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Thermoanalytical method for predicting the hydration effect permanency of dermal semisolid preparations

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Abstract Our aim was to develop potential dermal drug delivery systems (DDSs) with a good and lasting moisturizing effect. Lyotropic liquid crystals (LLCs), gel-emulsions and hydrogels were investigated by means of thermogravimetry, which can give information about the structure of these preparations, and we could study the water binding mechanisms indirectly in them. We found that the preparations with a complex structure and strong water bonds hydrate the skin well and lastingly by in vivo tests. Since the thermoanalytical results correlate with the in vivo test results, this method could be suited for predicting the moisturizing effect of the vehicles and provide the possibility to select the potential semisolid DDSs for in vivo tests cost and time effectively.

Keywords Gel-emulsion · Lyotropic liquid crystal · Skin hydration · Thermogravimetry · Water bond

Introduction

Thermoanalytical examinations have an increasingly greater role in the structural investigations of different pharmaceutical substances and dosage forms, especially in the case of solid dosage forms, but they have also been used successfully in the examination of semisolid systems [1–4].

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Thermogravimetry allows verifying the microstructure of various semisolid preparations [lyotropic liquid crystals (LLCs), gel-emulsions, hydrogels] through studying indirectly the water binding mechanisms in them [5]. This property is very informative in predicting at what rate they can release their water content [6]. By this analytical method, different forms of incorporated water (free, bulk, bound and interlamellar) could be detected, which were delivered from the preparations in different times, ensuring longer hydration on the skin. The knowledge of the proportion of various types of water is also important to get information about the structure, which has a strong effect on drug release from pharmaceutical formulations [7, 8].

Our study had multiple aims: (1) to develop semisolid dermal drug delivery systems (DDSs) with a good moisturizing effect which do not increase the transepidermal water loss (TEWL); (2) to examine the structure of our new developed preparations and their water binding mechanisms by thermogravimetric measurements; (3) to perform in vivo hydration and TEWL tests; (4) to find a connection between the moisturizing effect of the developed preparations and their structure. The studied samples were LLCs [9], gel-emulsions [10] and hydrogels.

Experimental

Materials

Lyotropic liquid crystals (LLCs) contained polyethoxylated 40 hydrogenated castor oil (BASF, Cremophor RH40 official in USP/NF) as emulsifier (Table 1). The water phase of the systems was purified water (Ph.Eur.6.), the oil phase was isopropyl miristate (Ph.Eur.6.). In our experiment we developed lamellar LLCs because their structure

Table 1 Compositions of the studied preparations

Components/%	LLC1	LLC2	Oil-free PTR1 gel	PTR1 gel-emulsion	PA gel	PA oil dispersion
Purified water	30	10	99.7	69.7	95	85.5
Isopropyl miristate	10	60				
Miglyol 812			0	30	0	10
Cremophor RH40	60	30				
PTR1			0.2	0.2		
Trolamine			0.1	0.1		
PA					5	4.5

demonstrates the greatest similarity to the lipid bilayer of the stratum corneum (SC). LLCs are expected to be ideal dermal vehicles with the ability to integrate into the structure of the SC and restore it [11].

Gel-emulsions were prepared with the use of the polymeric emulsifier Pemulen™ TR1 (PTR1) (Noveon, USA), which served as an emulsifier and a gel-forming agent, too. This is a cross-linked block copolymer of poly(acrylic acid) and hydrophobic long-chain methacrylates. It is able to stabilize o/w emulsions because its short lipophilic part integrates into the oil droplets whilst its long hydrophilic part forms a micro-gel around the droplets arresting their fusion. The aqueous phase was purified water, the oil phase was neutral oil (Ph.Eur.6., Miglyol 812). The neutralizing agent was trolamine (Ph.Eur.6.).

For the formulation of hydrogels 1,2-propandiol-alginate (PA) and purified water were used. In order to ascertain whether oil as an occlusive ingredient has an influence on skin hydration, we investigated LLCs containing 10% and 60% of oil, we formulated an oil-free and an oil-containing system with PTR1, and as PA is ready to incorporate a small amount of oil without added surfactant, PA oil dispersion was also prepared.

Methods

In vivo skin tests

Fifteen healthy subjects (11 females and 4 males) of ages between 22 and 51 years without any known dermatological diseases or allergy participated in the experiment. Informed consent was obtained from all volunteers and the study was approved by the local ethics committee. During the test period, the subjects were not allowed to use any other skin care products on their hands. To prove the standard circumstances, all the skin tests were performed after the adaptation of the volunteers to room conditions (30 min at 23–25 °C and 40–50% RH). During the experiment, the samples were applied on the dorsal hand of all the subjects. Electrical capacitance, indicating the hydration level of the SC, was determined by Corneometer® CM 825. TEWL was evaluated as an indicator of skin barrier integrity using Tewameter® TM 300 (all devices by Courage and Khazaka Electronic GmbH, Cologne, Germany) [12–14]. The electrical capacitance of the SC and the TEWL value were determined before and after the sample application. The measured values were compared with the values detected on the non-treated skin, the changes in moisturizing level and in TEWL were expressed in percentage [15, 16].

Thermoanalytical measurements

The thermogravimetric analysis was carried out using a MOM Derivatograph-C (MOM GmbH, Hungary) instrument. Samples were weighed (40–50 mg) in platinum pans (No.4). The reference was an aluminium oxide containing pan. Two types of measurements were performed. At a slow heating rate the samples were heated from 25 to 120 °C at 1 °C min^{-1}, at a fast heating rate the systems were heated from 25 to 200 °C at 10 °C min^{-1}. TG (mass loss % versus temperature) and derivative TG (DTG) curves were plotted. Each study was repeated three times.

Results and discussion

During the investigation with derivatograph, the samples lost water due to heating, the TG curves show this weight loss. In the case of the fast heating rate they could be divided by the DTG curves into sections, which indicate different types of water spaces. More peaks could be distinguished in the DTG curves of the preparations with a complex structure (LLCs, PTR1 gel-emulsion, PA emulsion) (Fig. 1), where the water is supposed to be bound through various binding mechanisms. One peak may correspond to free water at about 100 °C, which is able to diffuse to the surface at a faster rate than the evaporation process itself, hence the process represents free surface evaporation. The other peak at about 140 °C may correspond to the residual water being strongly bound within the system [7]. Besides the free water, the LLCs also contain

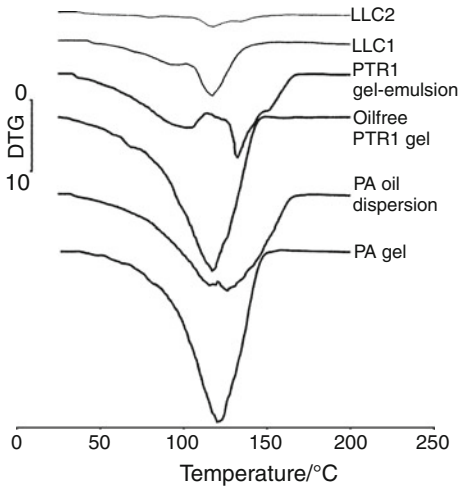

Fig. 1 The DTG curves of the investigated preparations (water distribution)

interlamellar water incorporated between the hydrophobic layers. The PTR1 gel-emulsion has a special structure, a part of the water is in a very strong bond around the oil droplet (micro-gel water), which is indicated by the second DTG peak, whilst in the PTR1 and PA gel the entire amount of water is bound but not so strongly as in the PTR1 gel-emulsion and PA oil dispersion, which is shown by the only DTG peak at 120 °C.

From the measured weight loss it was calculated how many percents of water evaporated from the preparations in the specified temperature ranges (Fig. 2a). It could be established clearly that the samples with more differentiated curves deliver the differently bound water in several steps, resulting in a lasting moisturizing effect.

It could be observed that the oil-containing PTR1 gel-emulsion, PA oil dispersion and the higher oil-containing LLCs hold approximately 5% water even over 150 °C. They have a significantly better water binding capacity than the oil-free samples. The reason for it could be that the oil arrests the evaporation. The occlusive effect of the oil was proved by corneometric measurements on the human skin, too, as the oil-containing PTR1 gel-emulsion and the PA oil dispersion showed a better moisturizing effect than the oil-free samples (Fig. 2b).

In order to examine the whole water content of the systems, a slow heating rate was used. A tangent was fitted to the TG curve in the peak of the DTG curve. From the slope of this tangent the maximum evaporation speed (MES) (mg/min) could be calculated. The steeper the curve is the faster the moisture evaporates from the preparation.

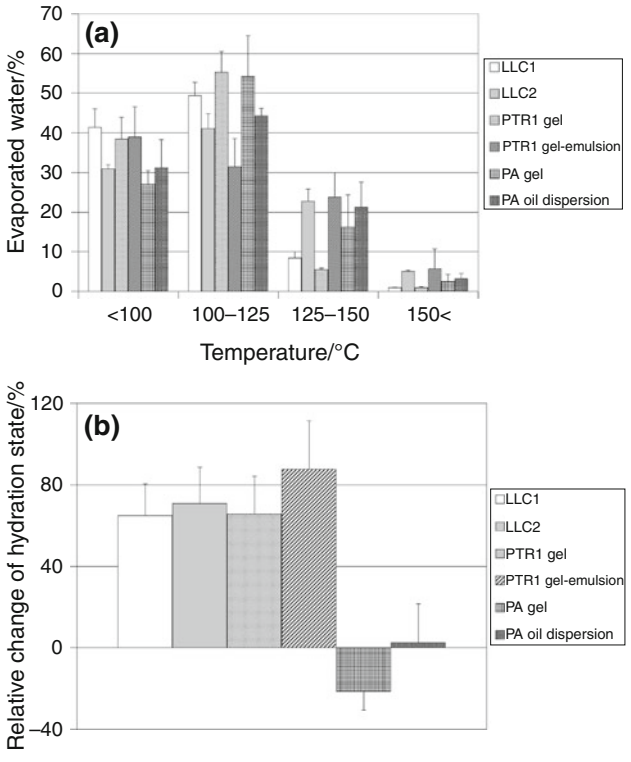

Fig. 2 **a** Percentage weight loss values over specified temperature ranges. **b** Mean values of the changes in the skin hydration of the volunteers

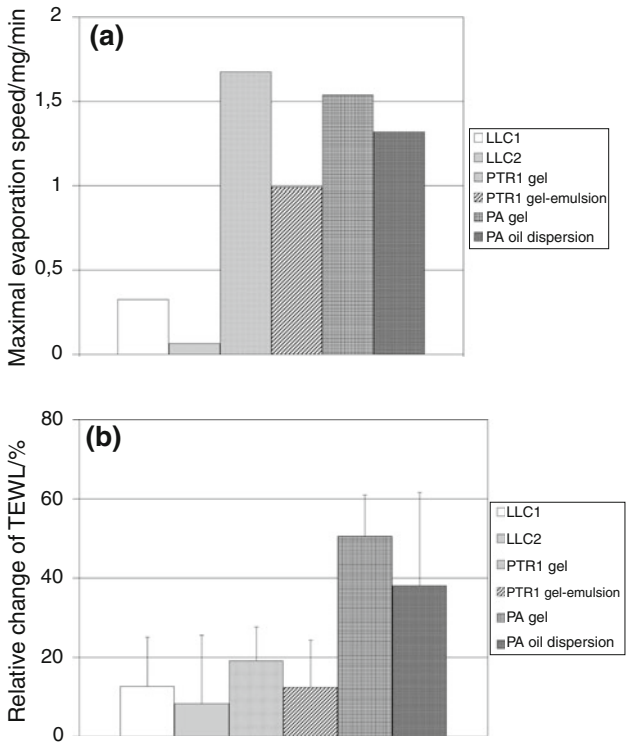

Fig. 3 **a** The MES of the investigated samples. **b** Mean values of the changes in the TEWL

The lowest MES shows the LLCs (Fig. 3a) and the least TEWL was also found in the case of the LLCs (Fig. 3b). The reason for it could be, on one hand, their lamellar structure with strong water bonds. Namely, they contain a major proportion of incorporated water concentrated in the layers between the hydrophilic domains. On the other hand, their lamellar structure is very similar to the human SC lipid bilayer, thus they are able to integrate into the structure of the skin and to restore its barrier function, arresting the TEWL [17].

A remarkable difference was found between the oil-containing and oil-free samples with respect to MES and TEWL changes. This could be explained with the more complex structure of the oil-containing PTR1 gel-emulsion and PA oil dispersion, which is made possible by the presence of water bound with different strengths in these preparations.

Conclusions

The ideal semisolid dermal drug delivery system ensures a good, lasting moisturizing effect and retards the evaporative water loss. It can be concluded from the results of our investigations that the oil-containing systems with a complex structure (LLC1, LLC2, PTR1 gel-emulsion) satisfy these requirements the most. The reason for their excellent moisturizing effect can be, on the one hand, that oil as an occlusive ingredient forms a protecting film on the skin surface, thereby arresting water loss. On the other hand, thanks to their complex structure (lamellar, micro-gel structure), they have a strong water binding capacity and they can deliver the differently bound water in several steps. These observations were also supported by thermogravimetric measurements as well as by corneometric and TEWL measurements on healthy volunteers. The results of the in vivo moisturizing tests are in accordance with the results of the thermoanalytical measurements. Thus, thermogravimetry can be used for characterizing the microstructure and water binding capacity of semisolid dermal vehicles, from which the rate of water release and the permanency of the skin hydrating effect can be concluded. Therefore, thermogravimetry seems to be a possible predicting method for the characterization of the hydrating effect of different semisolid preparations. It could be used for screening the potential DDSs cost and time effectively, reducing the number of in vivo tests.

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