sciendo Acta Marisiensis - Seria Medica 2023;69(4):280-284 DOI: 10.2478/amma-2023-0045

RESEARCH ARTICLE

Development of semisolid pharmaceutical forms with mometasone furoate

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Objective: This study aims to develop semisolid pharmaceutical forms for the topical administration of mometasone furoate. **Methods:** Two creams (O1 and O2) and four hydroxypropyl methylcellulose-based hydrogels were prepared (H3-H6). Two different sorts of hydroxypropyl methylcellulose were used in concentrations of 15 and 20%. Consistency, spreadability, viscosity, and pH were measured. In vitro drug release was determined by a vertical, Franz diffusion cell. Mathematical models were applied for a better understanding of release phenomena. **Results:** O1 and O2 presented lower values for penetration depth and spreadability. Hydrogel viscosity is influenced by the type and concentration of the gel-forming agent. Viscosity decreases in the order H6, H5, H4, and H3. pH varies between 4.6 to 5.92, fulfilling the requirements of European Pharmacopiea. Creams showed 5.49 and 6.59% of mometasone released after 6 hours. The lowest viscosity hydrogel presented the best dissolution of 40.11% mometasone after 6 hours. **Conclusions:** H3 hydrogel releases the highest amount of mometasone furoate after 6 hours. The release is best described by the Korsmeyer-Peppas model explained by water diffusion and polymeric chain relaxation happen during the swelling of the polymer.

Keywords: mometasone furoate, hydrogel, diffusion, dermal administration

Received 21 October 2023 / Accepted 6 November 2023

Introduction

Skin is the largest organ of the human body and the first line defense against external agents. Topical drug delivery means a localized drug action on the surface or dermal layer of the skin [1, 2]. Dermal administration offers advantages such as enhanced patient compliance, easiness, pain-free application, avoidance of frequent dosing, and constant drug plasma concentration [3].

Various pharmaceutical forms are suitable for dermal drug delivery. Ointments usually soften after application on the skin, but do not melt. Therapeutically, they are skin protectors and emollients. Creams are more easily washable and softer, because of their water content [4]. Hydrogels are semisolid preparations, that contains large organic molecules interpenetrated by water.

Hydroxypropyl methylcellulose, partially methylated and hydroxypropylated cellulose (HPMC), is mostly biocompatible [5]. Gelation of cellulose derivatives results from the exclusion of water from heavily methoxylated regions of polymer. The viscosity of gels depends on the molecular weight, concentration, and vehicle composition [4]. HPMC types E5 and E15, with 28-30% methoxy-groups and 7-12% hidroxypropoxy groups, and a viscosity of 5 and 15 mPa.s for a 2% dispersion [6-8]. Mometasone furoate is a potent glucocorticoid for dermatological use in case of psoriasis and atopic dermatitis [9]. It is a hydrocortisone derivative, a (2′) furoate-17 ester with chlorine substitutions at positions 9 and 21, designed to improve efficacy and reduce the incidence of adverse effects [10]. Is classified as highly potent in the Stoughton-Cornell classification framework [11,12]. Topical corticosteroids may have local (atrophy, telangiectasia, infections) and systemic side effects [13-15]. The potential for side effects was associated with prolonged or widespread use and usually correlates with increased clinical potency [10]. Mometasone furoate is a white powder, insoluble in water.

For the topical administration of glucocorticoids, various pharmaceutical forms are marketed, including ointments, creams, gels, lotions, solutions, shampoos, and foams. Multiple factors should be considered in choosing a pharmaceutical form for a particular situation [16, 17]. Ointments contain a high amount of lipophilic phase, have good penetrability (but tend to be occlusive), and are also highly recommended for thickened skin. Ointment formulations are generally more potent than creams explained by their occlusive effect [18, 19]. Creams are preferred in case of acute dermatoses. Lotions and gels are suitable for the treatment of scalp psoriasis. Dry skin is improved for psoriatic patients by the use of gel forms [20]. Shampoos and foams are mainly useful on the scalp and ensure patient compliance and even improvement of life quality [21-24].

This study aims to develop and characterize semisolid pharmaceutical forms (creams and hydroxypropyl methylcellulose-based hydrogels) for the topical administration of mometasone furoate. The Romanian market lacks hydrophilic dosage form for the administration of mometasone furoate, cream and ointment forms are available.

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Materials

Micronized mometasone furoate was from Origin Pharma SRL, solid paraffin and liquid paraffin were from SIMP (Italy), cholesterol was from Dishmann (Netherland), cetyl and stearyl alcohol were from VladaChem (Germany), hydroxypropyl-methylcellulose (HPMC) E5 and E15 were from JRS Pharma (Germany). Ethanol and glycerin were from Chemical Company (Romania). Preservative solution was from Elemental (Romania).

Preparation method

For O1 and O2 weighted amounts of solid and liquid paraffin were heated in a water bath (50oC) until forming a homogeneous liquid mixture, when cholesterol and cetyl- and stearyl alcohol were added and dissolved. Water was also heated to 50oC. The two phases were emulsified by mixing. The preservative solution was added in drops.

For the hydrogels, the gel former and the water was mixed at an agitation speed of 1500 rotation/minute for 15 minutes. The preservative solution was added in drops followed by a 24-hour repose for degasification.

Mometasone furoate was incorporated in all samples by dispersing it in a small quantity of blank base while mixing continuously to obtain a suspension topical form. Gradually, the whole amount of base was added.

Particle size of mometasone furoate was tracked using a Bresser LCD Micro 5 MP microscope (Bresser, Rhede, Germany). Recorder images were examined with ImageJ software (US National Institutes of Health, Bethesda, MD, USA). Finally, the average particle size was calculated using 50 different randomly selected individual particles.

Consistency was determined using a manual penetrometer with a penetration cone at room temperature. The penetration rate was recorded in milimeters using weights from 2 to 20 g. *Spreadability* was measured with the Del Poso-Ojeda apparatus as the surface covered by 1 g of gel between two glass plates after the addition of increasing weights (50-500 g). *Viscosity* was determined using a Rheotest RV viscometer, at room temperature, at 12-speed levels, firstly the speed levels were increased and then decreased gradually.

pH measurement: 25 ml solutions were prepared by dissolving 1.0 g of sample in distilled water. The pH value of each sample was measured after 10 minutes at 25°C using a pH meter (Consort C831 multi-parameter analyzer).

In vitro release study

Used apparatus: Vertical Franz diffusion cells with 14 ml receptor volume were used. The acceptor phase was ethanol and water 1:1 (v/v), maintained at 32°C±0.5°C [15]. From the acceptor compartment samples were withdrawn at 1, 2, 4, 5, and 6 hours. The acceptor phase was immediately replaced with fresh dissolution medium also maintained at 32°C±0.5°C. As membrane hydrated cellulose acetate (0.45 μm) was used.

The drug released or diffused at different time intervals was analyzed - using UV spectrophotometry at 249 nm (Shimadzu UV 1800, Japan).

Mathematical modeling of percent cumulative drug release was realized with the DDSolver Add-In Program, Microsoft-Excel software by model-dependent methods [25]. Model-dependent analysis was performed with widely used models (Table II) for hydrogels [26, 27].

Statistical analysis

All analyses were performed in triplicates and expressed as means ± standard deviation. One-way analysis of variance (ANOVA) was used to determine significant differences between groups. When P-value was lower than 0.05, the difference was considered statistically significant.

Table I. Compositions of the six formulated semisolid forms

Component	Amount (g)						Role of component
	O1	O2	H3	H4	H5	H6	
Mometasone furoate	0.05	0.05	0.05	0.05	0.05	0.05	API
Liquid paraffin	10	10	-	-	-	-	Lipophilic phase
Solid paraffin	10	10	-	-	-	-	Lipophilic phase
Cholesterol	1	0.5	-	-	-	-	Emulgent
Cetyl- and stearyl alcohol	0.5	1	-	-	-	-	Emulgent
HPMC E5	-	-	15	20	-	-	Gel forming agent
HPMC E15	-	-			15	20	Gel forming agent
Glycerin	-	-	5	5	5	5	Hydrating agent
Preservative solution	0.1	0.1	0.1	0.1	0.1	0.1	Preservative
Distilled water	28.35	18.45	29.95	24.95	29.95	24.95	Hydrophilic phase

Table II. Mathematical models and equations

No.	Mathematical model	Equation	
	0 order kinetic	$F = k_0.t$	F = % dissolved active ingredient at time „t"
	First order kinetic	$F = 100.[1-Exp(-k_1*t]]$	k = release constant
	Higuchi	$F = k_H.t^{1/2}$	k_H = Higuchi constant
	Korsmeyer-Peppas	$F = k_{KP}.t^n$	K_{KP} = Korsmeyer-Peppas constant

Results

Formulations O1 and O2 are white, homogenous creams. Hydrogels H3-H6 are transparent, slightly yellow homogenous gels.

Average particle size varies between 4.1 and 4.7 μm (4.1±0.1 for O1; 4.2±0.1 for O2, 4.6±0.1 for H3; 4.5±0.2 for H4; 4.5±0.2for H5; 4.7±0.1 for H16).

The maximum penetration depth after 20 g of added weight was measured for H3 and the minimum penetration depth for O1. Spreadability increases in the order O1<O2< H6< H5< H4 <H3 (Figure 1).

pH varies between 4.6-5.92. O1 and O2 present higher viscosity values as compared to the hydrophilic formulations (Figure 2).

After 6 hours the dissolved amount of mometasone furoate for the emulsion-type formulations is 5.49 and 6.59% (Figure 3). Hydrogels present over 20% of dissolved mometasone.

Mathematical modeling of dissolution leads to a better understanding of the driving forces of API release.

A best-fit model may be selected by R2 adj (Table III).

Discussion

Our study aimed at the formulation of mometasone furoate semisolid topical forms. Six formulations were prepared two creams and four hydrogels. O1 and O2 are creams, W/L emulsions containing over 10% hydrophilic phase, differing in the amount of cholesterol and cetyl and stearyl alcohol. As gel former two different types of hydroxypropyl-cellulose were used, HPMC E5 and E15 in two different concentrations of 15 and 20%. Mometasone furoate was suspended in the base in all cases.

The consistency of the two creams was very similar at every point. Comparing the two gels with the same HPMC type based gels (H3 and H4, H5 and H6) lower concentration confers lower penetration value, and comparing the same concentrations (H3 and H5, H4 and H6) HMPC E5 presents lower consistency. Penetration depth values decreas in the order H3>H5>H4>H6, 29>27.3>27>25.3 mm, respectively.

The spreadability of the creams after 500 g weight is 923.56 mm2 and 989.97 mm2. The highest surface value was measured at H3 hydrogels with HMPC E5 in 15%

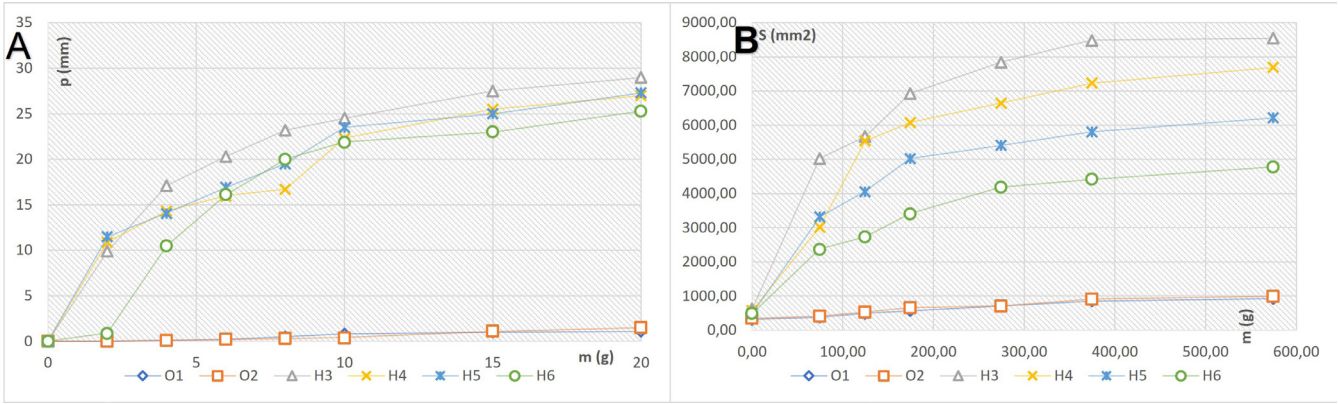

Fig. 1. Penetration curves (A) and spreadability (B) of samples

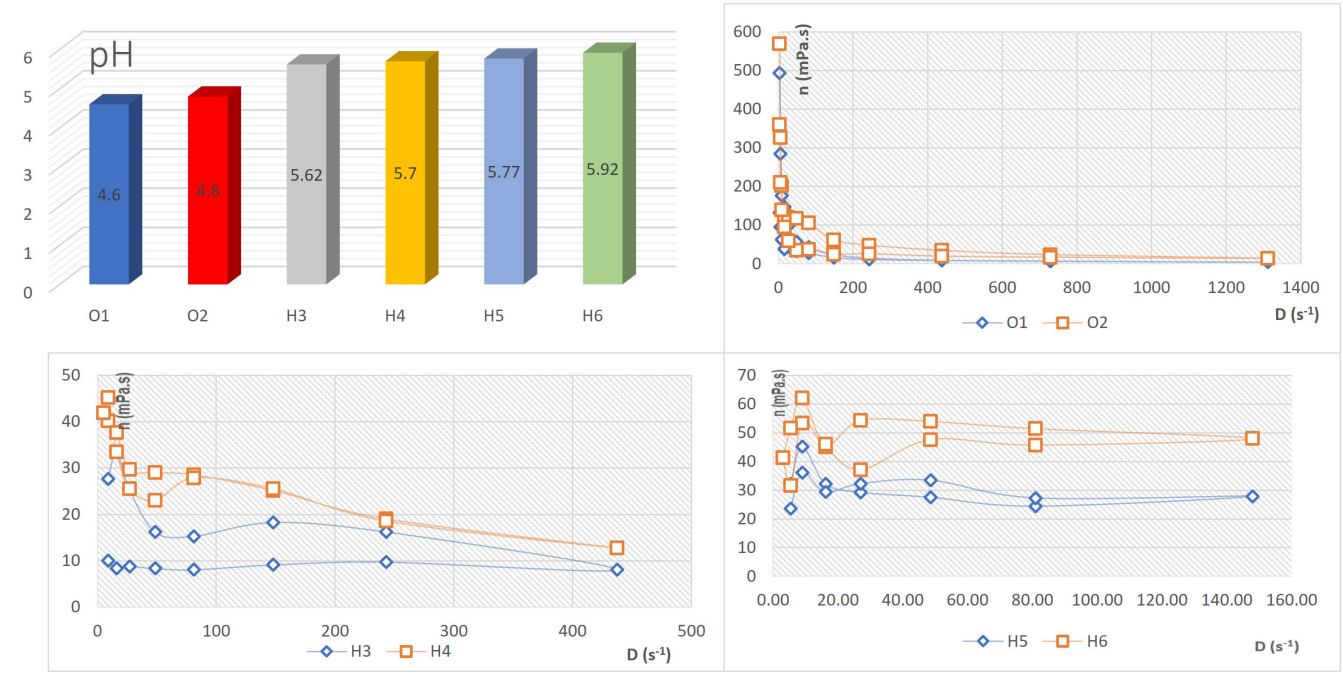

Fig. 2. pH and viscosity curves of the formulations

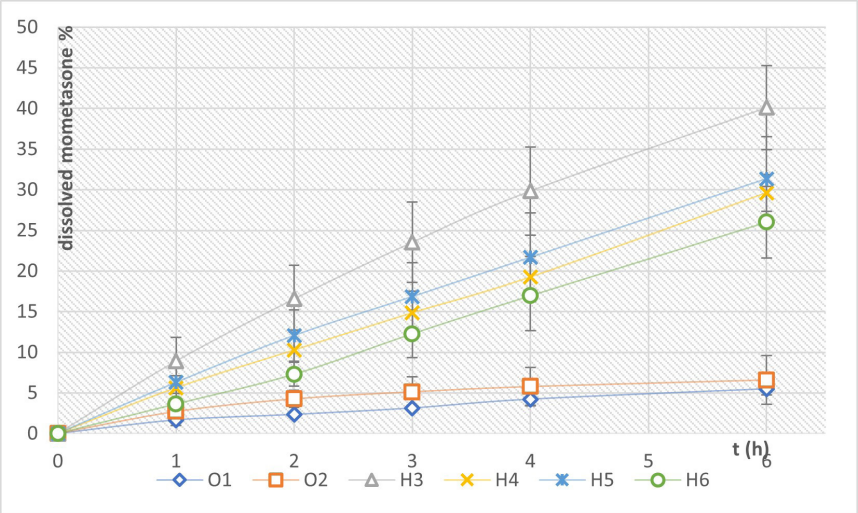

Fig. 3. Dissolution curves of the formulations

Table III Parameters of the mathematical models and R^2_adj for goodness of fit

Model	parameter	O1	O2	H3	H4	H5	H6
0 order kinetic	K_0	0.993	1.352	7.160	4.930	5.479	4.224
First order kinetic	K_1	0.010	0.014	0.087	0.056	0.063	0.047
Higuchi	k_H	2.017	2.831	14.436	9.805	11.003	8.296
Korsmeyer-Peppas (KP)	K_{KP}	1.561	2.855	9.083	4.775	6.452	3.543
	n	0.686	0.498	0.846	1.016	0.898	1.115

concentration, 8544 mm2. HPMC E15 presents lower spreadability compared to HPMC E5 (6217.99 and 4775.94 mm2, 8544 and 7693.79 mm2, respectively for 15% and 20%). Usually, the concentration of the gel former is inversely proportional to the spreadability [28].

The viscosity of creams is relatively high, above 500 mPa.s. From the hydrogels, H3 presents the lowest viscosity, followed by H4, H5, and H6. 15% HPMC for both types comes with lower viscosity. Hydrogels may be characterized as non-newtonian pseudoplastic behavior since their viscosity values decreased when the shear rate increased [29]. The shear stress results in the reordering of the molecules in the HPMC hydrogels [30]. For HPMC E5 the higher polymer mass was required to achieve the same viscosity as HPMC E15 (15% HPMC E15 has a viscosity of 45 mPa.s, 20% HPMC E5 also at a shear rate of 9 s-1).

pH values of creams are lower than 4.6 and 4.8. Hydrogels' pH is similar between 6.52 and 6.92.

In vitro release of mometasone furoate after 6 hours decrease in the order 40.11%, 29.62%, 31.34%, and 26.01% for H3, H4, H5, and H6. The highest amount of active substance is released from H3 with the highest spreadability, highest penetration depth, and lowest viscosity from the hydrogel formulation. The lowest dissolved amount is from H6 presenting the highest viscosity.

The lower release from the creams may be explained by the reduce mobility of mometasone furoate molecules in the formulation, the water droplets in the creasm are possible to slow down the diffusion of mometasone furote toward the membrane.

Mathematical modeling of the release curves explains drug release from the hydrogel matrix. Of the most used four models the highest R2 adj values were observed in the case of the Korsmeyer Peppas model. The Korsmeyer Peppas constant of the mathematical model describes the diffusion from the gel and n is the release exponent. In our case n varies between 0.498 and 1.115, meaning a non-Fickian release of mometasone furoate. During in vitro release, water is absorbed into the HPMC and disentangles the matrix (relaxation) causing swelling. This swelling leads to a rubbery state in the polymer in which the diffusion and mobility increase. The Fickian model does not describe the release properly because dissolution and matrix disentanglement, and not just diffusion are involved [31]. For formulation O2 the release may be described by diffusion with the Higuchi model.

Statistical analysis revelead no significant differenceses in penetration depth and spreadabity for creams (p values over 0.05). In the case of hydrogels there was no significant differences either.

Conclusions

In this study, six different formulations were prepared and studied. Two were W/L emulsions and four were hydrogels. As matrix former two types of hydroxypropyl methylcellulose, E5 and E15 were used in two different concentrations 15 and 20%. The consistency, spreadability, and viscosity of the hydrogels are dependent on the polymer concentration and type, HPMC E5 in 15% concentration has the lowest viscosity and the highest spreadability and penetration depth. Viscosity is inversely proportional to

the released amount of mometasone furoate. Hydrogel H3 releases over 40% of mometasone furoate.

Authors contributions

REM experimental determinations, collection of data, writing the manuscript; JB experimental determinations, summarizing the information, creating the figures; VRA experimental determinations, collection of data, editing the manuscript; AP collection of data, summarizing the information; TN collection of data, interpretation of experimental data, critical review of the manuscript, editing the manuscript; SE interpretation of experimental data, critical review of the manuscript; CA interpretation of experimental data, critical review of the manuscript.

Conflict of interest

None to declare.

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