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Research paper

# Effect of selected fluorinated drugs in a ''ringing'' gel on rheological behaviour and skin permeation

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**Abstract**

The purpose of the present study was to investigate the influence of different drugs exhibiting different solubility on the viscoelastic properties and on the skin diffusion profile of a ringing gel. In a preliminary rheology study with the placebo gel predominating elastic properties were confirmed and a temperature influence was indicated. Fluconazole, fludrocortisone-acetate, flumethasone-pivalate, flutamide and flufenamic-acid each 1% (w/w) were incorporated into the preparation and oscillatory measurements were performed at temperatures of 25, 28, 32 and 37 °C. In all drug containing formulations a high elastic $G'$ value predominated the viscous $G''$ value. The highest $G'$ value could be obtained with the incorporated flumethasone-pivalate. Additionally in almost all cases the $G'$ values decreased with increasing temperature compared to the placebo gel. Additionally in vitro standard diffusion experiments using Franz-type cells and porcine skin were performed. Following rank order of the cumulative drug release after 48 h was obtained: fluconazole > flufenamic-acid > flumethasone-pivalate > flutamide > fludrocortisone-acetate. Furthermore an excellent chemical stability of all incorporated drugs was confirmed over 10 weeks.


*Keywords:* Fluconazole; Fludrocortisone-acetate; Flumethasone-pivalate; Flutamide; Flufenamic-acid; Skin permeation; Rheology; Chemical stability

## 1. Introduction

For topical treatment of dermatological diseases as well as for skin care a wide array of vehicles ranging from solids to semisolids and liquid preparations are available. A major advantage using various drugs over the dermal or transdermal way is to eliminate negative side effects caused by using chemical drugs on the peroral route. Within the semisolid preparations, the use of transparent gels has expanded both in pharmaceuticals and in cosmetics. One group of very interesting formulations are ''cubic gels'', which might be structurally very closely related to microemulsions. Like microemulsions cubic gels are defined as a dispersion consisting of oil, surfactants, co-surfactants and aqueous phase, which are thermodynamically stable. Microemulsions and cubic gels have several advantages such as enhanced drug solubility, good thermodynamic stability, enhancing effect of transdermal ability over conventional formulations [1]. General forms are gels with a ringing behaviour. On one hand they are interesting because of their colloid-chemical structure, which is accessible only with physical–chemical experiments like small angle X-ray scattering or NMR-self diffusion experiments. On the other hand they are important as dermal drug delivery systems with optimal release characteristics and matrix behaviour. Recently a cubic gel has been characterised by NMR-self diffusion experiments and rheology [2]. In the present paper fluorinated drug candidates were selected, where it will be very easy in further studies to analyse the diffusion coefficients of the drugs with high sensitivity by $F^{19}$ NMR studies.

The aim of the study was to investigate the influence of different lipophilic drugs like fluconazole, fludrocortisone-acetate, flumethasone-pivalate, flutamide and flufenamic-acid on rheology parameters of this cubic gel. Furthermore in vitro skin permeation studies and chemical stability of these selected drugs will be analysed.

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## 2. Materials and methods

### 2.1. Materials

Fluconazole (CAS: 86386-73-4), flufenamic-acid (CAS: 530-78-8), flutamide (CAS: 13311-84-7) and flumethasone-pivalate (CAS: 2002-29-1) were purchased from Kemprotec (UK). Fludrocortisone-acetate (CAS: 514-36-3) was purchased from Sigma–Aldrich (St. Louis, USA). Polyoxyethylene-5-cetyloleylether and polyoxyethylene-10-cetyloleylether were kindly donated by Cognis (Düsseldorf, Ge). All other chemicals used were of analytical reagent grade and used as received without any further purification.

### 2.2. Formulations

The formulation was prepared by mixing 1.5 g of the surfactant mixture of polyoxyethylene-5-cetyloleylether and polyoxyethylene-10-cetyloleylether (1 + 1), 2.75 g of water and 0.8 g of paraffin liquid as the oily component at temperatures up to 70–80 °C. A clear semisolid stable very elastic ''ringing'' gel was formed [2].

The fluorinated drugs fluconazole, fludrocortisone-acetate, flumethasone-pivalate, flutamide and flufenamic-acid (each 1% w/w) were incorporated into the systems.

For the formulations with fluconazole, flutamide and flufenamic-acid transparent highly viscous formulations were built up. For fludrocortisone-acetate and flumethasone-pivalate a turbid but also highly viscous ringing gel formulation was built up.

### 2.3. Rheological measurements

Oscillatory shear experiments were performed on a Haake rheometer Rotovisco RT20 (Haake, Karlsruhe, Germany, thermo controller Haake F6/8). The rheometer tool was a thermostatically controlled tool with a 20-mm diameter plate/plate (PP20/Ti). The experiments were performed at four temperatures 25, 28, 32 and 37 °C. The sample amount was between 0.5 and 1 g. By this modus the induced response is measured (strain) when a sinusoidal stress is applied to the sample. After the identification of the linear viscoelastic region, samples were investigated over a frequency of 0.1–10 Hz. The parameters obtained were the complex modulus $G^*$ consisting of the elastic modulus $G'$ and the viscous modulus $G''$, $\tan\delta$, and $\omega$ the angular velocity of oscillatory stress. According to their correlations the parameters are calculated by:

$$G' = G * \cos(\delta)$$
$$G'' = G * \sin(\delta)$$
$$\tan\ \delta = G''/G'$$
$$\omega = 2\pi\nu$$

The measurements were performed in triplicate. The values in the figures are average values of three experiments.

### 2.4. Solubility in the acceptor medium

Of each drug the solubility in 0.012 M phosphate buffer (pH 7.4) was analysed. Therefore an excess of each drug was added to the buffer and stirred by a magnetic bar for 24 h at room temperature. Afterwards a filtration through a Minisart RC4 filter was performed and 20 μl of the filtration was injected into the HPLC system.

The experiments were performed in triplicate.

### 2.5. Skin preparation

Porcine abdominal skin was shaved and then prepared with a dermatome (GB 228R, Aesculap) set at 1.2 mm. The skin was stored in a freezer at −20 °C until use. Two hours prior to the experiment the samples were thawed.

### 2.6. Diffusion cell preparation

Permeation studies for the investigated drugs were performed using Franz-type diffusion cells having a permeation area of about 1 $cm^2$. The receptor compartment was filled with 2 ml of 0.012 M phosphate buffer (pH 7.4). Excised skin was mounted in the cell, stratum corneum uppermost, with the dermal side facing the receptor compartment. The diffusion cells were thermostated at skin surface temperature of 32 °C and stirred by magnetic bars. At defined time intervals 200 μl (2, 4, 6, 8, 24, 28, 32 and 48 h) was removed for analysis and replaced with fresh acceptor medium. Approximately 0.6 g of each formulation was applied. Three parallel experiments were performed for each formulation.

### 2.7. Chemical stability

From each drug containing gel formulation stability studies were performed. All formulations was stored in tubes under room temperature for 10 weeks. The drug amounts were analysed at the day of preparation (starting point) and afterwards weekly.

About 10 mg of the formulation were dissolved in 1 ml of methanol and vigorously shaken for 60 min. Then the solution was centrifuged for 6 min (3000*g*) and afterwards 20 μl was injected into the HPLC system.

### 2.8. HPLC analysis

All samples were quantified for their drug content by HPLC (Perkin-Elmer, US) consisting of an automatic auto sampler ISS-200, a pump and a UV-diode array detector. For all drugs the stationary phase was a Nucleosil 100 – 5C18 column (240 mm × 4 mm; ARC-Seibersdorf Austria).

At least eight different standard solutions per drug in the mobile phase were prepared and calibration curves were calculated on the basis of peak area measurements using standard samples. They were generated with a correlation coefficient between 1.0 and 0.9996 for all drugs.

#### 2.8.1. Fluconazole

For the quantification of fluconazole we used a modified method described by [3]. The mobile phase consisted of 0.012 M phosphate buffer (pH 7.4) and methanol (55:45 v/v) and 1 mmol octanesulfonic-acid. The detection wavelength was 260 nm and the flow rate was 1.0 ml/min. The retention time was ≈5.60 min. The concentration range of the standard solution for fluconazole was between 15.23 and 121.9 μg/ml.

#### 2.8.2. Fludrocortisone-acetate

For the quantification of fludrocortisone-acetate the mobile phase consisted of acetonitrile and water (40:60 v/v) as described by [4]. The detection wavelength was set at 240 nm and the flow rate was 0.8 ml/min. The retention time was ≈12.10 min. For fludrocortisone-acetate the concentration range of the standard solution was between 3.00 and 133.65 μg/ml.

#### 2.8.3. Flumethasone-pivalate

For the quantification of flumethasone-pivalate a previously reported method was used [5]. The mobile phase consisted of acetonitrile and water (40:60 v/v) and the detection wavelength was set at 240 nm. The flow rate was 1.0 ml/min and the retention time was ≈6.20 min. The concentration range of the standard solution was between 0.92 and 103.63 μg/ml.

#### 2.8.4. Flutamide

The mobile phase consisted of acetonitrile, methanol and water (30:25:45 v/v/v) and the detection wavelength was 300 nm as described by Leibinger [6]. The flow rate was set at 0.5 ml/min and the retention time was ≈20.18 min. For flutamide the standard concentration range was between 1.53 and 96.24 μg/ml.

#### 2.8.5. Flufenamic-acid

For the quantification of flufenamic-acid the mobile phase consisted of methanol, water and glacial acid (80:20:1 v/v/v). The detection wavelength was set at 245 nm, the flow rate was 1.0 ml/min and the retention time was ≈6.15 min. The concentration range of the standard solution was between 1.32 and 76.5 μg/ml.

### 2.9. Statistical data analysis

Results are expressed as means of at least three experiments ± SD. Statistical data analysis was performed using the $t$-test with $P < 0.05$ as a minimal level as significance.

## 3. Results

### 3.1. Formulations

The gels with fluconazole, flutamide and flufenamic-acid were transparent and semisolid, whereas the gels with flumethasone-pivalate and fludrocortisone-acetate exhibited a significant turbidity. All formulations showed a ''ringing'' effect.

### 3.2. Solubility

The solubility of the selected drugs was analysed in phosphate-buffer (pH 7.4) which is the most commonly acceptor fluid. In order to obtain sink conditions, the solubility in the acceptor medium was analysed and presented in Table 1. As a general rule, the concentration of the permeant should not be allowed to exceed 10% of saturation solubility [7].

### 3.3. Rheological investigations

Temperature can largely influence the viscoelastic properties of cubic phase systems [8]. In order to determine the temperature influence on the viscoelastic properties first changes in the ratio of viscous and elastic properties of the placebo gel were investigated with increasing temperature (Fig. 1). From the aspect of rheology, $\tan\delta$ is defined as $G''/G'$. As seen, the elastic modulus of the samples is dominating due to $\tan\delta$ far below 1. Attention should be paid to the fact that $\tan\delta$ is almost independent of the shearing frequency, which is completely different from results at the moderate and high temperatures. The result demonstrates a dominant elastic behaviour exhibiting strong crystal like properties of the cubic gel at the investigated temperatures. This is confirmed by a recent publication on a similar gel [8]. Except at the temperature of 37 °C the shape of the curves from 15 to 32 °C is very similar. One reason for the difference at 37 °C might be the approximation to the melting point of the cubic gel.

Next step should be the rheological investigations of the drug containing gels in terms of $G'$ and $G''$ at 25, 28, 32 and 37 °C compared to the placebo gel. In Fig. 2(A–F) the influence of the incorporated drugs on $G'$ and $G''$ at different temperatures is presented. Although only 1% (w/w) of model drugs was incorporated, significant differences in the elastic modulus $G'$ and viscous modulus $G''$ were observed compared to the placebo gel. The temperature exhibited an influence mainly on the elastic behaviour. One would expect a decrease of $G'$ as well as of $G''$ with increasing temperature, however the placebo gel (Fig. 2F) showed an increasing $G'$ until 32 °C and then a ''one third'' decrease of $G'$ at 37 °C compared to $G'$ at 32 °C.

Table 1
Saturation solubility of fluconazole, fludrocortisone-acetate, flumethasone-pivalate, flutamide and flufenamic-acid in mg/ml 0.012 M phosphate buffer (pH 7.4); $n = 3$

| Drug | Solubility ± SD (mg/ml) |
|---|---|
| Fluconazole | 5.961 ± 0.398 |
| Fludrocortisone-acetate | 0.026 ± 0.008 |
| Flumethasone-pivalate | 0.053 ± 0.001 |
| Flutamide | 0.020 ± 0.001 |
| Flufenamic-acid | 1.536 ± 0.026 |

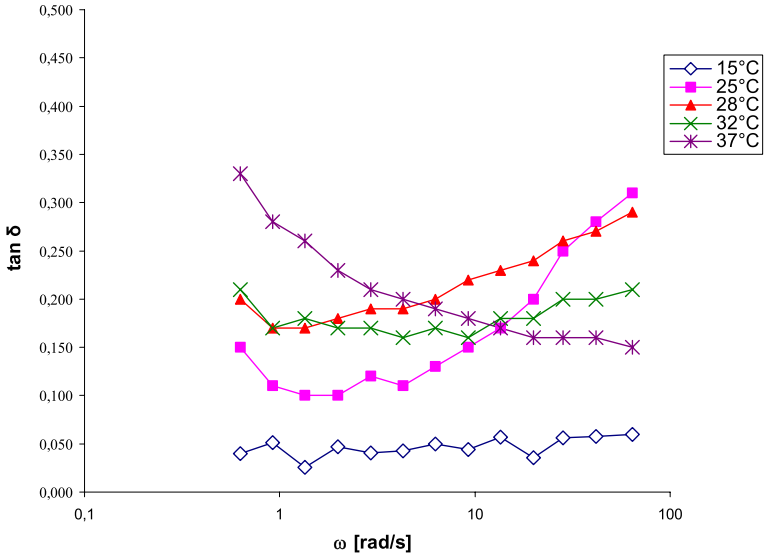


Fig. 1. Tan $\delta$ ($G''/G'$, the ratio of viscous and elastic components) as function of temperature and shear frequency for the cubic placebo-gel. Indicated values are means (±SD) of three experiments.

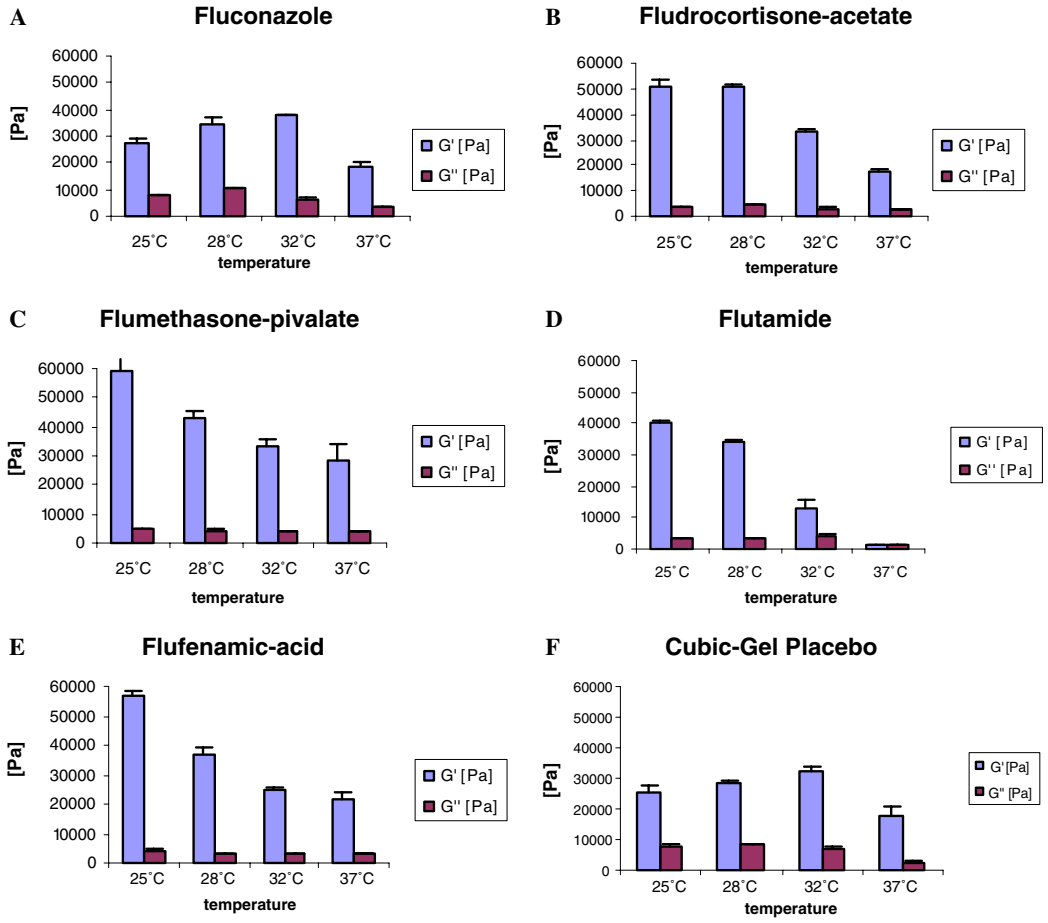


Fig. 2. (A–F) Comparison of the elastic modulus $G'$ and viscous modulus $G''$ of the drug containing cubic gel (each 1% drug) to the placebo gel at 25, 28, 32 and 37 °C measured at 10.2 Hz. Fluconazole (A), fludrocortisone-acetate (B), flumethasone-pivalate (C), flutamide (D), flufenamic-acid (E), placebo gel (F). Indicated values are means (±SD) of three experiments.

The pattern of the block-diagrams (Fig. 2A–F) shows no influence of fluconazole on the $G'$ values compared to the placebo gel. This indicates only a little interaction between the incorporated drug and the microstructure of the gel. On the other hand fludrocortisone-acetate, flumethasone-pivalate, flutamide and flufenamic-acid caused increased

$G'$ values at all tested temperatures compared to the placebo gel (Fig. 2F).

The highest $G'$ values at 25 °C were $5.9 \times 10^5$ and $5.7 \times 10^5$ Pa at 10.2 Hz measured with flumethasone-pivalate and flufenamic-acid, respectively. This fact implies a significant interaction of the incorporated drug with the microstructure of the cubic gel system. However, with further increase of the temperature the $G'$ value of fludrocortisone-acetate, flumethasone-pivalate and flufenamic-acid decreased to a value in the range of $G'$ of the placebo gel. At skin temperature of about 32 °C the gel with incorporated flutamide exhibited a different influence. In this case the $G'$ value of the flutamide gel showed the lowest $G'$ in comparison to the placebo gel. Moreover the elastic $G'$ and viscous $G''$ value decreased further at 37 °C and have about the same viscous and elastic properties. This behaviour might be due to the vicinity to the melting point of the gel-system. This is in agreement with literature data [8].

Regarding the viscous $G''$ values an influence of the drugs could be observed too. The $G''$ values of fluconazole-gels are in the same range as the $G''$ values of the placebo gel, whereas the $G''$ values of fludrocortisone-acetate-gels, flufenamic-acid-gels and fludrocortisone-acetate-gels were significantly lower.

### 3.4. Skin diffusion

The release data obtained in the present work are presented in Fig. 3. As shown in Fig. 3 the cumulative permeation rates of fludrocortisone-acetate, flumethasone-pivalate and flutamide are nearly in the same range between 9 and 19 μg/cm$^2$ after 48 h of diffusion and were not significantly different. Whereas the cumulative amount released of flufenamic-acid is about 21-fold higher after the same diffusion time. Interestingly the lag time was about 10 h in these four cases. For fluconazole the highest cumulative permeation rate was measured, which could be expected from the solubility data in the acceptor medium (Table 1). The amount was about 6-fold higher compared to the tested flufenamic-acid and about 125-fold higher compared to the other tested drugs.

### 3.5. Chemical stability

The chemical stability of fluconazole, fludrocortisone-acetate, flumethasone-pivalate, flutamide and flufenamic-acid is presented in Fig. 4. As indicated there was no significant decrease of the drug amount in the presented gel during the whole observation period. Moreover on the HPLC-chromatograms no degradation products could be detected. Beside this, the visual observation of all formulations showed no signs of microbial contamination.

## 4. Discussion

A transparent "ringing gel" consisting of surfactants, paraffin oil and water has been used as vehicle in order to investigate in vitro skin permeation-studies, chemical stability and rheological behaviour of selected different fluorinated drugs fluconazole, fludrocortisone-acetate, flumethasone-pivalate, flutamide and flufenamic-acid.

Incorporation of drug in cubic phase can cause phase transformation to lamellar or reversed hexagonal phase depending on the polarity and concentration of the drug, which may affect the release profile [9]. Depending on the physicochemical properties of the drug, it may reside in the lipid bilayer or the aqueous channels of the gel and the location of the drug in the gel may influence its release [9].

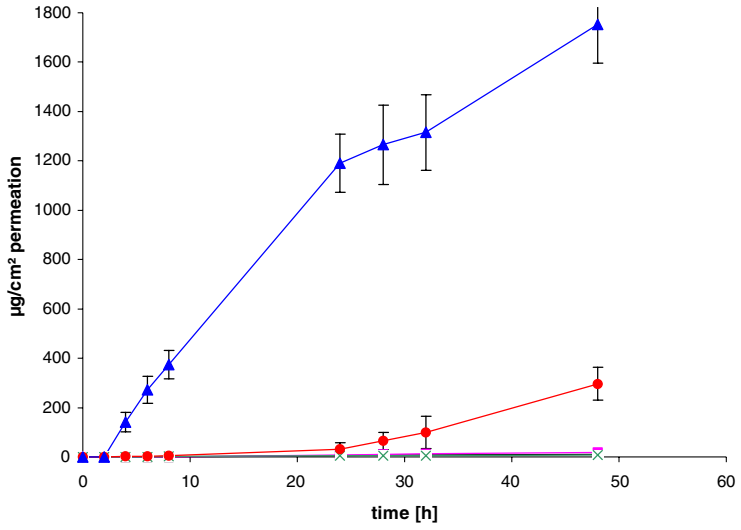


Fig. 3. Skin diffusion profiles of fluconazole, flufenamic-acid, fludrocortisone-acetate, flumethasone-pivalate and flutamide through porcine skin in μg/cm$^2$ over 48 h of diffusion. Fluconazole (♦), flufenamic-acid (●), fludrocortisone-acetate (▲), flumethasone-pivalate (■) and flutamide (×). Indicated values are means (±SD) of three experiments.

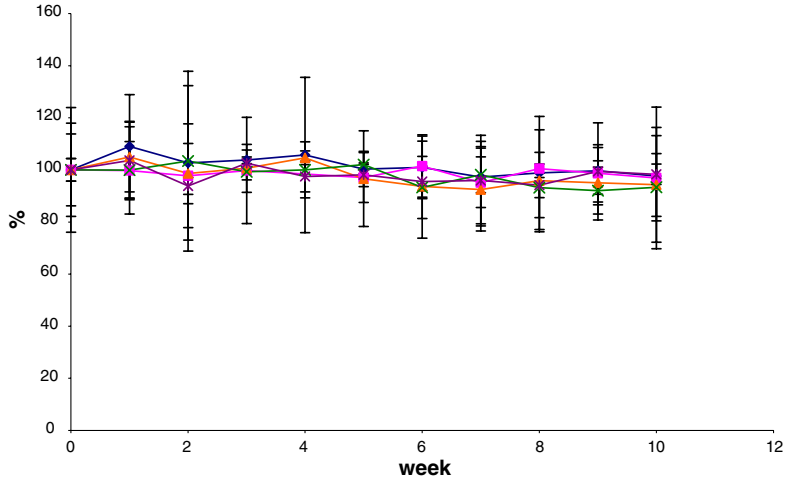


Fig. 4. Drug amount of fluconazole (♦), flufenamic-acid (●), flutamide (×), flumethasone-pivalate (■) and fludrocortisone-acetate (▲) in % (w/w) incorporated in the cubic-gel over an observation period of 10 weeks. Indicated values are means (±SD) of three experiments.

As already described in other reports gel microemulsions are good vehicles for fluconazole drug delivery [10]. These results could also be confirmed by our studies. Therefore for fluconazole an orally active antifungal agent which is used in the treatment of superficial and systemic candidiasis and in the treatment of cryptococcal infections the presented cubic gel showed excellent vehicle properties. The released cumulative amount of fluconazole from the presented cubic gel was even higher compared to a similar gel microemulsion described in another publication [10], where mice skin was used, which is known as much more permeable compared to porcine skin [11].

Regarding the lipophilic nonsteroidal anti-inflammatory flufenamic-acid with potent anti-inflammatory and analgesic effects mediated by the inhibition of prostaglandin synthesis the presented cubic gel showed also excellent vehicle properties. For the corticosteroid fludrocortisone-acetate, which is commercially available in compressed tablets [4] the cumulative amount released was in the same range as the mostly dermal used flumethasone-pivalate. Fludrocortisone-acetate is currently used for the treatment of several diseases from endocrine and non-endocrine origin [12]. For flumethasone-pivalate a difluorinated corticosteroid with anti-inflammatory and vasoconstrictive properties available in products like Locacorten®, Vioform®, etc., the cubic gel might be a possibility for a new drug vehicle.

Another agent with a hair growth potential is the nonsteroidal anti-androgen flutamide. This drug was introduced as a new potent compound for treatment or prostatic carcinoma. The systemic administration of flutamide causes several unwanted side effects, such as reducing libido and impairing spermatogenesis in men and feminizing male fetuses in pregnant women. Topical administration, therefore, is an important goal for such a drug, especially if indicated for skin disorders [13]. The release studies of flutamide from the cubic gel showed reasonable but lower skin permeation compared to a previous published report [13] where phosphate buffer and ethyl alcohol were used as acceptor medium. This additive could be one of the reasons for the higher cumulative released amount of flutamide to our results.

To explain a probable mechanism by which cubic gels, structurally closely related to microemulsions, enhance the release and percutaneoeus absorption of drugs efficiently, the histological and histochemical structure of the stratum corneum must be taken into consideration.

A dermally applied microemulsion is expected to penetrate the stratum corneum and to exist intact in the whole horny layer, altering both the lipid and the polar pathways [10]. The lipophilic domain of the cubic gel can interact with the stratum corneum in many ways. The drug dissolved in the lipid domain of the microemulsion can directly partition into the lipids of the stratum corneum, or the lipid vesicles themselves can intercalate between the lipid chains of the stratum corneum, thereby destabilizing its bilayer structure. These interactions will lead to increased permeability of the lipid pathway to the drugs.

On the other hand, the hydrophilic domain of the cubic gel can hydrate the stratum corneum to a greater extent, and plays an important role in the percutaneous uptake of drugs. When the aqueous fluid of the cubic gel enters the polar pathway, it will increase the interlamellar volume of the stratum corneum lipid bilayers, resulting in the disruption of its interfacial structure. Since some lipid chains are covalently attached to corneocytes, hydration of these proteins will also lead to the disorder of lipid bilayers. Similarly, swelling of the intercellular proteins may also disturb the lipid bilayers; a lipophilic penetrant can then permeate more easily through the lipid pathway of the stratum corneum.

In fact, no such mechanism could be considered in explaining the superiority of the microemulsion or cubic gel over the other vehicles, but the combined effect of both the lipophilic and hydrophilic domains was responsible for its enhancing activity [10].

But not only the excellent vehicle properties of the cubic gel might be an advantage, but also the high chemical stability of the incorporated drugs could be an important factor for using the cubic gel as drug delivery system. As mentioned in earlier reports the chemical stability of various drugs incorporated in this new gel formulation was very high [14]. This could also be confirmed by our studies. High chemical stability of the model drugs could be obtained over the whole observation period. However, the here investigated drugs showed also good chemical stability properties in other matrices like tablets, solutions and powders [4,10,15].

As mentioned above as well the chemical structure of the incorporated drugs as the temperature has an important effect on rheological behaviour of the microstructure of the cubic gel. At moderate temperature, the rheological properties and inner structure of cubic liquid crystal change hugely. Furthermore, the influence of the incorporated drugs on the viscoelastic properties was dependent on their chemical structure and can probably be related to the micro-structure of the cubic gel. This effect might be confirmed also by the low aqueous solubility of the model drugs. As mentioned above the cubic gel with the incorporated flumethasone-pivalate and fludrocortisone-acetate exhibited a significant turbidity. This could be an indication that drug particles may be suspended in the aqueous component of the gel, which might influence the elastic behaviour of the gel system. This fact could be a reason for the high elastic $G'$ of those two incorporated drugs. Therefore additional biophysical experiments like micro-DSC and NMR-self-diffusion experiments are in progress to specify more the changes in liquid crystalline microstructure and molecular movement.

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