Original Paper

The Evaluation of Concentration - In-Vitro Release Relationship for Topical Semisolid Formulations of Sodium Cromoglycate

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ABSTRACT: Purpose. The aim of the study was to evaluate the concentration - in-vitro release relationship for topical semisolid formulations of sodium cromoglycate. **Materials / Methods.** According to usual pharmaceutical compounding practice, commercially available cosmetic emulsions were used as vehicles for topical semisolid dosage forms containing 0.5, 2, 4 and 10% disodium cromoglycate (CS). The *in-vitro* release profiles and structural parameters of the resulting formulations was evaluated in a correlated manner, in order to reveal potential differences in the *in-vivo* performance. **Results.** Depending on the hydro-lipophilic characteristics of the vehicle and on the quantity of drug dissolved or dispersed, the structure and the release kinetics are distinct. **Conclusions.** The results suggested that current lack of an unitary approach for the compounding of semisolid dosage forms of CS, resulting from the lack of widely available, standardized dosage form could be a reasonable explanation for the apparent discrepancy in the reports of clinical outcome after topical administration.

KEYWORDS: *sodium cromoglycate, pharmaceutical compounding, in-vitro release, hysteresis loop test*

Introduction

Disodium cromoglycate (cromolyn sodium; CS) is an active pharmaceutical ingredient used for the systemic and topical treatment of various pathological conditions, mainly based on its ability to stabilize the mast cells membranes [1,2]. Its utility in the treatment of atopical dermatitis or cutaneous mastocytosis was intensively debated [3-5], despite the existence of several promising reports based on clinical study data [6,7]. Currently, the topical formulations are not widely available, therefore the pharmaceutical compounding remains a frequent approach for local delivery of this promising drug, either as stand-alone therapy or as part of a combined therapeutic protocol (oral and topical administration [8]). It has been frequently questioned if the variability in terms of qualitative or quantitative composition of the vehicle, liquid or semisolid, is the leading cause for the inconclusive therapeutic outcome [9]. Moreover, the dose strength varies largely between 0.2 and 10% [2]. CS is a hydrophilic chemical entity with acidic properties (as dicarboxylic acid, having a pKa value of 2 [2,10]. The calculated polar surface area is high, whereas the n-octanol water partition coefficient is negative (125Å^2, respectively logP value of -1.25 [11]). As a direct consequence, the theoretical permeability across the stratum corneum as a typical lipidic barrier is limited. The severity of the pathological condition, as well as the area of the affected skin surface, can significantly alter the barrier properties, facilitating the access of xenobiotics to the hydrophilic viable dermis. In these instances, the thermodynamic activity of the drug in the pharmaceutical formulation becomes the critical factor for the optimal delivery to the site of action. It was previously stated that CS dissolved in hydrophilic formulations (e.g. aqueous solutions or oil-in-water emulsions [12]) displays adequate bioavailability, compared to the dispersions in lipidic matrix [7]. The systemic exposure was low and variable (0.01 to 2.75% from the locally applied dose, based on the amounts recovered in urine [13]), reducing the incidence of specific adverse events during the long-term therapy.

The aim of the current study was to assess the extent to which the selection of the vehicle and of the strength of the dosage form alters the release of CS from topical semisolids. Commercially available cosmetic emulsions of highly complex compositions were used without any addition of supplementary inactive ingredients as oil-in-water basis for standardized dispersion or dissolution of CS in a wide range of concentrations. The resulting semisolid formulations were subject to compendial *in-vitro* release (IVR) testing and structural evaluations, in a correlated approach able to reveal potential differences in the *in-vivo* performance.

Materials and Methods

Topical formulations containing 10%, 4%, 2% and 0.5% CS (purity higher than 95%) were

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prepared at room temperature by standardized mixing the weighted amounts of drug with the following cosmetic emulsions or bases purchased commercially: *A-Aderma Avoine Rhealba®, creme emolliente Exomega D.E.F.I.*, Pierre Fabre Dermo-Cosmetique, Laboratoire Dermatologique A-Derma, France (matrix A, formulations coded F1 to 4); *neo-PCL® w/o* (ready to use autoemusifying mixture of cetearyl ethylhexanoate, ceresin, lanolin, sorbitan sesquioleate, mineral oil - paraffinum liquidum, stearyl heptanoate, hydrogenated castor oil, sopropyl myristate and stearyl caprylate), Acofarma, Spain, used as 25% dispersion in purified water in which the drug has been dissolved (matrix B, formulations coded F5 to 8); *Nivea® Baby, pure & sensitive milk*, Beiersdorf, Germany (matrix C, formulations coded F9 to 12); a magistral cream base composed of lanolin, cera alba, cetaceum, cholesterol, olive oil, vitamin A, sodium tetraborate and water (matrix D formulations coded F13 to 16). The preparation was performed on a Heidolph RZR 2020 overhead mechanical stirrer (Heidolph, Germany), using a pivoting blade impeller at 2000 rpm for 20 min. The formulations were stored in ambient conditions at least 24 hours and were visually checked for uniformity before further testing.

For the *in-vitro* release evaluation, a Hanson Microette system (Hanson Research Inc., US) was used according to the general recommendations available in the <1724> Chapter of the United States Pharmacopoeia 37 / National Formulary 32 [14]. The static vertical diffusion cells with 12 mL net volume were mounted serially on a multiple position magnetic stirrer and thermostated at 32±0.5°C. Artificial membranes of cellulose esters (Technokroma, Spain) with a declared mean pore diameter of 0.45 μm were soaked for at least 30 min in the receptor media, consisting of 30% ethanol in purified water, previously degassed by filtration under vacuum (900 mBar). After superficial drying of the membranes, approximately 300 mg of each formulation was applied using dedicated polytetrafluoroethylene dosage wafers. The tests were performed in triplicate, using occlusive conditions. The receptor compartment was homogenized using magnetic stirrers with stainless steel helix adaptors at 600 rpm. Samples of 0.5 ml were collected manually at 30, 60, 120, 180, 240, 300 and 360 minutes after test debut. The quantitative evaluation of the released quantities of CS was performed spectrophotometrically (d_1=248 nm), using an Agilent 8453 Spectrophotometer (Agilent Instruments, Germany). The mean release profiles were fitted with the Higuchi model (USP36/NF31, 2013), applicable to both solution and suspension systems. The IVR rate was calculated as the slope of the regression line corresponding to the cumulative amount of CS per surface unit (1.767 cm^2) versus time.

For the assessment of structural differences existing between the vehicles, as well as between different strengths prepared with the same emulsion matrix, a hysteresis loop test was performed using a rotational viscosimeter (Haake VT550, Thermo GmbH; SV-DIN spindle at shear rates of 0-25 sec^{-1}, for rump-up / rump-down consecutive runs; sample volume: 10 mL). Six evaluations were performed on each formulations, with 3 min rest period between consecutive runs.

All the other reagents were purchased from Sigma Aldrich and used as received. The purified water was obtained using a SGW Ultraclear UV Plus™ system.

Results

The mean IVR profiles of CS displayed an increased dependency on the properties of the vehicle, particularly on its hydro-lipophilic characteristics and consistency or structure. The Higuchi model (square root law [15]) was applicable in all instances, the coefficient of correlation associated with the regression line being higher than 0.99. The variability of experimental data was low and no saturation occurred, due to the high solubility of CS in the receptor. Advanced depletion of the receptor compartment was not noticed, nor the significant back diffusion process, by the end of testing interval. The release rate increased proportionally to the concentration of the drug in the donor (Fig.1). The highest values of this parameter were concluded for matrix C (738.7±22.2 $\mu g/cm^2/min^{0.5}$ for formulation F9, respectively 31.8±1.1 $\mu g/cm^2/min^{0.5}$ for formulation F12). The use of matrix B generated semisolid vehicles with higher consistency, therefore displaying an increased diffusional resistance and low release rates (2.9 to 20.2% from the values recorded for the corresponding formulations based on matrix B).

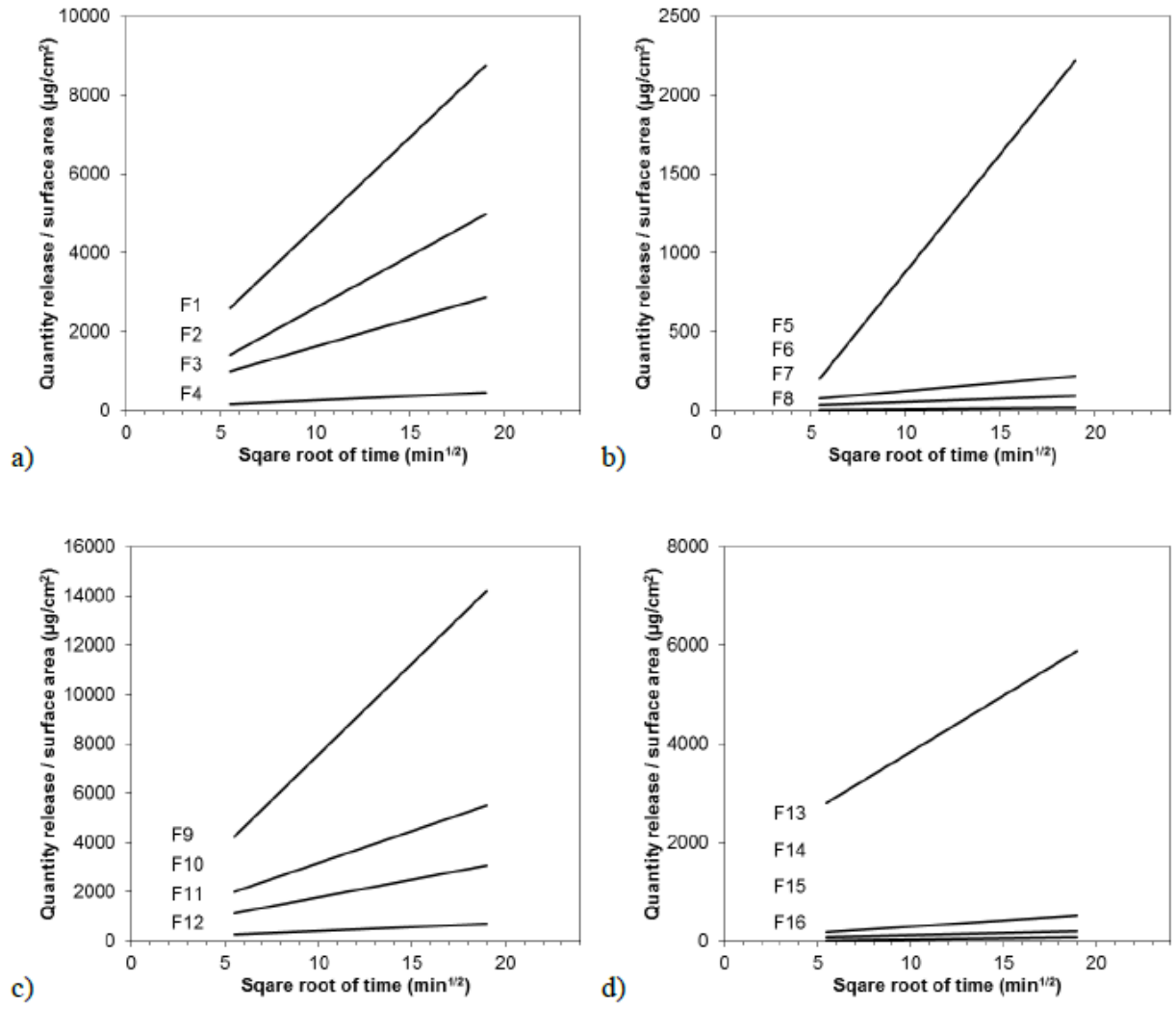

Fig.1. The mean IVR profiles of CS (n=3) from the semisolid formulations prepared in cosmetic emulsions

All the prepared formulations displayed a pseudo-plastic behaviour, the controlled deformation profile being adequately described by the Ostwald de Waele model [15]. The dependence of consistency on the concentration of CS dissolved or dispersed in the matrix had a distinct pattern (Fig.2). For matrix A, the decrease of concentration triggered a proportional decrease of consistency index values (from 35.2 Pa/sec for F1 to 14.8 Pa/sec for F4). At the same time, the highest strength prepared using matrix D displayed an increased spreadability and the most significant changes in structural parameters, compared to the blank vehicle. Reduced if any structural modifications were concluded in the remaining two instances. The flow behaviour index was lower than one, confirming the observed shear thinning patterns and without a direct relation with the release rate. It became apparent that, depending on the cumulative influence of several composition factors and of the drug amount as the single variable for a given matrix, the physico-chemical characteristics of CS are reflected to a different extent in its state of aggregation and in the micro-structural properties.

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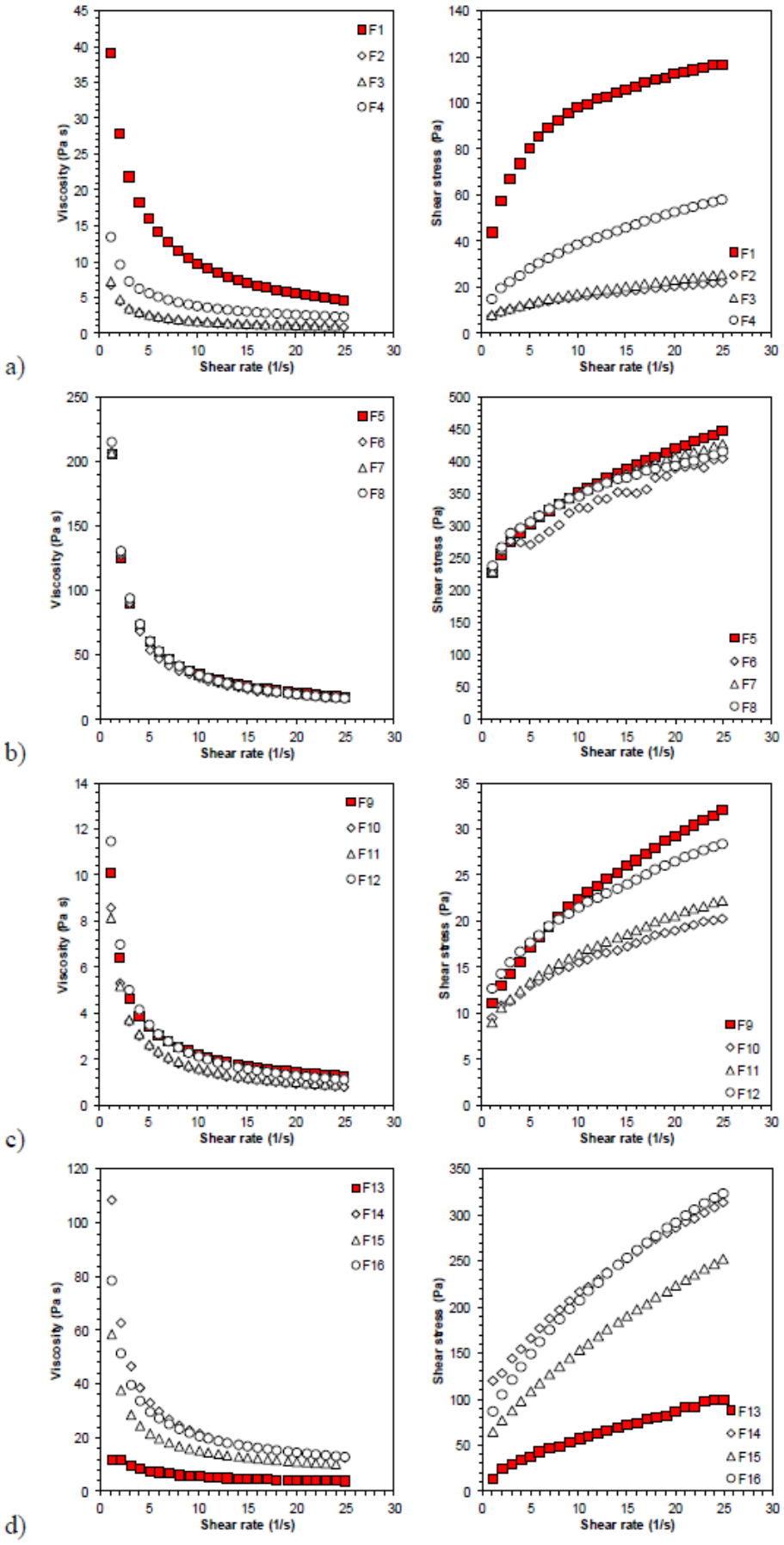

Fig.2. The variation of viscosity and of shear stress with the shear rate (mean profiles, n=6)

Discussion

None of the four selected matrix were anhydrous, therefore it is reasonable to assume that a variable fraction of drug was dissolved in the semisolid matrix. For the autoemulsionable water-in-oil vehicle (matrix B), the partition between the internal phase and the lipophilic medium becomes the rate-limiting step for the release process across the artificial membrane. This is a possible reason for the low release rates (0.9±0.2 to 149.3±8.8μg/cm^2/min$^{0.5}$). On the other hand, for the 10% strengths of both matrix B and D significant shifts from the dose-release rate dependence pattern were observed (Fig.3). Either the quantity of water present in the formula didn't allow a complete dissolution of CS or the diffusional resistance of the semisolids is critically altered by its acidic characteristics, beyond the 4% concentration threshold. The kinetic differences arose from the quantity and physical state of the drug resident in the continuous lipidic phase.

In case of matrix A, the drug is suspended in the lipophilic vehicle. There was a linear dependence between the release rate and the concentration of CS, confirming the results obtained by Pillai R et al [16]. For molecularly dispersed states induced by the presence of high quantities of water (matrix C), the release rates increased proportionally with the quantity of drug. Both cases are highly representative for the development of sequential strengths of the same topical products using the essentially similar vehicles and the same manufacturing process. The predictability of the dose-release relationship in these conditions was previously proposed for waiving the bioequivalence requirements after clinical evaluation of the highest strength, as well as for the development of intermediate strengths [17].

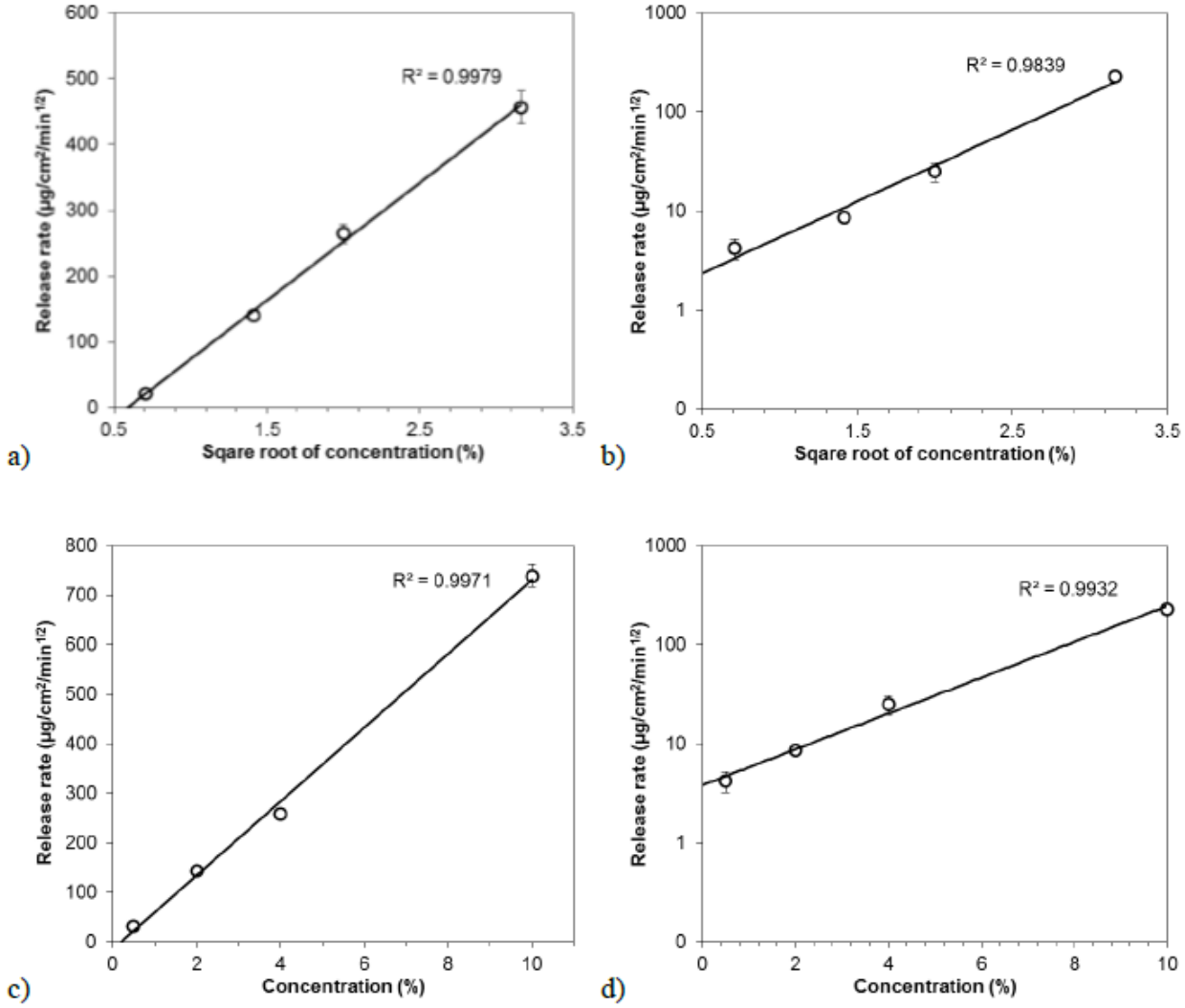

Fig.3. The dependence of the IVR rate on the concentration of CS in the semisolid vehicle (mean ± standard deviation; n=3)

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The clinical significance of these results are difficult to assess. The in-vitro in-vivo relations or correlations for topical semisolids are considered feasible [18], even when artificial membranes are used for testing. The accurate interpretation of data must initially considered the rate limiting step of the *in-vivo* performance. In critical instances such as atopical dermatitis or mastocytosis, in which the barrier properties of the skin are altered to a variable extent and on variable areas, the IVR methodology can serve as an adequate safety evaluation [19]. The penetration through the complex tissue structure at the site of administration is influenced by the diffusional resistance controlled by the composition factors. It is the opinion of the author that oil-in-water formulations containing completely solubilized CS in concentrations up to 4% represent the optimal pharmaceutical compounding approach in cases where the integrity of the stratum corneum has been compromised. Besides providing an increased biocompatibility, they generate the adequate thermodynamic activity for the considered active pharmaceutical ingredient. This assumption is supported by available data suggesting beneficial effects when water based lotions are used [6]. If significant barrier properties are maintained, the role of absorption promoters able to increase the permeability of the stratum corneum by various mechanisms becomes essential. Noteworthy, the composition of the vehicles selected for this study included various tensioactive agents which may alter the fluidity of the biological interfaces.

Secondly, one must consider the relevance of the current results for the quality control evaluation of the semisolid dosage forms. For the assessment of scale-up post approval changes [20], the applicant must submit proofs of adequate methodological development and validation. One of the key parameters is the demonstration of discriminatory character in terms of drug concentration, e.g. sensitivity for 50 to 200% variation in content of the active entity. The current data indicate that in some instances, the drug can change the physical state within the same vehicle, therefore the relationship between dose and release rate might not be linear.

Conclusion

The current results suggest the need for a unitary approach for the compounding of semisolid dosage forms of CS. The lack of widely available, standardized dosage form could be a reasonable explanation for the apparent discrepancy in the reports of clinical outcome after topical administration. The data confirms that the use of various commercially available cosmetic vehicles generate different physical states for the active ingredients, distinct release patterns and particular dependences of the kinetic parameters on the concentration of CS.

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