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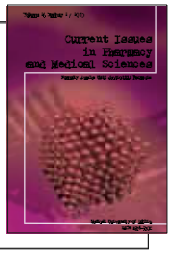

Comparison of fluconazole release from hydrogels with Syntalen MP and Syntalen KP and from hydrophilic cream

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ABSTRACT

Fluconazole is popular antifungal medicine, usually used per os in Candida spp. infections of the skin and mucous membranes, pityriasis versicolor, candidiasis organs, and also in the prophylaxis of fungal infections in patients with cancer and AIDS. There are attempts of formulation of the different forms of drug because of many side effects of fluconazole in oral administration. These are eye drops, injections and semisolid skin preparations. Thus, the aim of the study was preparing two hydrogels with Syntalen MP and Syntalen KP and hydrophilic cream, containing 1% of fluconazole and comparing the release of the substance from obtained preparations. At the beginning, gels and hydrophilic cream have been subjected to physical tests such as: slip and spreadability. Further, their rheological properties were evaluated. In the slip and spreadability tests, the cream had the best parameters, the rheological tests showed pseudoplastic character of flowing of gels and plastic flowing of the cream. All these three preparations showed the thixotropy. The release studies, conducted using the extracting chamber (according to FP IX) in Paddle Apparatus showed that the amount of released substance from gels is about two times bigger than from the cream, but the releasing from the gel with Syntalen MP is slightly better than from the gel with Syntalen KP.

Keywords: fluconazole release, hydrogels, hydrophilic cream, rheology

INTRODUCTION

Fluconazole is the synthetic antifungal substance, a derivative of the triazole. It is used in treatment of the throat and esophageal candidiasis caused by C. albicans and by other species (eg C. parapsilosis, C. tropicans, C. glabrata) [13].

It is also effective in treatment of the surface mycoses of the skin such as: tinea corporis, tinea cruris, tinea faciei, tinea mannum and tinea pedis [3].

The fungicidal activity is the inhibiting of 14α – demethylase which is responsible for the synthesis of ergo- sterole – the compound required for the synthesis of cell wall [8].

Now, fluconazole is available in tablets and injections, but the oral administration causes many side effects such as nausea, vomiting, abdominal pain, headache, liver and kidney damage [4]. Furthermore, there are many negative interactions with other drugs: hydrocortisone, midazolam, phenytoin, losartan. For these reasons, other routes of administration of the drug, bypassing the gastrointestinal tract are examined. The skin gels [1,4,10,15], emulsions [3], iniections [14] and eye gels [16] were tested by the other authors.

Carbopols- carbomers are used as gelling agents. Due to their bioadhesive properties, the compatibility with the most of the ingredients, good thermal stability, excellent organoleptic characteristics and good patient acceptance they are widely used in pharmaceutical and cosmetic industries [11]. Carbopols are used as emulsifiers (0.1–0.5%), in suspensions as viscosity agent (0.5–1.0%) and in dermatologic preparations, gels and ointment bases (0.5–2.0%) [17].

In previous reports the release of fluconazole from hydrogels has been studied. However, the comparative studies between gel and cream are not described.

That is why the aim of this study was comparison of fluconazole release from hydrogels with Syntalen MP and Syntalen KP and from hydrophilic cream.

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MATERIALS AND METHODS

Chemicals. Fluconazole, Syntalen MP and KP, Salinip, Lanatte wax N PH, Speciol V95G were received as a gift from 3V Sigma SPA, IMCD, Warsaw; Triethylamine(TEA) – P.P.H. POCh Gliwice; Ethanol, Methanol - P.P.H. "Stanlab" Lublin; Liquid paraffine – Galenic Laboratory Olsztyn; White Petrolatum – Galenic Laboratory PZF Cefarm Lublin; Propylene glycol (PPG-1,2) – Laborchemie Apolda, Germany.

Apparatus. Rheotest 2 Medingen viscometer (NRD); Extensometer; Ultratermostat MLW UH 4 – VEB MLW Medingen Germany; Mixer Cito-UNGUATOR c/s – EPRUS; Magnetic stirrer- Type MM 6,Spectrophotometer Helios Omega UV-Vis, SpectroLab, Poland; Paddle Apparatus Erweka DT-600, Germany; Dialysis membrane Visking® Serva.

Preparations

Three kinds of preparations (two hydrogels P I, P II and hydrophilic cream P III) have been prepared. Their composition is given in Tab. 1.

Table 1. The composition of the preparations with fluconazole

Ingredients	P I	P II	P III
Fluconazole	2.0	2.0	2.0
White petrolatum	-	-	20.0
Liquid paraffin	-	-	10.0
PPG-1,2	10.0	10.0	-
Syntalen MP	1.0	-	-
Syntalen KP	-	1.0	-
Speziol V95	-	-	2.0
Lanettae WPH	-	-	10.0
TEA	1.0	1.0	-
Salinip	0.1	0.1	0.1
Ethanol (760g/l)	10.0	10.0	10.0
Water	75.0	75.0	46.0

Preparing of the two hydrogels (P I, P II)

Syntalen MP (P I) or Syntalen KP (P II) was dissolved in the water, then propylene glycol and ethanol solution of fluconazole was added. The solution was mixed by magnetic stirrer for 3h, and next it was neutralized by the addition of triethylamine in order to accelerate the gelation process.

Preparing of the hydrophilic cream (P III)

Wax lanatte, liquid parafine and white petrolatum were melted in the dish on a water bath. Then Speciol V 95G (dissolved in water at 75°C) and fluconazole (dissolved in ethanol) were added with continuous stirring.

All preparations were homogenized in Unguator® in order to obtain the uniform consistency.

Evaluation of the physical properties of preparation

Determination of the spreadability. Determination of the spreadability was conducted in extensometer at 25 ± 0.1°C [2, 9]. The relationship between the load and stretched surface of the preparations (cm^2) are showed on Fig. 1.

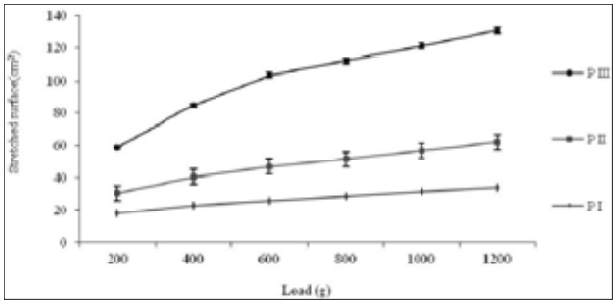

Fig. 1. Spredability of the preparations P I, P II, P III

Determination of the slip. In slip test the load, causing the move of two plates with the preparation between them, was measured. The average of three measurements is in Tab. 2.

Table 2. Studies of the slip

Preparations	Weight (g)	Weight (g)	Weight (g)	Mean average weight in (g)	SD ± (g), n=3
P I	11.83	11.71	12.05	11.86	± 0.1
P II	11.76	11.70	11.96	11.96	± 0.08
P III	5.87	5.87	5.87	5.87	± 0.0

Rheological studies. Rheological properties of the skin preparations allow to predict their behavior during production, storage and using, what is more, they determine the quality, utility and intended use of the drug [5,11, 12,18].

The studies were conducted at 25°C, using "RHEOTEST-2" with thermostat. The measurements were performed at shear rate (Dr) between 1.5–656.0 s^{-1} The flow curves are showed on Fig. 2, 3, 4.

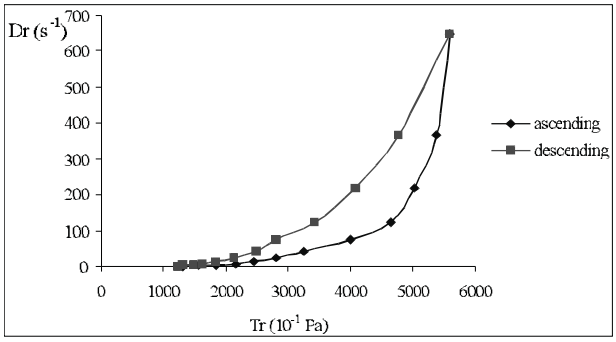

Fig. 2. Ascending and descending rheogram for the P I

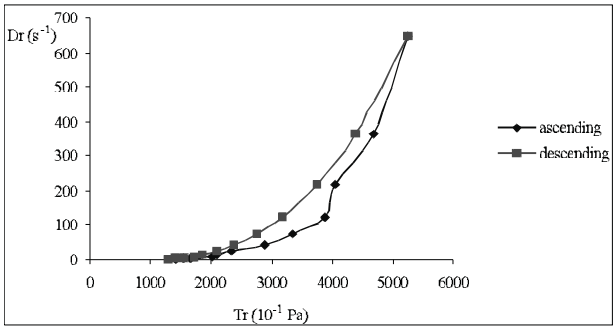

Fig. 3. Ascending and descending rheogram for the P II

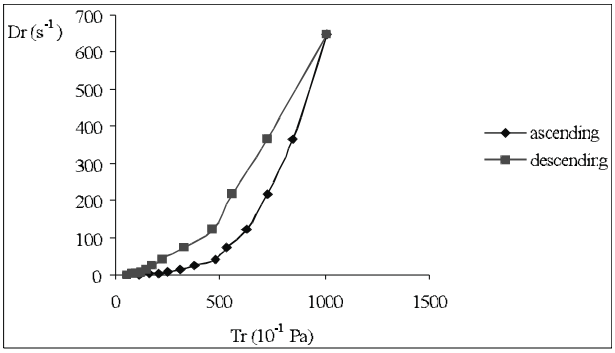

Fig. 4. Ascending and descending rheogram for the P III

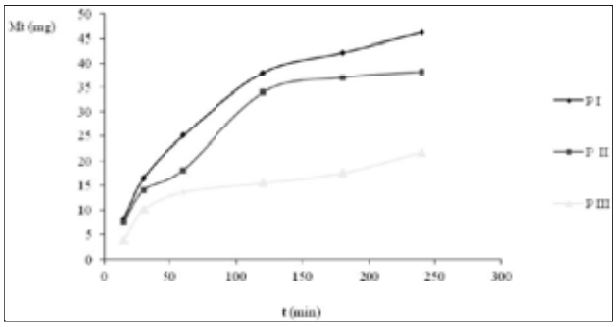

Fig. 5. The amount of released fluconazole from the preparations

Drug release studies

UV spectrum analysis of fluconazole. Standard stock solution was obtained by dissolving 100 mg of fluconazole in 100 ml of methanol. From this stock solution 10 ml was taken and transferred into a 100 ml volumetric flask. The volume was completed with methanol (100 μg/ml).

The estimation of fluconazole was carried out by spectrophotometer. The standard solution was scanned in the range of 200–400 nm to obtain the maximum wavelength.

The maximum absorbance was at the 260 nm wavelength.

Calibration graph of fluconazole. The standard solutions of fluconazole at concentrations 10, 20, 40, 60, 80, 100 μg/ml were prepared by appropriate dilution of fluconazole stock solution with methanol. The absorbances of these solutions were measured spectrophotometrically against blank of methanol at 260 nm. This procedure was repeated six times.

The estimation of fluconazole content. Three 1 g samples of preparations PI, PII, PIII were accurately weighed. The samples were transferred into 100-ml volumetric flasks and completed with methanol to the mark. Then the volume of 10 ml of each solution was diluted to 100 ml with the same solvent and the content of fluconazole was determined. The determination was repeated three times.

Fluconazole release studies were conducted by dialysis method, in the extraction chamber and in Paddle Apparatus according to FP IX [6,7,18] in the presence of phosphate buffer (pH= 6.8) at 32°C ± 1°C. The speed rate of paddle was 75 rpm. An amount of 3g of each preparation was weighed into the extraction chamber. The releasing was conducted through dialysis membrane Visking® Serva with pore diameter 0.45μm previously hydrated in acceptor solution. The samples (5 ml) were taken after 15, 30, 60, 120, 180, 240 min, the rest was completed with the phosphate buffer to the starting volume. Fluconazole release was determined spectrophotometrically at 260 nm and the fluconazole concentration was calculated from the regression equation taking into account the dilution.

The results are showed as the average ± SD of five calculations (Fig.5).

DISCUSSION

Two hydrogels P I and P II and one hydrophilic cream P III were prepared.

In an organoleptic examination hydrogels were homogenous, transparent and they had good spreadability on the skin. The hydrophilic cream had semisolid consistency, white color and very good spreadability on the skin.

The tests showed that the cream has the best spreadability; after 6 min., at a load 1200g, the spread surface is 68.32 cm^2 ± 0.43 cm^2 and hydrogels are worse; their spreadability is respectively P I 34.01 cm^2 ± 0.18 cm^2 and P II 27.94 cm^2 ± 0.12 cm^2.

The results of slip tests for hydrogels P I and P II are similar 11.86–11.96 g, for hydrophilic cream is two times lower 5.87 g ± 0.

The rheological studies showed the hydrogels have plastic character and the cream has pseudoplastic character of flowing. The viscosity of the obtained preparations at the shear rate D_r = 24.3 s^{-1} was respectively 11599 mPa·s (PI), 9602 mPa·s (PII) and 1532 mPa·s (PIII). All the preparations have thixotropy what is demonstrated by the closed hysteresis loop areas on rheograms. The most thixotropy has hydrogel PI and the cream PIII has the smallest. The hysteresis loop areas were respectively 421224.8 (10^{-1}Pa) (PI), 193357.4 (10^{-1}Pa) (PII) and 77198.7 (10^{-1}Pa) (PIII).

For quantitative analysis of fluconazole we adopted the analytical procedure published previously [19] with some modifications introduced.

The selectivity of the used method for the analysis of fluconazole was evaluated by analysis of placebo blank and the resulting absorbance readings were the same as reagent blank, inferring no interference from the placebo. These results confirm the selectivity of the used method.

To evaluate linearity, the standard solutions in the range of 10–100 μg/ml were assayed. The calibration curve expressed by the regression equation is presented in Tab. 3. Good linearity between the absorbance and the concentration of fluconazole was observed with coefficient correlation (r = 0.9995) and was confirmed by using residual analysis.

Table 3. The statistic estimation of standard curve ABS = f(c)

Concentration [µg/ml]	Precision	ABS average	± SD	± RSD [%]	Regression equation
10	DP	0.0250	0.000632	2.53	Y=0.00236x + 0.00062 R^2= 0.9995
	BDP	0.0250	0.000632	2.53	
40	DP	0.0950	0.000632	0.67	
	BDP	0.0950	0.000816	0.86	
80	DP	0.1940	0.000632	0.33	
	BDP	0.1933	0.001350	0.70	

ABS – absorbance, SD – standard deviation, RSD – relative standard deviation, DP – day precision (n=5), BDP – between day precision (n=15)

To check the precision of the used method, solutions containing three different concentrations of fluconazole were prepared and analyzed in five replicates during the same day (intraday precision) and three consecutive days (interday precision), and the results were summarized in Tab. 3. The low values of the percentage relative standard deviation (RSD: 0.33–2.53% for intraday) and (RSD: 0.70,2.53% for interday) indicate the high precision of the used method.

The adopted method was applied for the determination of fluconazole in the prepared hydrogels (P I, P II) and cream (P III). The drug content in the preparation was found to be 2.02% ± 1.62% (RSD) for P I, 2.01% ± 3.10% (RSD) for P II and 2.03% ± 3.48% (RSD) for P III. The accuracy of this method was confirmed after application of Student's t-test. There was no significant difference between the mean recovery of fluconazole (P I: 101.17%; P II: 100.73%; P III: 101.35) and 100% (Tab. 4).

Table 4. The estimation of fluconazole content

Preparations	Content [µg/ml]	± SE	± SD	RSD [%]	Recovery [%]
P I	20.2340	0.0670	0.3283	1.62	101.17
P II	20.1458	0.0127	0.6239	3.10	100.73
P III	20.2693	0.1441	0.8062	3.48	101.35

SE – standard error, RSD – relative standard devation, SD – standard deviation

The release studies showed that fluconazole releases from hydrogels better than from cream.

After 240 min. 77.12% ± 0.4% of fluconazole released from the hydrogel P I, 63.59% ± 0.24% from the hydrogel P II and 36.46% ± 0.17% from the cream P III.

CONCLUSIONS

1. The hydrophilic cream had better slip and spreadability but fluconazole release was two times worse than from hydrogels.
2. The hydrogel P II (with Syntalen KP) had slightly better slip and spreadability but fluconazole release from hydrogel P II is worse than hydrogel P I (with Syntalen MP).
3. Among the three bases the hydrogel P I (with Syntalen MP) is the best for transdermal delivery of fluconazole.

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