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Research paper

Modified water containing hydrophilic ointment with suspended hydrocortisone-21-acetate – the influence of the microstructure of the cream on the in vitro drug release and in vitro percutaneous penetration

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Abstract

Water containing hydrophilic ointment DAB 1997 was modified by the incorporation of ethanol and the effects of ethanol on the evaporation, the drug liberation and the permeation through human excised stratum corneum were investigated. Creams with 10%, 20%, 30% (v/v) and without ethanol were produced. As a model drug 2% (w/w) hydrocortisone-21-acetate was suspended in the o/w cream. The evaporation of the creams decreased with an increasing amount of ethanol which was unexpected because the vapor pressure of ethanol is higher than that of water. From this result it was concluded that ethanol might be interlamellarly fixed in the mixed crystal of the polyhydrate of the emulsifier to a higher extent than it is distributed within the aqueous bulk phase. In context with the liberation studies, ethanol decreased the drug liberation from the cream. This is in accordance with the above hypothesis of the ethanol partitioning within the cream, because the solubility of the drug in ethanol is higher than that in water. Therefore the interlamellar drug concentration should be higher than the solubility of the drug in the bulk phase, with the assumption that the gel network of the emulsifier polyhydrate is finally responsible for the delay in drug liberation. The permeation through stratum corneum showed no significant differences between the alcohol-free and the alcohol-loaded formulations. Obviously the decrease in drug liberation by ethanol was compensated for by the penetration enhancing effect.

Keywords: O/w creams; Hydrocortisone-21-acetate; Drug liberation; Percutaneous penetration enhancement

1. Introduction

Water containing hydrophilic ointment (WHS) DAB 1997 [1] is often used as a vehicle for the incorporation of drugs. In the present study this cream of oil in water type was modified by the incorporation of ethanol. Ethanol may serve in different ways in o/w creams: (i) as a penetration enhancer [2], (ii) to avoid the need for preservatives [3], (iii) to increase the cooling effect of the cream due to its higher vapor pressure in comparison with water. Creams with an increasing amount of ethanol were manufactured in a closed processing machine [4,5] The creams were composed of 9% Lanette® N, 10.5% paraffin, 10.5% white petrolatum and 70% water or water/ethanol, respectively (Table 1).

As a model drug the creams contained 2% of hydrocortisone-21-acetate, suspended in a micronized state. Glucocorticoids are used in dermatology because of their antiinflammatory effects in treating inflamed skin diseases [6]. The stability of hydrocortisone-21-acetate in the ethanol-loaded creams was described elsewhere [7,8].

A prerequisite for the therapeutic effect desired after application of the formulation on the skin is: (i) the drug liberation from the vehicle and (ii) the percutaneous pene-

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tration of the drug. Since the uppermost skin layer, i.e. the stratum corneum, provides the main barrier for permeation processes [9], it seems reasonable to study the permeation via excised human stratum corneum instead of full thickness skin. This holds especially for corticosteroids, because in vitro permeation studies with full thickness skin have demonstrated an enrichment of the drug in the dermis, which does not take place under in vivo conditions [10].

The aim of the present investigation was the influence of ethanol on drug liberation from these creams and on drug permeation through excised human stratum corneum. Furthermore, the creams were compared with commercial formulations of hydrocortisone-21-acetate.

2. Materials and methods

2.1. Materials

Emulsifying cetostearyl alcohol was used as Lanette N® (Henkel, Düsseldorf, Germany). Liquid paraffin DAB 10 (Mainland, Frankfurt, Germany), white petrolatum DAB 10 (Hansen and Rosenthal, Hamburg, Germany), ethanol 96% (v/v) and hydrocortisone-21-acetate (Synopharm, Hamburg, Germany) were of pharmacopoeial grade. Water was used in bidistilled quality. For comparing the drug permeation with commercial formulations, Ebenol Creme® and Soventol Hydrocortison Creme® were used.

For the preparation of the phosphate buffer (pH 7.4), 2.38 g sodium monohydrogenphosphate and 0.19 g potassium dihydrogenphosphate (Merck, Darmstadt, Germany) were dissolved in 1000 ml water, 0 l mM sodium EDTA was added.

2.2. Manufacturing of the creams

The creams were manufactured with a processing machine (Unguator®, GAKO Konietzko GmbH, Hamburg, Germany) in a specific container which at the same time serves as dispenser for the application [4,5]. The lipophilic compounds – weighed to give 50 g cream – were heated in a microwave oven (Siemens HF0606, München, Germany) at 600 W for 8 min up to 70ºC. Water with a temperature of 70ºC and ethanol with a temperature of 60ºC were combined with the lipophilic phase. Cooling and homogenization were performed in three cycles of 10 min cooling in a refrigerator at 4ºC and 20 s homogenization at 200 rev./min. Homogenization of the drug, which was added after cooling to room temperature was achieved at 2000 rev./min for 2 min.

2.3. Liberation studies

For the liberation experiments a modified Franz cell [11] was used with the cream in the donor compartment and the phosphate buffer as the receiver. Donor and receiver compartment were separated from each other by a siliconized Spectrapore membrane MWCO 6000-8000 (Spectrum Medical Industries, Los Angeles, CA). The experiments were run in triplicate for 8 h. Aliquots were taken from the receiver every 30 min, after 2 h every 60 min and replaced with fresh buffer. To maintain sink conditions, the receiver was substituted completely by fresh buffer after 4 h. The amount of hydrocortisone-21-acetate in the samples was analyzed using a HPLC method.

2.4. Permeation studies

For the preparation of the stratum corneum the method of Kligman and Christophers [12] was used.

The permeation studies were run in triplicate, at least. For the permeation experiments the same modified Franz cell was used as in the liberation experiments with the exception of human stratum corneum as the membrane. For higher mechanical stability the stratum corneum was placed onto a polycarbonate filter of 5 μm pore size (Millipore, Ireland). Every 8 h the receiver phase was substituted by fresh buffer to prevent a chemical deterioration of the drug in the buffer. Samples were taken every 4 h for up to 30 h and analyzed by HPLC.

2.5. HPLC analysis

Analysis was performed by reverse phase chromatography using a column of Hypersil® ODS 5 μm, 250 × 4 mm (Grom, Herrenberg, Germany), the mobile phase was methanol/water (60:40). The HPLC system consisted of a Beckman System Gold Solvent Delivery System 126, an UV detector Beckman System Gold Detector Module 166 (Beckman, München, Germany) and an Autosampler Promis II (Spark, Emmen, The Netherlands). Peak area determination was achieved with Beckman System Gold Software within a range from 25 ng/ml to 2.5 μg/ml.

2.6. Thermogravimetry (TG)

Samples of 5 mg to 10 mg weight were measured in open aluminium pans, a TG 220 with a Data Disk Station 5200 H (Seiko. J-Tokyo) was used in isothermal mode at 32ºC.

Table 1

Composition and mass loss of the creams

	Composition (% w/w)		Mass loss after 20 min
	Water	Ethanol	(%, w/w)
WHS	70	0	47.3%
WHS 10%	60	10	44.0%
WHS 20%	50	20	38.4%
WHS 30%	40	30	34.6%

2.7. Differential scanning calorimetry (DSC)

The samples were measured in sealed aluminium pans, a DSC 220 C with a Data Disk Station 5200 H (Seiko, Tokyo, Japan) was used. The creams were heated from 5ºC to 90ºC with a heating rate of 5ºC/min.

2.8. Solubility of hydrocortisone-21-acetate in the creams

Drug solubility at saturation was determined following Ref. [13]. Increasing amounts of the drug were incorporated into the base. After 3 days of equilibration at room temperature the creams were evaluated for crystals. The lowest drug concentration where crystals could be found was determined as solubility at saturation. Drug-free bases of the commercial creams were kindly provided by the suppliers and treated the same way.

3. Results and discussion

3.1. Evaporation measurements

For comparing the evaporation from the creams an isothermal thermogravimetric (TG) analysis at skin temperature (32ºC) was carried out. As the vapor pressure of ethanol is higher than that of water, a faster evaporation was expected with an increasing amount of ethanol. However, the TG data in Table 1 show that the evaporation from the alcohol-free cream was the fastest. With increasing amounts of ethanol in the creams, the evaporation decreased. Previous investigations on WHS without ethanol have shown that one part of the water is interlamellarly fixed in a mixed crystal of sodium cetylstearyl alcoholsulfate and cetylstearyl alcohol whereas the other part is in the aqueous bulk phase [14]. The exchange of water in WHS by increasing amounts of ethanol from 5 to 30% (w/w) results in macroscopically homogeneous creams of which the microstructure visualized by transmission electron microscopy is the same as that of ethanol-free WHS whereas differential scanning calorimetry reveals a lowering of the transition temperature of the polyhydrate from the crystalline into the molten state and an increase of the respective transition enthalpy [15]. From these findings together with the results presented may be concluded, that the ethanol is not statistically distributed in the bulk phase and the polyhydrate. Instead, ethanol is fixed interlamellarly to a higher extent than it participates in the bulk phase. The interlamellarly fixed ethanol is also not available for the evaporation. Therefore the evaporation decreases with an increasing amount of ethanol.

3.2. Liberation studies

With the drug liberation studies, the influence of increasing amounts of ethanol on the drug liberation from the creams was investigated.

Fig. 1 shows the liberation of hydrocortisone-21-acetate from creams with 2% drug and an increasing amount of ethanol. The highest drug liberation was measured from the alcohol-free cream. The addition of ethanol reduced the liberation of the drug significantly. If the concentration of ethanol in the mixed crystal is higher than that in the bulk phase of the cream, probably more hydrocortisone-21-acetate will also be fixed interlamellarly because the solubility of the drug in ethanol is higher by a factor of 450 than that in water [16]. The mixed crystal works as barrier for the drug release. However, the overall drug solubility at saturation in the cream is not increased by the addition of ethanol but remains constant at 0.001% (w/w) for all creams [17].

3.3. Permeation studies

Drug liberation from a cream is a prerequisite for dermal availability. Additionally, the presence of penetration enhancers has a distinct influence. Ethanol is a typical penetration enhancer [2].

Therefore, the permeation of hydrocortisone-21-acetate through excised human stratum corneum was investigated. The results of the permeation studies are summarized in Fig. 2. Any significant differences between the creams without or with increasing amounts of ethanol cannot be proven. Obviously, the penetration enhancing effect of the ethanol was compensated for the decrease in drug liberation with increasing amounts of ethanol.

For comparing drug permeation from the different hydrophilic creams with commercial formulations, Ebenol Creme® and Soventol Hydrocortison Creme® were included in the study. Both creams are also o/w formulations. They contain just 0.25% hydrocortisone-21-acetate which is only 12.5% of the drug in the creams studied above. Hence, the low concentration of hydrocortisone-21-acetate makes the commercial products non-prescription drugs. Both creams contain penetration enhancers, i.e. propylene glycol [18] in the Ebenol Creme® and 2-propanol [2] in the Soventol Hydrocortison Creme®, respectively. According to the supplier, further ingredients of Ebenol Creme® are cetostearyl alcohol, cetomacrogol 1000, simethicone, diammonium

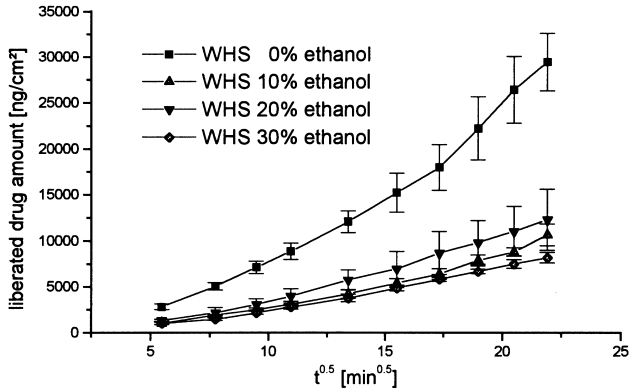

Fig. 1. Liberation of hydrocortisone-21-acetate from the creams with increasing amounts of ethanol (mean ± SD, $n = 3$).

hydrogencitrate, EDTA-sodium salt, potassium sorbate, wool alcohol ointment. The water content is 56% (w/w) determined by thermogravimetry. Transmission electron microscopy revealed oily droplets dispersed in a lamellar network similar to WHS. DSC measurements proved a transition at 56.6°C (onset) with an enthalpy of 5.1 J/g. Probably this transition belongs to the melting of the hydrated gel network (data not shown, see Ref. [17]). Drug solubility at saturation was determined as to 0.005% (w/w).

The composition of Soventol Hydrocortison Creme® is as follows: ammonia, carbomer, liquid wax, isopropyl myristate, macrogol 400, EDTA-sodium salt, liquid paraffin, isopropyl alcohol. purified water and perfume. The water content is 64% (w/w) determined by Karl-Fischer titration and that of isopropyl alcohol is 18% (w/w) calculated from the difference between thermo gravimetrical weight loss and Karl-Fischer titration of water. For Soventol Hydrocortison Creme® no transition could be detected by means of DSC. Transmission electron microscopy revealed oily droplets dispersed in a hydrogel (data not shown, see Ref. [17]). Drug solubility at saturation was determined as to 0.05% (w/w).

Fig. 3 shows the permeation data of these creams in comparison with WHS without ethanol. Although the drug concentration in Soventol Hydrocortison Creme® is only 12.5% of that in WHS, the permeated amount through stratum corneum is about three times higher in comparison with WHS. Drug permeation from Ebenol Creme® is even lower, although the drug concentration in this cream is also 12.5% of that in WHS. The investigations show the distinct vehicle effect on drug permeation through human stratum corneum. Both the colloidal structure of a cream and the presence of penetration enhancers are likely to influence the drug permeation through the skin rather than the total drug concentration in the cream does. Within the commercial creams the saturation limit of the drug dissolved is higher by factor 5 (Ebenol Creme®) and 50 (Soventol Hydrocortison Creme®), respectively, than that in WHS with and without ethanol. Furthermore, for creams with a suspended drug, the saturation limit of the drug dissolved may vary depending on possible interactions with the microstructure of the cream.

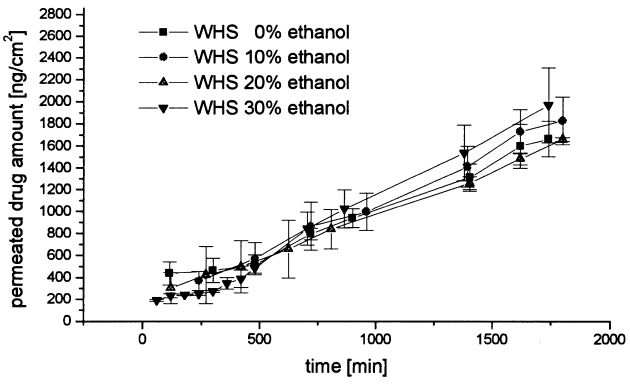

Fig. 2. Permeation of hydrocortisone-21-acetate through excised human stratum corneum from the creams with increasing amounts of ethanol (mean ± SD n = 3–6).

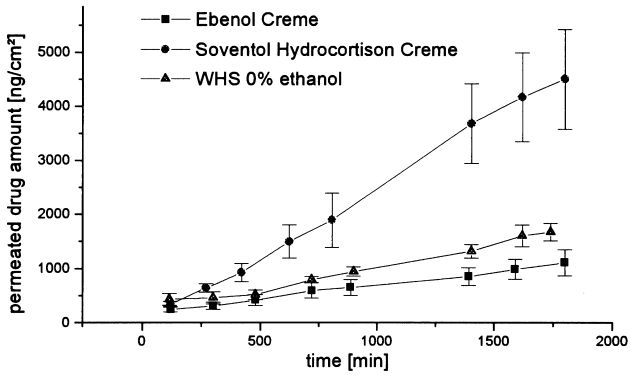

Fig. 3. Permeation of hydrocortisone-21-acetate through human excised stratum corneum from commercial formulations in comparison with WHS (mean ± SD, n = 3–6).

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