THE INFLUENCE OF STRUCTURAL CHARACTERISTICS ON THE *IN VITRO* DRUG RELEASE RATE OF TERBINAFINE FROM TOPICAL GELS

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Abstract

The paper presents the results of correlated, rheological and *in vitro* drug release evaluation for various hydrophilic gels of terbinafine hydrochloride 1%. Linear dependence was observed between diffusion coefficient values (Higuchi model) and the concentration of cellulose derivative (1 to 4%). For the semisolid systems with concentrations of active pharmaceutical ingredient near the saturation point, selection of the nature and concentration of gel-forming excipients allows an accurate control of the delivery profile.

Rezumat

Lucrarea prezintă rezultatele evaluărilor corelate, reologice și ale cedării *in vitro* pentru diferite geluri hidrofile conținând terbinafină clorhidrat 1%. A fost observată o dependență liniară a valorilor coeficienților de difuzie (model Higuchi) și concentrația derivatului de celuloză (1 - 4%). Pentru sistemele semisolide cu concentrații ale substanței farmaceutice active apropiate de valoarea de saturare, selecția naturii și concentrației excipienților cu rol de formator de gel permite un control adecvat al profilului de cedare.

Keywords: terbinafine hydrochloride, hydrophilic gel, rheology, diffusion

Introduction

The development of new semisolid dosage forms imposes accurate evaluation of physico-chemical characteristics of the active pharmaceutical ingredient (API), correlated with the properties of the first biological interface for the *in vivo* penetration process, the stratum corneum. In several instances, the long clinical experience contradicts the rules developed for selection of drug candidates with acceptable bioavailability pattern. It is the

case of several antifungal drugs, such as terbinafine, included in the pharmaceutical formulations as hydrochloride. The lipophilic character [1], estimated by the n-octanol - water partition coefficient, indicates that the active entities are outliers, when the optimal 1 to 3 interval is considered [2]. One can reasonably assume that the transfer between lipidic vehicles (such as the ointments, creams or emulsions available on the market) and the corneocytes layer is a very slow process, since the solubility of the API in the two compartments could be similar. The alternative approach is the use of anhydrous, alcoholic systems, able to provide the requested thermodynamic activity [3]. Drawbacks are foreseen, since the initially high release rate generated by the loss of volatile ingredients and consecutive generation in situ of supersaturated systems leads to accelerated precipitation of the non-absorbed fraction, potentially limiting the bioavailability. The use of high quantities of tensioactive agents alters the structure of the vehicle, but also questions the biocompatibility.

Our group has previously evaluated the *in vitro* diffusion pattern of several antifungal drug products, underlining the existence of considerable differences in both structure and mechanism of release [4]. The biological relevance of these results is difficult to predict. Several reports presented a considerable contribution of the excipients to the overall clinical outcome, a particularity of the percutaneous route of administration [5]. The activity of "inactive" ingredients must be considered as key factor, inducing a time-dependent changes of the thermodynamic activity of the API, of the integrity of the biological barrier during the delivery process and of the structural properties of the vehicle.

It is assumed currently that structural similarity of semisolid dosage forms is essential for generation of equivalent drug exposure profiles [6]. Although there are no defined criteria for rheological pattern comparison, it is considered as a valuable quality control procedure in the research and development process.

Therefore, the aim of the experimental plan was to develop new, hydrophilic gel systems of terbinafine. The formulations, together with the available reference drug products, were further investigated by rheological and *in vitro* drug release evaluations, focusing on the relevance of the structural and compositional differences.

Materials and Methods

Hydrophilic gels containing 1 to 4% either hydroxypropyl-methyl cellulose (HPMC), hydroxyethyl-cellulose (HEC) and methyl cellulose (MC, 5140 mPa sec), as well as binary combinations of each

macromolecular agent (1%) were prepared by separate hydration (with 70% of the water quantity available in the formula) for 48 hours at 2-8°C. Each formulation is further identified by the abbreviated name of the cellulose derivative, followed by its percent concentration. Terbinafine (1%) was added after dissolution in a hydro-alcoholic mixture composed of remaining water, ethanol absolute, isopropanol, polyethylene glycol 200 (PEG 200) and Cremophor® EL (polyoxyl 35 Castor oil). Each formulation was mixed for 10 minutes at 2000 rpm, using a Heidolph RZR 2020 mechanical stirrer. The structural and drug release evaluations were performed after at least 24 hours of storage in ambient conditions.

Table I

Composition of the experimental formulations

Component	**Quantity (g/100g formulation)**
Terbinafine hydrochloride	1
Cellulose derivative	1-4
Ethanol absolute	10
Isopropanol	5
Polyethylene glycol 200	5
Cremophor® EL	1
Purrified water for	100

The rheological evaluations were performed on a rotational viscometer Rheometer type RC1, RheoTec GmbH, Germany, with CC14 coaxial cylinder (share rate values interval: 0 – 150 s^{-1}, on ascending and descending routes, at 25°C; volume: 3 ml). Rheo 3000 software, version 1.2.1328.1., RheoTec Messtechnik GmbH - Brookfield Engineering Labs., Inc. was used for data acquisition, analysis (including basic statistics and tixotropy area) and flow profile modeling (power low model, Ostwald de Waele [4]).

For the in vitro drug release, the methodology was previously described in detail [1]. Briefly, the procedure included a Hanson Microette system (Hanson Research Inc., USA) of 12 ml vertical diffusion cells, with 30% ethanol absolute in purified water as receptor media. Approximately 300 mg of each formulation was applied on polysulfone membranes (Tuffryn®, PALL Life Sciences HT-450, 0.45 μm average pore size, batch no. T72556), with 0.5 ml samples collected at 15, 30, 60, 90, 120, 150 and 180 minutes after application. The tests were performed in triplicate, at 32±0.5°C and at 400 rpm stirring rate.

The samples were analyzed for terbinafine content using a spectrophotometric method, at 223.4 nm, on a Jasco UV-Vis V-530 spectrophotometer (equipped with Spectra Manager software for Windows 95/NT, version 1.54.03).

Isopropanol Rotisolv® HPLC was purchased from Carl Roth GmbH Co.KG, Germany. All the other reagents and the analytical standard of terbinafine hydrochloride were purchased from Sigma Aldrich. The purified water was generated by a SGW Ultraclear UV Plus™ system. Cremophor® EL was a gift from BASF Ludwigshafen, Germany.

As references, Lamisil® Cream (batch no. K01798A), Lamisil® DermGel (batch no. K01202B) and Terbisil® Cream (batch no. G03001B) were included in the analysis, the *in vitro* drug release profiles being previously reported [1].

Results and Discussion

The composition of hydro-alcoholic mixture was selected based on the lowest concentration of each excipient requested for maintaining the solubility of terbinafine hydrochloride in the formulation. The structural differences induced by the large interval of concentrations implemented for the matrix forming macromolecular agent were transposed in various degrees of structure alterations induced by the mechanical stress. The amplitude of deformations increased with the concentration of each cellulose derivative, with almost an exponential dependence of thixotropic areas (Table II). All formulations displayed a pseudoplastic behavior, confirmed by flow index values lower than 1.

Table II

The thixotropic areas and consistency index values

Parameter	Cellulose derivative	Concentration (%)			
		1	2	3	4
Thixotropic areas (Pa/sec)	HPMC	94,0	470,3	8097,9	66163,4
	MC	109,4	330,2	8210,7	34698,4
	HEC	130,3	1311,0	1150,0	33375,0
Consistency index (Pa/sec)	HPMC	1,00	24,05	62,85	1296,15
	MC	1,55	30,77	149,50	686,68
	HEC	1,59	73,62	164,62	1996,09

It concerns the structure and deformation profile similarity, the mixture of gel forming agents generated the most appropriate flow parameters for a semisolid dosage forms administered locally, comparable to cream drug products included in the analysis (Figure 1). For example, the thixotropic area ranges from 5297 Pa/sec for HPMC-HEC to 6872 Pa/sec for HPMC-MC, with a value of 6404 Pa/sec reported for Terbisil® Cream.

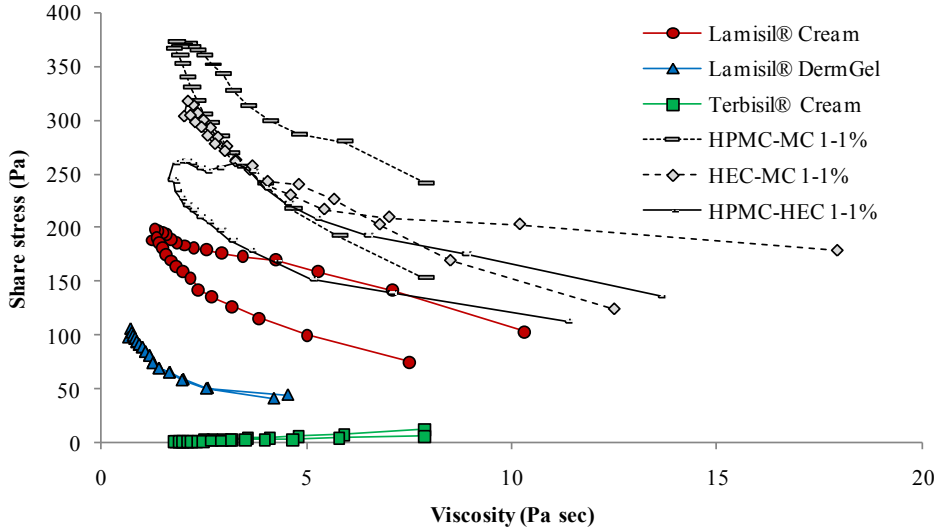

Figure 1

The rheological profiles of reference drug products and experimental formulations containing mixtures of cellulose derivatives

Also, the rheological profile of the hydrophilic gels changes dramatically compared to unassociated 1 to 2% cellulose derivatives (Figure 2). It is to be pointed out that there are obvious differences between the patterns obtained for reference products, theoretically leading to the same release profiles after in vivo administration.

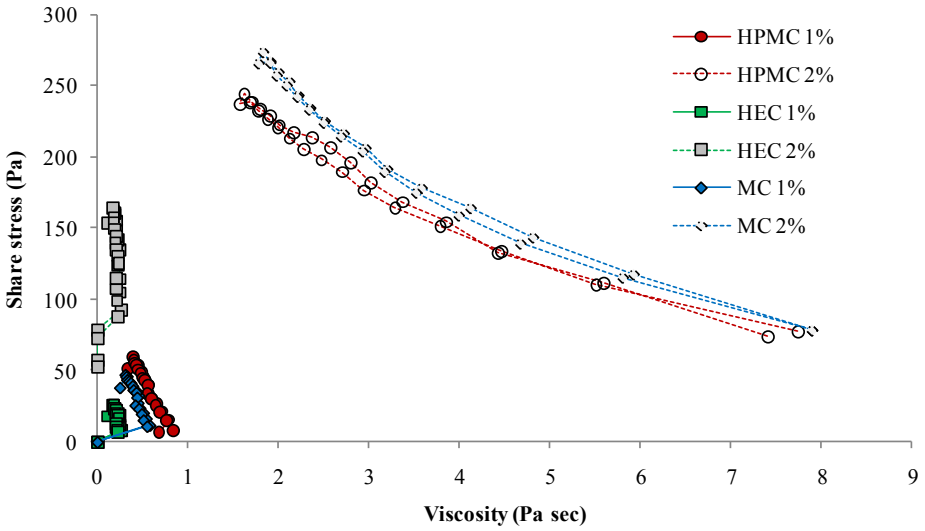

Figure 2

Flow pattern of the hydrophilic gels generated by 1 and 2% cellulose derivative

The *in vitro* drug release rates range is highly dependent on viscosity, ranging from 87.96 to 119.57 μg/cm^2/min$^{1/2}$ (Higuchi model; Figures 3 and 4) and increasing almost linearly with the concentration of cellulose derivatives (correlation coefficient, R^2, of 0.993, for MC; Table III).

Table III

The dependence of the diffusion coefficient values (μg/cm^2/min$^{1/2}$) on the concentration of cellulose derivatives

Cellulose derivative	Concentration (%)			
	1	2	3	4
HPMC	118,04	109,50	107,70	104,16
MC	119,57	105,83	98,61	108,51
HEC	107,81	97,69	95,08	87,96

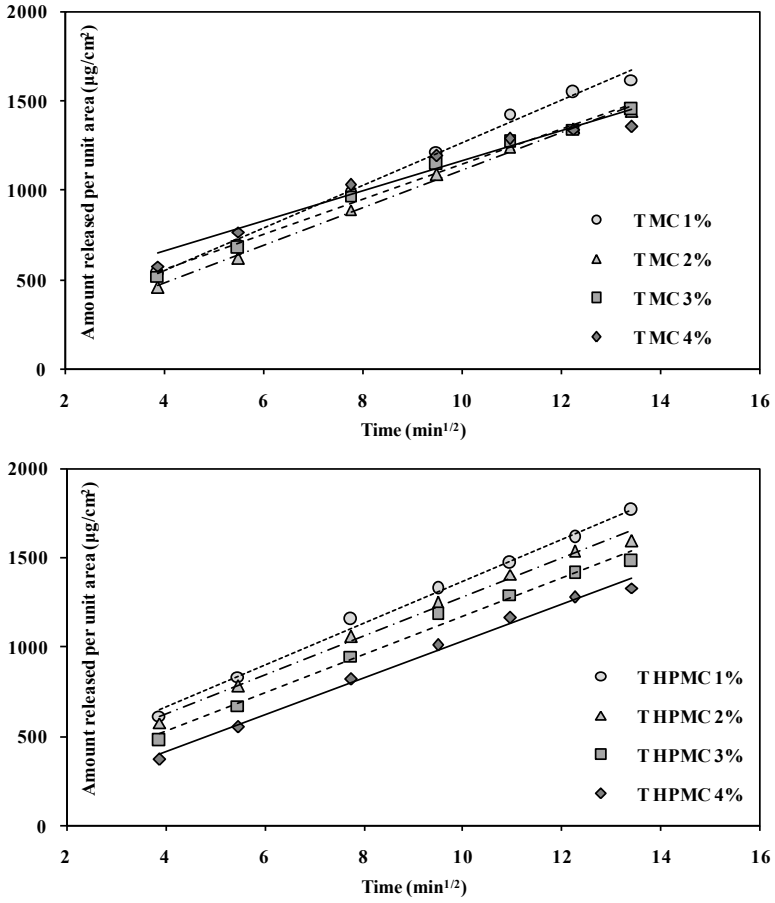

Figure 3

In vitro drug release profiles of hydrophilic gels

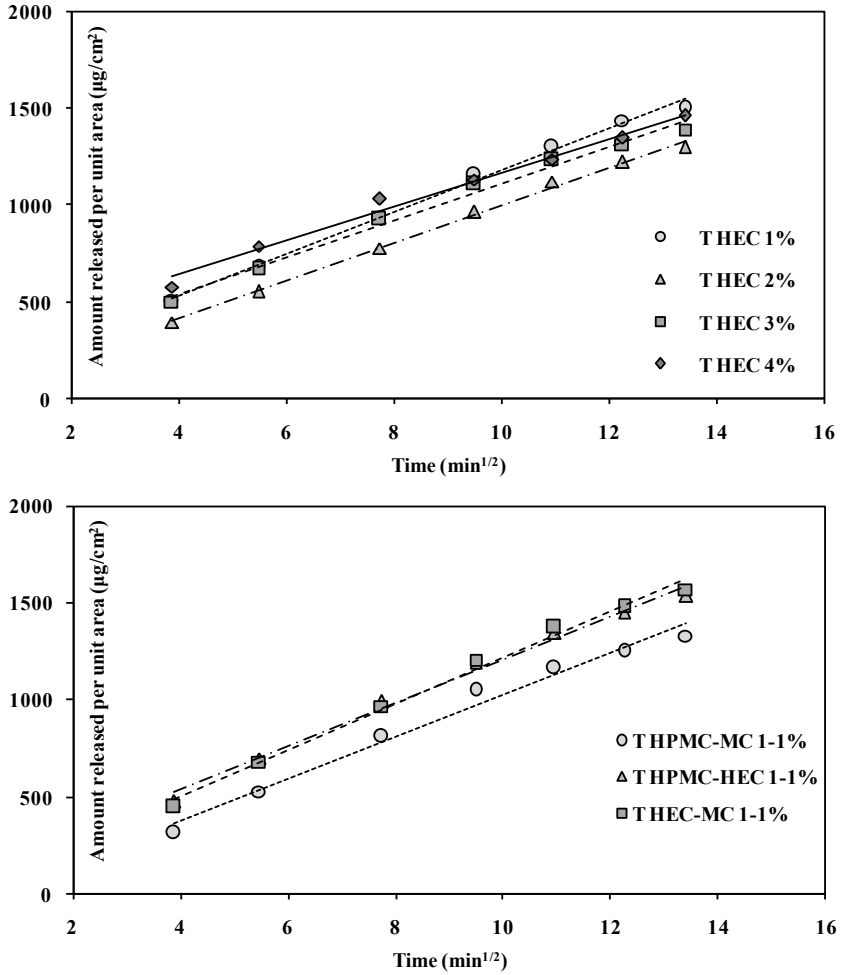

Figure 4

In vitro drug release profiles of hydrophilic gels

Compared to previously reported release profiles of the reference products [1], there is a considerable increase in the release rate for the newly developed formulations. They behave as semisolid systems where terbinafine concentration is near the saturation point for the given mixture of cosolvents, thus the single limiting factor of the thermodynamic activity is the structural viscosity.

Nevertheless, the currently recommended test conditions [7], e.g. using either polysulfone or cellulose-based membranes and aqueous receptor media, usually generates lower values of the diffusion coefficient for the lipid-based drug products [4], compared to hydrophilic gels. It seems

that the biological relevance is dependent not only on the physico-chemical properties of the active drug [8], but also on the dual mechanism of action for several component (solubility increasing agents and absorption enhancers, e.g. isopropanol). Since the nature and concentration of the cellulose derivative is the single composition difference, the data indicates that one could consider the control of terbinafine release by accurate selection of concentration for the macromolecular compound as a reliable approach in developing generic semisolid drug products.

Conclusions

New semisolid topical formulations containing 1% terbinafine hydrochloride were developed based on various cellulose derivatives. The drug was included in the hydrophilic matrix after dissolution in simple cosolvent mixture containing low amounts of alcoholic components.

The rheological and in vitro drug release evaluations indicated the critical impact of structural differences generated by various concentrations and associations of the gel-forming agent. The formulations displayed a typical pseudoplastic behavior, with considerable higher diffusion coefficients compared to available, reference drug products. The data suggests the accurate control of terbinafine in vitro delivery pattern by adequate, structure-based selection of the nature, concentration and/or association of macromolecular excipients, for system with API concentration near the saturation point.

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