Drug Development and Industrial Pharmacy, 25(5), 679–684 (1999)

COMMUNICATION

Dermal Patches for the Controlled Release of Miconazole: Influence of the Drug Concentration on the Technological Characteristics

P. Minghetti,* F. Cilurzo, A. Casiraghi, F. A. Molla, and L. Montanari

Istituto di Chimica Farmaceutica e Tossicologica, Università degli Studi di Milano, Viale Abruzzi, 42, 20131 Milano, Italy

ABSTRACT

The aim of this work was to evaluate the effect of different amounts of miconazole nitrate (MIC) on the technological characteristics (drug release profile, adhesiveness, and water vapor permeability) of a nonocclusive dermal therapeutic system (DTS) for the treatment of tinea unguium infection. Artificial silk was used as a backing layer. The self-adhesive matrix was made of a mixture of Plastoid® E 35 L (PL L), an adhesive hydrophilic polymer, and Eudragit® NE 40 D (EU NE), a nonadhesive hydrophobic polymer able to modify the drug release. Plastoid E 35 L is a copolymer of dimethylaminoethyl methacrylate and neutral methacrylic ester. Eudragit NE 40 D is a copolymer of ethylacrylate and methylmethacrylate. Formulations containing different amounts of MIC, ranging from 2% to 16% w/w of the dried matrix, were designed. Drug crystals were observed by polarizing light microscopy, proving the incomplete solubilization of MIC only in the matrices containing 8% w/w or more of this compound. All systems provided an in vitro control of drug release for at least 24 hr. The amount of the drug released increased with drug loading in all DTS. The percentage of the drug released was the same in all the DTS containing detectable crystals of MIC. When the MIC was completely dissolved in the matrix, the released percentage decreased when drug loading increased. The water vapor permeability and the adhesive properties of the DTS were excellent.

*To whom correspondence should be addressed. Telephone: 0039 2 29502255. Fax: 0039 2 29514197.

INTRODUCTION

The high efficacy of topical miconazole (MIC) for the treatment of dermatomycoses has been well documented (1); the drug is usually administered as a 2% cream. Dermal therapeutic systems (DTSs) may prove to be a good alternative to the conventional topical forms. This could be of particular interest in the case of tinea unguium infection as topical creams rarely work (2). The system should not be occlusive because occlusion produces water accumulation, which may result in maceration of the skin, detachment of the therapeutic system, and favor growth of pathogenic microorganisms (3).

The aim of this work was to evaluate the effect of different amonts of MIC on the following characteristics of a nonocclusive monolayer DTS: ability to control the release of MIC in vitro, adhesive properties, and water vapor permeability (WVP). Seven types of formulations containing amounts of drug ranging from 2% to 16% w/w of the dried matrix were designed to obtain an amount of drug released in vitro in 24 hr above 0.052–0.104 mg/cm^2, which are the doses normally applied with ointments (4).

On the basis of our previous studies, artificial silk, composed of fibers of rayon acetate, was used as a backing layer (5). The self-adhesive matrix was made of a mixture of an adhesive polymer, Plastoid® E 35 L (PL L), and of a nonadhesive polymer able to modify the drug release profile, Eudragit® NE 40 D (EU NE) (6). Plastoid E 35 L is a hydrophilic copolymer of dimethylaminoethyl methacrylate and neutral methacrylic esters. Eudragit NE 40 D is a hydrophobic copolymer of ethylacrylate and methylmethacrylate.

All the prepared DTSs were characterized by drug assay, light microscopy, dissolution test, tack-and-peel adhesion tests, WVP test, and moisture content.

MATERIALS AND METHODS

Materials

Micronized miconazole nitrate was from Industrie Chimiche Italiane, Milan, Italy. Plastoid E 35 L (PL L) (Röhm, Darmstadt, Germany) is a copolymer of dimethylaminoethyl methacrylate and neutral methacrylic esters neutralized by fatty acids. It is supplied as an aqueous solution that has a dry weight of 34% w/w. Eudragit NE 40 D (EU NE) (Röhm) is a neutral copolymer of ethylacrylate and methylmethacrylate. It is supplied as an aqueous dispersion at 40% w/w. The composition of the suspending medium was not indicated by the producer. All the polymers were kindly donated by Rofarma-Röhm, Milan, Italy. Artificial silk, based on fibers of rayon acetate, was used; the supplier's specifications include thickness 130 μm; weight 70 g × m^2; warp/weft 42/26 yarns/cm; elongation at break 15%; tensile strength 45 MPa (Bouty, Milan, Italy). All the solvents were of analytical grade.

Preparation of Matrix Mixtures

The polymeric formulation of the matrix was the same for all DTS prepared: the adhesive polymer (PL L) was mixed with the nonadhesive polymer (EU NE) in the fixed percentage of 65/35% w/w of the dried matrix. The MIC contents in the dried matrices are listed in Table 1. The components were mixed using a paddle stirrer under vacuum, and they were stirred at 50 rpm for 1 hr.

Preparation of Dermal Therapeutic Systems

The DTSs were prepared using a laboratory coating unit Mathis LTE-S(M) (Zurich, Switzerland). The mix-

Table 1

Composition of the Dried Matrices of Miconazole Patches

Formulation	MIC (% w/w)	Plastoid E 35 L (% w/w)	Eudragit NE 40 D (% w/w)
1	0	65.0	35.0
2	2	63.7	34.3
3	6	61.1	32.9
4	7	60.5	32.5
5	8	59.8	32.2
6	9	59.1	31.9
7	12	57.2	30.8
8	16	54.6	29.4

ture was spread on the backing layer at a constant rate of 1 m/min and at the thickness of 370 μm. The systems were dried at 60°C for 15 min, covered with the protecting foil, and stored in an airtight container until used.

Drug Content

A sample of 9 cm^2 of DTS was solubilized with 50 ml methanol. The sample was filtered through Durapore filters with a pore size of 0.22 μm (Millex GV, Millipore, Bedford, MA). Solutions were assayed by high-performance liquid chromatography (HPLC) with the method reported below. Each value represents the average of three readings.

Microscopy

The presence of solid particles in the matrices was evaluated using a Zeiss mod. Axioscope microscope (Oberkochen, Germany) fitted with a polarizing objective. The thermal behavior of the solid particles was examined using a microscope fitted with a Kofler condenser (Kofler, Reichert, Austria).

Dissolution Test

A modified cell method Ph. Eur. (2.9.4.2) was used for the dissolution test. The support of the extraction cell was modified: (*a*) the cavity intended to hold the reservoir patch was eliminated; (*b*) the lower part was designed to minimize the dead volume between the cell and the bottom of the vessel. The patch was cut into appropriate size fragments (2–9 cm^2) and put flat on the cell with the release surface uppermost with a Cuprophan® membrane (AKZ0 Nobel Faser AG, Wuppertal, Germany) on it. A distance of 25 ± 2 mm was maintained between the paddle blade and the surface of the patch. The temperature was kept at 32°C ± 0.5°C, the paddle speed was 50 rpm, and 900 ml of acetate buffer pH 4.5 was used as the dissolution medium. At specified times, 100-ml samples were withdrawn from the vessels and replaced by fresh medium. The samples were filtered and assayed by the following HPLC method. Each value represents the average of six sample readings.

The release rate constant was calculated according to Higuchi's equation (7) as follows:

$$M_t/M_\infty = kt^{-0.5}$$

where M_t was the amount of drug released at time t, M_∞ was the drug loading in the matrix, and k was the release rate constant expressed as hr^{-1}.

Drug Assay

The MIC concentrations in the dissolution medium were assayed by HPLC with ultraviolet (UV) detection. The HPLC system was a Waters mod. LC Module 1 (Milford, MA). The column was a C18 reverse-phase (C18 Spherisorb S5 ODS2, 15 cm, phase sep HPLC (Deeside, U.K.). The wavelength was set at 232 nm. The composition of the eluent was methanol/ammonium carbonate 0.1 N/tetrahydrofurane (78/20/2 v/v/v). The drug concentrations were determined from MIC standard curves (1–50 μg/ml). The total amount of MIC released (concentration in μg/ml × volume of the receptor phase) and amount of MIC released per unit area (μg/cm^2) were calculated. The theoretical quantitative detection limit was about 0.5 μg/ml. The standard curves have coefficients of correlation of $0.9997 \pm 2.05 \times 10^{-4}$ (mean ± SD, $n = 5$). The coefficient of variation was 6.35% for a 5-μg/ml standard solution ($n = 10$).

Moisture Content of the Dermal Therapeutic Systems

A sample of 25 cm^2 of each DTS was weighed immediately after preparation, frozen at −18°C, and then dried to constant weight by freeze-drying with a lyophilization unit (Modulyo 4 K Freeze Dryer, Edwards, Crawley, England). Each value represents the average of three determinations.

Water Vapour Permeability Evaluation

The WVP was determined with the foam dressing method (BP 1993 ed., Appendix XXJ). The air-forced oven was substituted with a natural air circulation oven (5). Each WVP value represents the average of five determinations.

Adhesion Properties Evaluation

Peel Adhesion 180° Test

For the peel adhesion 180° test (8), immediately after preparation, adhesive patches were cut in strips, 2.5 cm in width, and applied to an adherent plate made of stainless steel, smoothed with a 4.5 pound roller five times, and pulled from the stainless steel at a 180° angle and at a rate of 300 m/min. The test was performed with a tensile testing machine Acquati mod. A 10 I (Arese, Milan, Italy). The matrix had to strip cleanly from the plate, leaving no visually noticeable residue. The force was expressed in centinewton (cN) per centimeter width of

Table 2

Theoretical Percentage of Miconazole Loaded and Experimental Drug Content in the Patches and Data of the Dissolution Test

Formulation	MIC Loaded (% w/w)	MIC Content (μg/ml ± SD)	$k \times 10^3$ [a] (h^{-1} ± SD)	MIC Released in 24 hr (μg/cm^2 ± SD)
2	2	139.5 ± 6.5	198 ± 8	118 ± 2
3	6	395.4 ± 1.6	189 ± 8	275 ± 10
4	7	463.3 ± 4.5	173 ± 8	307 ± 9
5	8	592.1 ± 9.2	126 ± 1	331.5 ± 11
6	9	621.9 ± 22.2	127 ± 8	342.7 ± 35
7	12	834.3 ± 8.0	125 ± 5	458.7 ± 39
8	16	1189.2 ± 70.3	124 ± 2	661.4 ± 14
MIC[b]	—	—	11 ± 3	—

[a] k is the release rate constant calculated according to Higughi's equation.
[b] Data related to a dissolution test performed in the same condition using MIC powder.

adhesive tape under test. Peel adhesion values represent the mean of three determinations.

Thumb Tack Test

For the thumb tack test (9), the thumb was pressed lightly to have contact on a sample for a short time and then quickly withdrawn. By varying the pressure and time of contact and noting the difficulty of pulling the thumb from the adhesive, it is possible to perceive how easily, quickly, and strongly the adhesive can form a bond with the skin. All the tests were simultaneously performed and were blind.

RESULTS AND DISCUSSION

The drug contents of each patch are reported in Table 2. Some large and irregularly-shaped crystals were visible by microscopy only in the DTS containing 8% w/w or

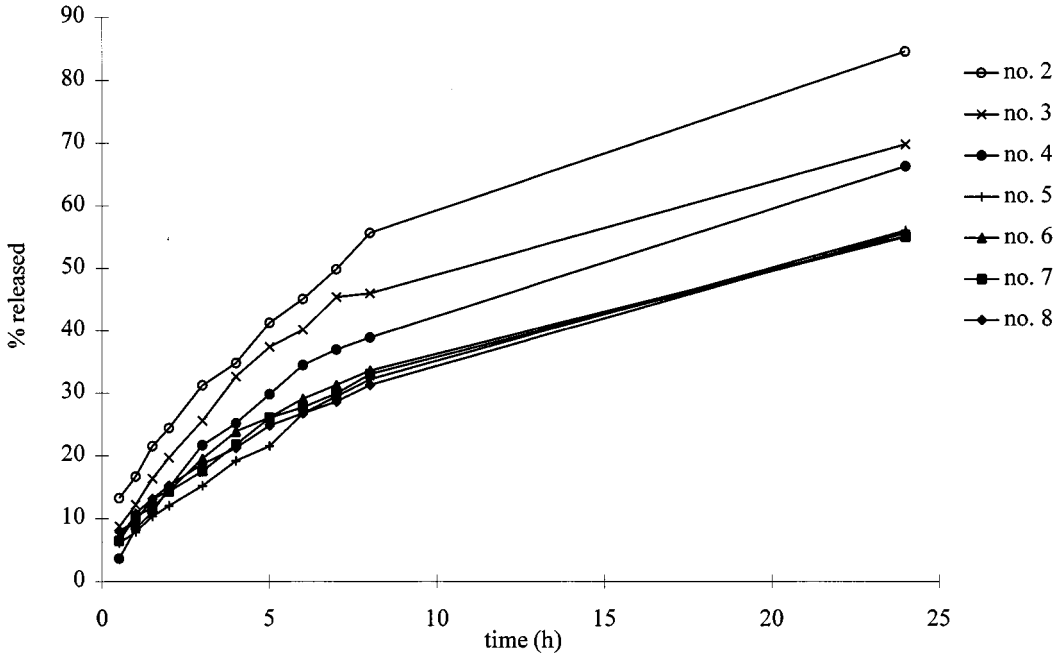

Figure 1. Percentages of MIC released from DTS 2–8 (n = 6; error bars are SD).

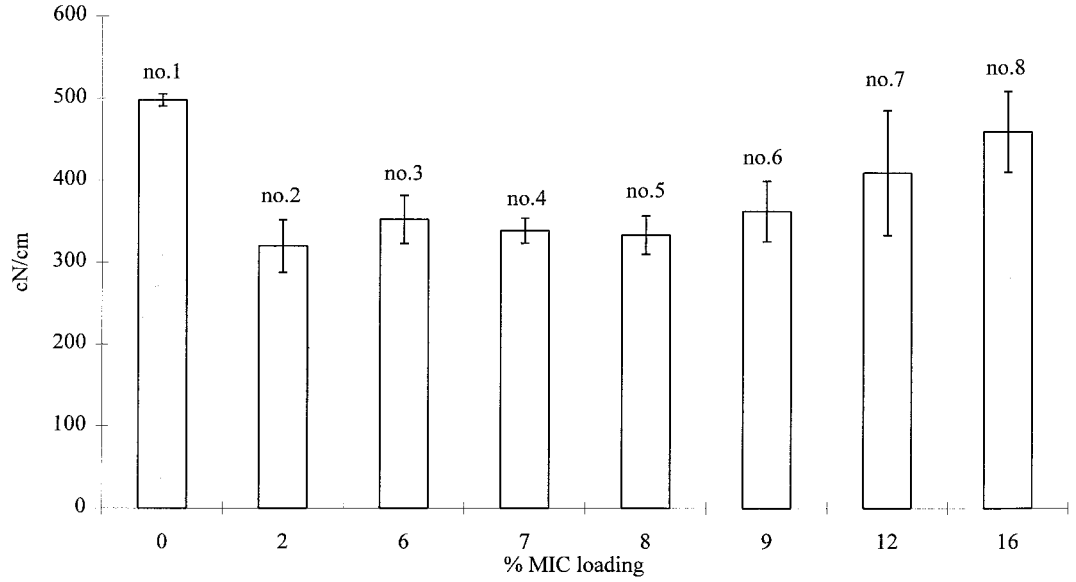

Figure 2. Peel adhesion values of DTS 1–8 ($n = 3$; error bars are SD).

more of MIC (formulations 5, 6, 7, 8). As the quantitative determination of the solubility of the drug in the dried matrix requires a specific study, for our purposes we assumed that the solubility of MIC in the matrix was included in the range 7–8% w/w.

The crystals were observed to melt when the temperature was increased to approximately 100°C. The crystals came from the incorporated MIC, even though this melting point was well below that of the pure drug (182°C–184°C). This temperature was more than 35°C above the one determined for the endogenous surfactant of the EU NE (50°C) (10) and also above the melting point of the miconazole base (83°C–87°C).

The MIC released in the considered period increased with drug loading in all DTS independently of the detectable presence of MIC crystals (Table 2).

Formulation 2 showed an almost complete drug release in 24 hr; in the same period, formulations 3 and 4 released more than 65% of the drug content, while formulations 5, 6, 7, and 8 released 55% of the total MIC loaded (Fig. 1). The drug release was controlled by the diffusion of MIC from a monolithic matrix and followed the relationship of the square root of time in the first 8 hr ($.991 < r^2 < .997$).

Patches with crystals showed the same release rate constant k, while in the DTS containing solubilized MIC, k increased when the drug content decreased (Table 2). In every case, the release rate constant was greater than the dissolution rate constant of the pure MIC. The amounts released in 24 hr (Table 2) were higher than the dose normally applied using ointments (0.052–0.104 mg/cm^2 per day) for all DTSs (4).

The weights and moisture contents of the patches were not significantly different for all the formulations and were, respectively, 171.3 $\pm$ 2.2 g/m^2 and 22.2 $\pm$ 1.16 g/m^2.

The WVP was excellent for all the prepared DTSs and was influenced by the MIC loading in a very slight way. The placebo patch (no. 1, Table 1) had a WVP value of 1359 $\pm$ 51 g/m^2 $\times$ 24 hr, while the WVP of the patches containing MIC were between the minimum of 1304 $\pm$ 72 g/m^2 $\times$ 24 hr (no. 8) and the maximum of 1556 $\pm$ 61 g/m^2 $\times$ 24 h (no. 2).

Even if the peel adhesion values of the DTSs containing MIC were always lower than the value of the placebo patch, the adhesive properties were satisfactory for all the therapeutic systems (Fig. 2). During the test, all the patches were stripped cleanly from the plate and left no visually noticeable residue. This proved that the anchorage of the matrix to the backing layer and the cohesion of the matrix were good.

The thumbtack test results confirmed the good adhesive properties of the DTSs on the skin. Formulations 1 and 8 showed the best adhesion properties.

CONCLUSION

The mixture of Plastoid E 35 L and Eudragit NE 40 D, 65/35% w/w of the dried matrix, laminated on the artificial silk proved to be suitable for the preparation of controlled-release therapeutic systems of MIC. All the systems provided a drug release control in vitro for at least 24 hr. The amounts released in 24 hr were higher than the dose normally applied using ointments. This suggests the suitability of these DTSs for preliminary in vivo studies.

The MIC crystals were observed in patches containing a drug concentration of 8% w/w or more in the dried matrix. We assumed that the solubility of MIC in the matrix was included in the range 7–8% w/w. The release rate constant of the MIC dispersed in the matrix was higher than the dissolution rate constant of the pure drug. The calculated release rate constant decreased when the percentage of loaded MIC increased until the drug was solubilized in the matrix. When crystals were detected, a higher amount of drug did not affect the percentage released in time. Therefore, the presence of only solubilized drug or of both solubilized and crystalline drug seems to be an important parameter as far as drug release rate is concerned. The physical state of MIC has to be considered during formulation studies, as well as in stability tests.

The addition of MIC slightly influenced the adhesion properties and the WVP of the patches, and both were very satisfactory.

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