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Preparation and evaluation of a novel dosage form for onychomycosis

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ABSTRACT

Onychomycosis is a common infection of the nail caused by dermatophyte affecting mostly toenails in adults being associated with limited treatment options. In this study novel dosage forms were prepared and evaluated for their suitability in treatment of onychomycosis. Films were prepared comprising polymeric excipients such as chitosan, (hydroxypropyl)methyl cellulose, hydroxyethyl-cellulose, carboxymethylcellulose according to solvent evaporation method. Developed formulations were evaluated in terms of physical appearance, stability and adhesiveness. Furthermore skin and nail irritation studies were conducted. Five potential formulations (F1–F5) were designed while F1 and F4 exhibited the most promising results in terms of stability with 26 min and 40.67 min, respectively, and suitability in nail application. F1 as the most favorable dosage form revealed with 2.9438 kg/m/s in terms of adhesive force the most adhesive properties in contrast to the other preparations. All formulations were found to be non-skin irritating and safe to use. Taken together, these findings suggest novel designed films containing polymeric excipients as a fruitful platform for the treatment in onychomycosis.

1. Introduction

Predominantly, the majority of fungal infections (dermal and nail) are caused by dermatophytes, such as Trichophyton rubrum known as one of the most prominent (Akhtar et al., 2016). Among fungal infections, nail infections or onychomycosis exhibit the most difficulties and limitations in their treatment (Westerberg and Voyack, 2013). Onychomycosis affects around 5–10% of the population in the world (Turner et al., 2016). More precisely, populations infected by these fungi is 23% across Europe, 20% in East Asia and 14% in North America (Ghannoum and Isham, 2014). This suffering can be painful and lead to permanent disfiguration decreasing patient's quality of life. Nowadays, oral and topical antifungals are the first choice latter lacking in poor nail permeation and transungual delivery. The research field in nail infections focusses on three basic strategies: developing topical antifungals based on oral ones (I), designing new chemical entities (II) and developments of new formulations of existing antifungals (III) (Daniel, 2013).

Pharmaceutical formulations are divided in liquids such as lacquers, solids such as tablets or semi-solid formulations such as ointments. The commercial available liquid formulations in the treatment of onychomycosis lack in the high frequency of application reducing the patients' compliance. The semi-solids available in the treatment of nail infections comprising ointments and creams exhibit the uncomfortable way of application by smudging and blurring the dosage form leading to diminishing patient's acceptance (Elewski, 1998).

Therefore, there is an urgent need in developing novel promising dosage forms for the treatment of onychomycosis improving and maintaining the patients' compliance. In this study, well-known polymeric excipients were chosen for novel dosage systems prepared by the solvent evaporation method. These solid formulations were evaluated in terms of stability, flexibility, folding endurance, moisture content, irritation profile and their suitability for the treatment in nail infections. The prepared films were promising for their adhesiveness on the nail plate rendering in less frequency of application, comfortable and clean mode of application leading to higher patients' compliance and improved quality of life.

2. Materials and methods

2.1. Materials

Carboxymethylcellulose sodium salt (NaCMC) (high viscosity), Chitosan (low molecular mass 150 kDa, degree of deacetylation, 83–85%), 2-Hydroxyethyl-cellulose (HEC) (average Mw 90.000 Da), (Hydroxypropyl)methyl cellulose (HPMC), Triethyl citrate (TEC)

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(98.0%) were purchased from Sigma Aldrich (Steinheim, Germany). Polyvinylpyrrolidone (PVP) was received from BASF (Ludwigshafen, Germany), Propylene glycol (PPG) was obtained from Gatt-Koller (Absam, Austria). All other chemicals were analytical grade and obtained from commercial sources.

2.2. Preparation of films

Five formulations of nail films were prepared by solvent evaporation method with the help of film forming polymers. Formulation 1 (F1) was obtained while dissolving 1.0 g HEC in 20 mL of ethanol filled in a beaker; in the next step, 0.4 g NaCMC and 0.2 g HPMC, respectively, were added to the mixture and lastly PPG as plasticizer was subjoined. After 10 min under vigorous stirring, the prepared solution was poured in a petri dish. The content of the petri dishes was allowed to evaporate overnight. Formulations 2–5 were prepared in the same manner following the compositions and procedure as shown in Table 1.

2.3. Characterization of films

F1-F5 (diameter of 14 mm) were weighed, respectively, with a digital balance (Sartorius AG, Göttingen, Germany) while means were calculated (n = 3). Thickness of three films of each formulation was determined with a caliper (MarCal 16EWRI, Mahr GmbH, Göttignen, Germany). The surface pH was ascertained by adding a drop of water to the formulations and measuring the pH with a pH micro electrode (VWR, Austria). Physical appearance was determined in terms of dryness, smoothness, stickiness, wrinkles and transparency. Folding endurance was investigated by repetitions in folding the films at the same place until breaking/disruptions or folding over 300 times without breaking was observed.

2.4. Irritation study

2.4.1. Skin irritation study

In order to determine and identify presence of skin reactions erythema and edema a skin irritation study was performed (Held et al., 2001). Irritation study was executed on three healthy human volunteers. After washing and shaving the forearm surface, skin was left overnight to refresh. Prepared formulations F1–F5, respectively, were applied to the skin and observed for skin reactions over 2,4,8,12 and 24 h (Agner and Serup, 1990). Draize scoring method ascribed the skin reaction (Draize et al., 1944). Furthermore, primary irritation index values and Draize scoring index were elucidated in Tables 2 and 3.

2.4.2. Nail irritation study

Second irritation study was performed on toenails of three healthy male humans in order to determine the nail coloring and the nail texture before and after application. Developed formulations F1–F5, respectively, were applied to the nail for predetermined time points 1, 2, 4 and 6 h. Moreover, scoring index and primary irritation values were tabulated in Table 4.

Table 2
Classes of irritation in accordance to Primary dermal irritation index.

Primary dermal irritation index	Classification of irritation
Less than 0.5	No
0.5–2.0	Barely perceptible
2.0–5.0	Moderate
More than 5.0	Severe

Table 3
Dermal reactions and scoring allocated according to Draize scoring criteria.

Erythema	Edema	Score
No	No	0
Very slight	Very slight	1
Well defined	Slight	2
Moderate to severe	Moderate	3
Severe to slight Eschar formation	Severe	4

Table 4
Nail reactions and scoring.

Nail color	Nail texture	Score
Colorless	Original texture	0
Slightly colored	Minor alteration	1
Well defined	White spots	2
Discolored	Disintegrated	3
Completely discolored	Completely disrupted	4

2.5. Scanning electron microscopy measurements

Formulations F1-F5 were investigated in terms of their surface morphology by scanning electron microscopy (SEM) using a ZEISS EVO LS 10 connected with SmartSEM program (Oberkochen, Germany) instrument. For this purpose each formulation was cut into 1 cm^2 pieces, respectively, and mounted on SEM stub. By using a sputter coater (SC 7640; Polaron Quorum Technologies, LOT-QuantumDesign GmbH, Darmstadt, Germany) films were then coated with gold metal (Mididoddi and Repka, 2007).

2.6. Rheological measurements

The viscoelastic properties of all formulations were determined with a thermostatically controlled plate–plate viscometer (Thermo Haake Mars, Haake GmbH, Karlsruhe, Germany). 1% (w/V) of each formulation F1–F5 was prepared and transferred to the rheometer. The apparent viscosity (η) was measured immediately after equilibration. The shear stress was set at a range of 0.5–500 Pa

Table 1
Composition of formulations containing polymers.

Ingredients	Chitosan [g]	Ethanol [mL]	HCl [mL]	HEC [g]	HPMC [g]	NaCMC [g]	PPG [g]	PVP [g]	TEC [mL]	Water [mL]
F1	–	20	–	1.0	0.2	0.4	0.23	–	–	–
F2	–	20	–	–	–	0.4	0.23	1.0	–	–
F3	0.5	20	10	–	–	–	0.23	0.4	–	–
F4	–	20	–	1.0	0.2	–	–	–	0.5	–
F5	–	20	–	1.0	–	0.4	0.23	–	–	10

HCl: Hydrogen chloride; HEC: Hydroxyethyl cellulose; HPMC: Hydroxypropyl methylcellulose; NaCMC: Carboxymethyl cellulose sodium salt; PPG: Polypropylene glycol; PVP:Polyvinylpyrrolidone; TEC: Triethyl citrate.