium paper as an inert support placed on a glass tube with a diameter of 3 cm. The amount of water loss was determined gravimetrically under standard experimental conditions: 30° C and 50% relative humidity. Once the emulsion had been applied to a support, the weight loss, as determined gravimetrically, was considered as water loss. The data are presented in terms of percentage of water loss considering the weight of the applied sample as 100%.

2.6. In vitro percutaneous absorption

In vitro percutaneous absorption of glucose and metronidazole was determined with modified Franz cells (membrane surface area, 1.77 cm^2; cell volume, 6.7 cm^3). Abdominal skin was excised from male hairless rats (350–400 g, Iffa Credo, L'Arbresle, France), immediately mounted in the cells and allowed to equilibrate with the environment for 12 h. The receptor chamber was filled with an 0.05 M phosphate-buffered saline (pH 7.4) containing 0.01% (w/v) of $HgCl_2$ as preservative. The receptor phase, maintained at 37° C, was continuously stirred with a small magnetic bar to ensure homogeneity.

Experiments were carried out at finite dose. In these experiments the upper chamber (donor compartment) was left open so that volatile components of the emulsions could escape in order to mimic the use conditions. About 12 mg ($\cong 6$ mg/cm^2) of the emulsions were applied to the skin with a glass rod and the exact dose was determined by measuring the glucose (by radioactivity) or the metronidazole (by HPLC) remaining on the rod after application.

After application of the preparations, serial sampling was performed at specified times by totally removing the receptor fluid and refilling with fresh solution. The amount of glucose or metronidazole in the receptor fluid was determined as described in our previous studies.

At the end of the experiments with the emulsions containing glucose, the radioactivity remaining on the surface of the skin was determined by washing twice with 200 μl of Cetrimide at 0.05% and three times with 200 μl of water and removing the residue with a cotton swab. The washing solvent, pipette tips and cotton swab were added to a bottle containing 30 ml of ethanol. The radioactivity of the washing liquid was measured in a 1 ml aliquot of the alcoholic solution added to 15 ml of Picofluor 40®. The epidermis was mechanically separated from the dermis with spring nippers. The epidermis and dermis were digested with 1 and 2 ml of Soluene 350®, respectively, overnight at 60° C. 15 ml of Hionic Fluor® was added and the radioactivity was determined.

2.7. X-ray diffraction

X-ray diffraction experiments were carried out using the synchroton radiation source of LURE (University Paris Sud) on station D43. A single bent Si monochromator (111 reflection) was used to select the wavelength 1.5 Å and to focalize the beam. The size of the beam was limited by a collimator with a circular aperture of 0.3 mm diameter. Two-dimensional patterns were recorded on Kodak Phosphor Imagy Plates in transmission geometry with the plates lying perpendicular to the incident beam. The plates were scanned on the Molecular Dynamics Phosphor Image 400E with a pixel size of 172×172 μm^2. The patterns were obtained with the stratum corneum parallel or perpendicular to the X-ray beam at a sample detector distance of 400 mm (small-angle X-ray diffraction – SAXS) or 87 mm (wide-angle X-ray diffraction – WAXS).

The angle of diffraction (2θ) between the incident beam and scattered beam is related to the periodicity d giving rise to the diffraction peaks by Bragg's law: $\lambda = 2d \sin \theta$ where λ is the wavelength. The SAXS setting corresponds to the periodicity range 200–20 Å and the WAXS setting to the periodicity range 3–30 Å.

The human SC specimens used were obtained during plastic surgery. Epidermis was separated from dermis by heat (60° C; 1 min); then the epidermis was treated with trypsin at room temperature for complete removal of the granulosum layer. Trypsin (Prolabo, France) was used at 0.05% in 0.05 M Tris-HCl buffer, pH 7.9 for 60 min.

Experiments were repeated three times using different SC samples.

2.8. Statistical analysis

Tests for significant differences between means were made by analysis of variance (ANOVA). Reference to significant difference in the below text denotes that the test was carried out at level $p < 0.05$.

3. Results and discussion

3.1. Characteristics of emulsions

Three different emulsion types (o/w, w/o/w and w/o) containing glucose and metronidazole were obtained with exactly the same composition of each constituent, while the emulsification conditions were different. The characteristic parameters of these emulsions, which clearly demonstrate that the three different emulsion types were obtained, have been reported in our previous studies.

The yield of the w/o/w emulsion containing glucose was 95.8%. This means that only 4.2% of the total glucose concentration could have leaked

Table 1
Yield of the w/o/w emulsion containing metronidazole

Emulsion phase		Metronidazole		Conductivity [b] (μS)	
Phase	Volume ratio (ml)	Mass (g)	Concentration [a] (% w/v)	Before	After
Internal aqueous	56	0.39	0.69	–	–
External aqueous	20	0.11	0.56	45	81

[a] Concentration (w/v) of metronidazole into each aqueous phase.
[b] Conductivity of the external aqueous phase before and after centrifugation/filtration procedure (see text).

into the external aqueous phase. The yield of the w/o/w emulsion containing metronidazole was 77.6% (Table 1). The paraffin oil/water partition coefficient of metronidazole in the presence of the lipophilic surfactant (0.13) was found to be favourable towards water. It would be expected, therefore, in the case of a stable w/o/w emulsion, that a higher yield would be found. The microscopic aspect and the conductivity analysis confirmed that the multiple character was not in question. On other hand, the conductivity values of the external aqueous phase show a slight increase after centrifugation/filtration, which was negligible compared to that of a 0.7% $MgSO_4 \cdot 7H_2O$ solution (4500 μS). This solution corresponds to the complete mixing of the internal and external aqueous phase and, consequently to 100% of breakdown of the multiple droplets. Therefore, the breakdown of the multiple droplets during the centrifugation/filtration procedure was considered negligible.

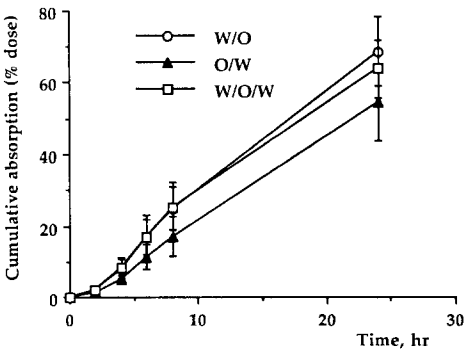

Fig. 1. Percutaneous absorption profiles of metronidazole from o/w, w/o/w and w/o emulsions across hairless rat skin. Values are the means ($n = 6$) ± SD.

It should to be noted that the concentration of metronidazole in the internal aqueous phase was higher than that of the external phase, however, this difference was much smaller than expected. This suggests that the transport of metronidazole across the oil membrane from internal aqueous phase to external phase was rapid and almost reached equilibrium.

3.2. *In vitro percutaneous absorption*

3.2.1. *Metronidazole*

The in vitro percutaneous absorption profiles following application of metronidazole as a finite dose show that the extent of absorption was similar for the three emulsions studied and ranged from 55 to 69% of the applied dose (Fig. 1). However, differences between emulsions deserve comment. The difference between the w/o/w emulsion and the two simple emulsions (o/w or w/o) was not statistically significant, whereas that between the o/w emulsion and w/o emulsion was statistically significant (Table 2). One possible explanation for the slightly greater absorption from the w/o emulsion could be attributed to the

Table 2
Cumulative absorption (% dose) of metronidazole and glucose from emulsions at 24 h

Emulsion	Metronidazole	Glucose
o/w	54.6 ± 10.7 [a]	4.2 ± 1.2 [c]
w/o/w	63.8 ± 8.0 [b]	1.5 ± 0.5
w/o	68.6 ± 9.8	1.0 ± 0.5

[a] Values are significantly different from the w/o emulsion.
[b] Values are not significantly different from the o/w and w/o emulsions.
[c] Values are significantly different from the w/o/w and w/o emulsions.

extent of spreading of this emulsion, while the o/w emulsion remained after application as a discrete droplet. Permeation is proportional to the amount of skin surface area. Furthermore, w/o emulsions are more occlusive.

The comparable absorption found from the emulsions studied is in agreement with the results of the yield of entrapment in the w/o/w emulsion, which showed that the transport of metronidazole across the oil membrane was rapid. The release rate of metronidazole from the formulations to the skin was similar.

3.2.2. Glucose

The percentages of glucose found in the receptor as a function of time are presented in Fig. 2. Total absorption ranged from 1 to 4% of applied dose and was smaller than that observed for metronidazole. At 24 h, the percentage of absorbed glucose from o/w emulsion was 2.8-fold greater than that observed from the w/o/w emulsion and 4-fold that of the w/o emulsion. Absorption from the w/o/w emulsion was greater than that from the w/o emulsion, but this difference was not statistically significant (Table 2). The o/w emulsion showed greater absorption of glucose throughout all the test period.

It is interesting to note that the glucose flux seemed to increase with time for the three emulsion types studied (Fig. 3). This was unexpected since the dose per unit area ($\cong 6$ mg/cm^2) was small and non-steady-state transport with decreasing flux generally characterizes this type of application. However, very little glucose permeated and no exhaustion of the donor compartment was observed. The increase in flux of glucose observed from 8 to 24 h was similar for the three emulsions.

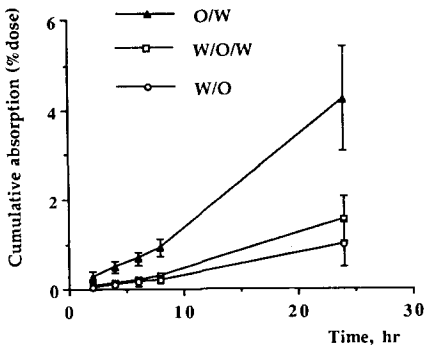

Fig. 2. Percutaneous absorption profiles of glucose from o/w, w/o/w and w/o emulsions across hairless rat skin. Values are the means ($n = 6$) $\pm$SD.

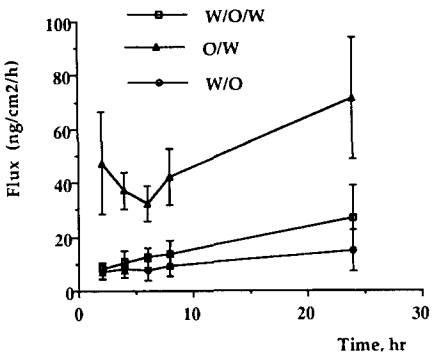

Fig. 3. Glucose flux across hairless rat skin from o/w, w/o/w and w/o emulsions as a function of time.

Since differences between emulsions were observed, it was interesting to study the distribution of glucose within the skin (epidermis and dermis) in order to verify whether the absorption found in the receptor correlated with either drug delivery into or retention in the skin.

The in vitro uptake of glucose into skin from the emulsions at the end of the 24 h test period is presented in Table 3. Upon combining the radioactivity found in the receptor, in the surface, in the epidermis and in the dermis, complete mass balance (90–94%) for glucose was found for the three emulsions studied. The large standard

Table 3
Distribution of glucose (expressed as % dose applied $\pm$ SD) into hairless rat skin 24 h after application of the o/w, w/o/w and w/o emulsions ($n = 6$)

Emulsion	Surface wash	Epidermis	Dermis	Total recovery
o/w	81.0 $\pm$ 5.9	4.8 $\pm$ 1.6 [a]	3.5 $\pm$ 1.1 [b]	93.6 $\pm$ 3.9
w/o/w	82.7 $\pm$ 4.9	8.6 $\pm$ 5.1	1.7 $\pm$ 0.5	94.6 $\pm$ 3.9
w/o	79.8 $\pm$ 8.9	7.3 $\pm$ 3.3	2.4 $\pm$ 1.4	90.5 $\pm$ 6.5

[a] Values are not significantly different from the w/o/w and w/o emulsions.
[b] Values are significantly different from the w/o/w and w/o emulsions.

deviation found in the epidermis obscures statistically significant differences between the emulsions. This variation could be attributed to the procedure used to wash drug from the skin; the rinsing solvent was aqueous and dissolves glucose well, but not the non-volatile residue (paraffin and surfactants). Non-absorbed glucose precipitated or dissolved in this non-volatile residue could be more or less thoroughly removed mechanically by the cotton swab. On the other hand, the amount of glucose found in the dermis seems to depend on the emulsion type. When the o/w emulsion was applied significantly greater glucose delivery was observed in comparison with the w/o/w emulsion. The difference between the o/w emulsion and w/o emulsion was statistically significant at the level $p < 0.1$.

It appears that the greater absorption found in the receptor from o/w emulsion correlates well with the more substantial delivery into the skin. However, for vehicles containing volatile components, the flux of a drug will change as the vehicle evaporates and is expected to be proportional to the concentration of the drug in the vehicle (Chiang et al., 1989). Therefore, differences between the emulsions could equally well be attributed to both the evaporation rate of the volatile components and the structure remaining on the skin after application has ceased (Langlois and Friberg, 1993).

3.3. Evaporation of water

The evaporation loss from the emulsions containing metronidazole is presented in Fig. 4. Surprisingly, the evaporation rate was faster in the w/o/w emulsion than in the o/w emulsion during the first 2 h. This can be attributed, on the one hand, to the rapid loss of outer aqueous phase, which is 20% of the total formulation and, on the other, to the fact that the oil layer on the surface of the aqueous compartments in a variety of w/o/w emulsions is extremely thin. It is well known that the permeation of water, under an osmotic pressure gradient, between the two aqueous phases is dependent on one of the functional properties of the very thin oil layer (Matsumoto, 1987). Furthermore, the area exposed to the atmosphere is an essential factor for the evaporation. In fact, we observed that the spreadability of the w/o/w emulsion on an aluminium sheet was better than that of the o/w emulsion.

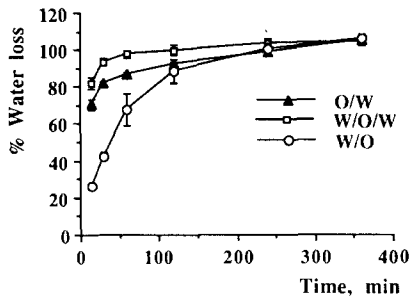

Fig. 4. Evaporation of water from emulsions containing metronidazole as a function of time. The data are expressed as percentage of water loss of the applied amount.

As expected, the water loss from the w/o emulsion was the slowest. However, for the three emulsions studied about 90% of the water had evaporated after 2 h.

The evaporation rate of the emulsions containing glucose is demonstrated in Fig. 5. The rates were essentially similar to those obtained with the emulsions containing metronidazole: evaporation from w/o/w or o/w emulsions was more rapid than that obtained with the w/o emulsion and the water was completely removed in 2 h for the former and in 4 h for the latter. These results are consistent with those obtained by Friberg and Langlois (1992); for a system with a hydrocarbon of low vapor pressure (hexadecane) the rate of

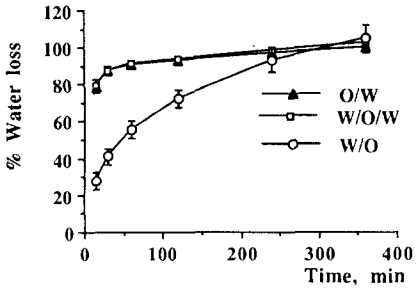

Fig. 5. Evaporation of water from emulsions containing glucose as a function of time. The data are expressed as percentage of water loss of the applied amount.

evaporation was faster from aqueous continuous phase emulsions and a pronounced reduction of the evaporation rate was observed after inversion.

These results are in accordance with those obtained for percutaneous absorption following application of metronidazole as a finite dose. The composition of vehicle applied changes only during the first 2 h of administration and thereafter remains constant throughout the time of percutaneous absorption measurements for the three emulsions studied. For the emulsions containing glucose a similar evaporation pattern was observed for w/o/w or o/w emulsions, while for the w/o emulsion the changes of the vehicle occurred during the 4 h after application. This would explain partially the results of absorption of glucose. The concentration of glucose in the w/o emulsion, taking into account vehicle evaporation, would be at its lowest during the initial hours after application. On other hand, the w/o/w or o/w emulsions presented similar patterns of evaporation but different absorption profiles. This suggests that other factors besides the evaporation rates influenced the absorption kinetics. Thus, it is possible that the structure remaining on the skin surface, after evaporation ceased, was dependent on the emulsion type and played a determining role in the percutaneous absorption of glucose.

3.4. X-ray diffraction

The SAXS patterns on parallel geometry from a control sample of SC are shown in Fig. 6a. Various diffraction arcs are visible on the equator (normal to the SC plane). These arcs have been attributed by Garson et al. (1991) to two different and independent lamellar structures formed by intercellular lipids. The localization of the scattered intensity on the equator indicates that these layers lie preferentially parallel to the SC plane.

The corresponding SAXS pattern of w/o/w emulsion-treated SC is shown in Fig. 6b. The patterns for o/w and w/o emulsions are nearly identical with that of the w/o/w emulsion. Comparison between the patterns is easier when con-

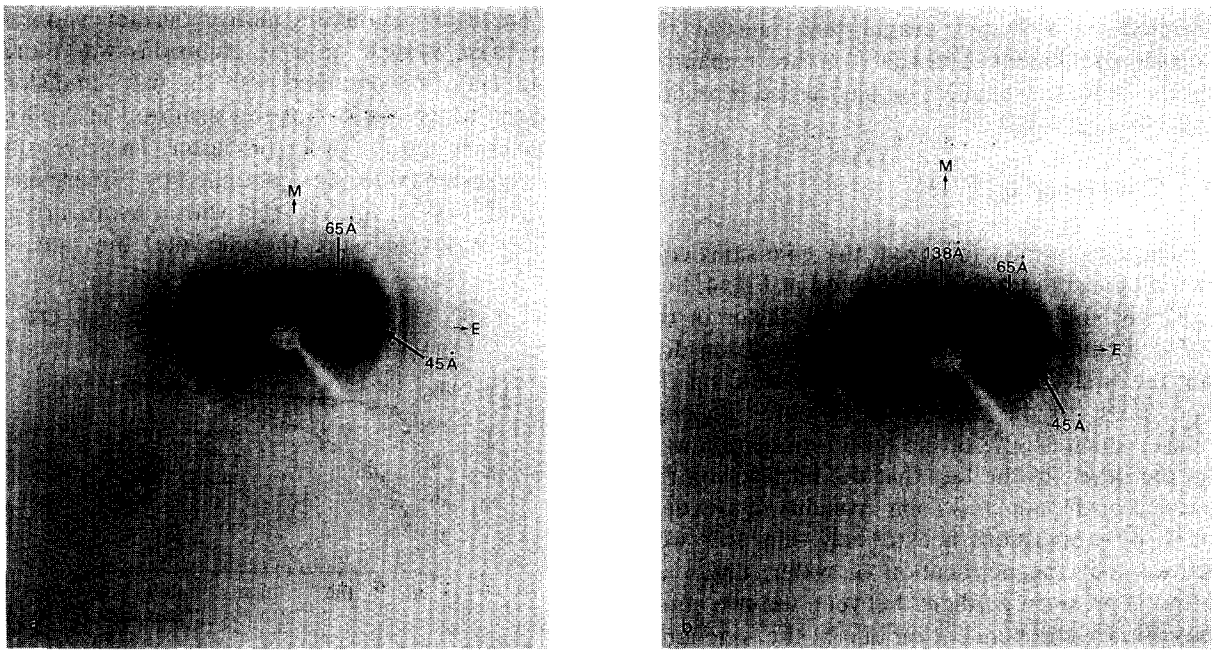

Fig. 6. Small-angle X-ray diffraction patterns in parallel geometry: from control stratum corneum sample (a) and from w/o/w emulsion-treated SC (b); M, meridian; E, equator.

sidering the intensity profiles as shown in Fig. 7. These meridian profiles corresponding to the three emulsions are identical but different from the control SC profile, since they display an additional peak around 138 Å. The origin of this peak is not yet clear. We observed it neither with a hydrated sample nor with the application of the non-volatile residue (paraffin and surfactants). In addition, it did not appear when the emulsions were deposited on an inert support (glass). Consequently, it can be assumed that the appearance of the peak at 138 Å arises from a modification of the SC structure, probably a re-ordering of the intercellular lipid matrix induced by the emulsion form of the preparation. Further investigations are needed to interpret this effect.

It is interesting to note that a reticular distance around 130 Å is not unknown. Bouwstra et al. (1991) observed a reticular distance of 134 Å on human SC after recrystallization and White et al. (1988) showed lamellar diffraction patterns of 131 Å on the SC of hairless mice.

Finally, the WAXS patterns for the emulsion treated SC and the control SC did not display any significant differences. This observation proves that the intralayer lipid organization of SC is not modified by the application of the emulsion. In conclusion, the X-ray diffraction patterns corresponding to the three emulsions do not display any difference, but are somewhat different from the SC control pattern.

Thus, the results of the percutaneous absorption of glucose cannot be explained by the structure remaining on the skin after evaporation from emulsions has ceased. We could not exclude the possibility that the extent of absorption was proportional to glucose sorption into the stratum corneum at early times after application. During evaporation, the amount of glucose released into the SC from the o/w emulsion (where glucose is

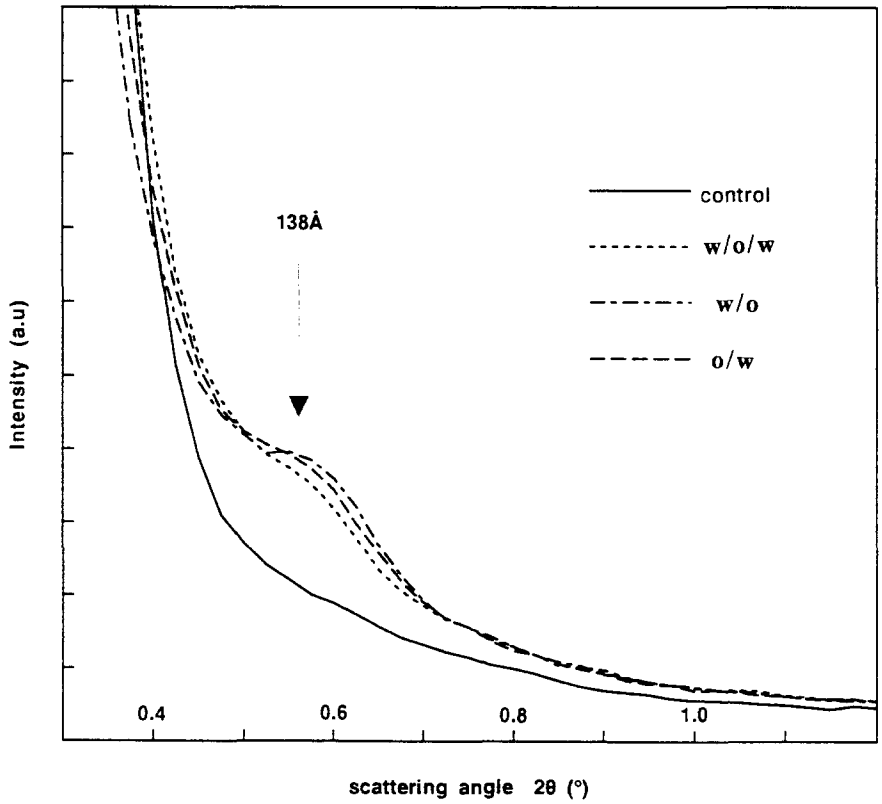

Fig. 7. Scattering curve of the X-ray diffraction patterns from control SC and SC treated with w/o/w, o/w and w/o emulsions.

available) would be greater than that from the w/o/w or w/o emulsion (where glucose is not available). Once evaporation ceased, release of glucose from preparations was similar for the three emulsions. A detailed investigation of the SC as a reservoir for drugs was conducted by Rougier et al. (1990), who demonstrated a correlation between percutaneous delivery and the amount of the drug found in the SC at the end of a 30 min application.

4. Conclusion

The percutaneous absorption of metronidazole and glucose from three emulsion types (o/w, w/o/w and w/o) obtained with the same composition was studied.

When a model hydrophilic drug with intermediate polarity (metronidazole) was considered, its absorption was comparable for the three emulsions studied. The yield of the w/o/w emulsion is in agreement with these results and demonstrated that the transport of metronidazole across oil membrane was rapid.

However, when a model drug of high polarity (glucose) was studied, its absorption was greater from the o/w emulsion than that from the two other emulsions. Differences between the emulsions can be attributed to neither the evaporation rate of water from emulsions nor the structure of the residual film. It is possible that the glucose absorption could be related to the amount sorbed by SC during early times after application.

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