Econazole Nitrate-Loaded MCM-41 for an Antifungal Topical Powder Formulation

VALERIA AMBROGI,[1] LUANA PERIOLI,[1] CINZIA PAGANO,[1] FABIO MARMOTTINI,[2] MASSIMO MORETTI,[3] FABIOLA MIZZI,[1] CARLO ROSSI[1]

[1]Dipartimento di Chimica e Tecnologia del Farmaco, Via del Liceo 1, 06123 Perugia, Italy

[2]Dipartimento di Ingegneria Civile ed Ambientale, Via G. Duranti 93, Perugia, Italy

[3]Dipartimento di Specialità Medico-Chirurgiche e Sanità Pubblica, Via del Giochetto, Perugia, Italy

Received 17 February 2010; accepted 15 March 2010

Published online 18 May 2010 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.22183

ABSTRACT: The aim of this article was to prepare a topical powder for the treatment of fungal infections, such as *Candida* intertrigo and tinea pedis. Thus, an econazole nitrate (ECO) formulation with improved drug dissolution and proper moisture adsorption was designed. ECO was melt with the mesoporous silicate MCM-41 (drug/MCM-41 1/3) and the resulting inclusion compound was characterized by X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC). The drug loading was confirmed by the decrease of specific surface area and pore volume between MCM-41 and the inclusion compound. Formulations containing the inclusion compound were prepared and submitted to *in vitro* dissolution test and *in vitro* antifungal activity. A remarkable dissolution rate improvement as well as a higher antifungal activity was observed for the inclusion compound if compared to a commercial product. Moisture sorption properties for MCM-41 and formulations were evaluated as well. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:4738–4745, 2010

Keywords: mesoporous materials; skin mycotic infections; inclusion compound; X-ray diffractometry; drug dissolution; adsorption; crystals; formulation; moisture sorption; excipients; physical stability

INTRODUCTION

ECO is an antifungal agent largely used for the treatment of many mycotic infections[1,2] of skin, hair, and mucous membranes. Tinea corporis, tinea pedis, and *Candida* intertrigo are common superficial fungal infections.[3] Tinea corporis and tinea pedis are caused by keratinophilic organisms that thrive in the epidermis, hair, and nails. *Candida albicans* is the yeast most often responsible for superficial mycoses. It is ubiquitous and becomes pathogen in particular conditions, such as decrease of immunity, administration of antibiotics, diabetes mellitus, malignancy, disturb the host defense mechanisms. Examples of superficial *Candida* infections include intertrigo, oropharyngeal thrush, vaginitis, and diaper dermatitis. Intertrigo is an inflammation of skin folds caused by skin-on-skin friction.[4] This condition is characterized by initial mild erythema that may progress to a more intense inflammation followed by erosions, oozing, exudation, and maceration. Intertrigo is facilitated by moisture trapped in deep skin folds where air circulation is limited. These conditions offer a fertile breeding ground for various microorganisms and give rise to secondary cutaneous infections.

The most common approach to these fungal infections is a topical treatment with antifungal lotions, creams, and powders. In the case of intertrigo, since minimizing moisture and friction is also required, the use of either adsorptive powders such as talc, cornstarch, or barrier cream is associated with drug treatment.

ECO, a drug typically used in the treatment of these infections, shows great antifungal activity; however, its efficacy is limited by its poor aqueous solubility and dissolution rate.[1,2] Previous studies showed that both dissolution properties and consequently microbiological activities of econazole can be improved by applying technological approaches such as complexation with cyclodextrins.[5–7] Thus, the aim of the present work was to realize an ECO topical powder formulation with improved drug dissolution and adsorption properties in order to obtain a faster

Correspondence to: Valeria Ambrogi (Telephone: +39-075-5855135; Fax: +39-075-5855135;
E-mail: valeria.ambrogi@unipg.it)

Journal of Pharmaceutical Sciences, Vol. 99, 4738–4745 (2010)

release of the drug. This formulation may have a positive effect for the treatment of these fungal infections accompanied by the presence of moisture.

Recently, a silicate mesoporous compound, MCM-41, has been proposed as an agent for improving the dissolution rate of poorly water-soluble molecules namely the growth plant hormone, 3-indolbutyric acid,[8] the nonsteroidal anti-inflammatory agent piroxicam,[9] and the antiepileptic drug carbamazepine.[10] MCM-41[11] is characterized by narrow pore size distribution, varying from 1.5 to 10 nm, and high surface areas (above 700 m^2/g). It has a hexagonal array of unidimensional and parallel channels with negligible pore-blocking effects.[12] Its surface presents free hydroxyl groups which are easily accessible for specific interactions with molecules susceptible of making hydrogen bonds. Once adsorbed, as previously observed,[8–10] the drug is not arranged in crystalline form and is distributed in a high surface area. These conditions favor its fast dissolution when in contact with biological fluids. Other potential advantage in using MCM-41 is its water sorbent property because of the abundant presence of number of free silanol groups on its amorphous surface structure.[13] Therefore, by forming hydrogen bonds, a large amount of water can be adsorbed and this can contribute to adsorb the moisture present in skin–skin fold, responsible for maceration and microorganism growth.

EXPERIMENTAL

Materials

Cetyltrimethylammonium chloride (25% wt) and sodium metasilicate were obtained from Sigma–Aldrich Chemical (Milano, Italy). ECO was purchased from Comifar (Ellera, Perugia, Italy). Deionized water was obtained by a reverse osmosis process with a Milli Q system (Millipore, Rome, Italy). Other reagents and solvents were of reagent grade and were used without further purification.

Methods

Characterization

X-ray powder diffraction (XRPD) patterns were taken by a computer-controlled PW 1710 Philips diffractometer (Lelyweg, the Netherlands), using the Ni-filtered Cu Kα radiation.

Differential scanning calorimetry (DSC) analyses were performed using an automatic thermal analyzer (Mettler Toledo DSC821^e). Temperature calibrations were achieved by using indium standard. Holed aluminum pans were employed for all samples and an empty pan, prepared in the same way, was used as a reference. Samples of 3–6 mg were weighted directly into the aluminum pans and thermal analyses were conducted at a heating rate of 5°C/min from 20 to 300°C.

Thermogravimetric analyses were carried out by a thermoanalyzer (TG-DTA Netzsch STA 490) at heating rate of 10°C/min with 30 mL/min air flow.

Nitrogen adsorption–desorption isotherms were determined with an apparatus Micromeritics ASAP 2010 (Norcross, GA) at 77 K on the samples degassed overnight at room temperature. The specific surface area were calculated by applying the Brunauer, Emmett, and Teller (BET) method,[14] while the pore size characterization was detected by using the BJH–KJS method.[15]

^{1}H-NMR spectra were recorded by a Brucker AC 200 instrument in DMSO solution.

ECO computer model was obtained by *Molecular Operating Environment* (*MOE*) (Chemical Computing Group, Inc., Montreal, Quebec, Canada, version 2005–2006).

Synthesis of Mesoporous MCM-41

MCM-41 was synthesized according to Schulz-Ekloff procedure[16] pouring an aqueous solution (300 mL) of sodium metasilicate (30 g, Sigma–Aldrich Chemical) into an aqueous solution (1000 mL) of cetyltrimethylammonium chloride (CTACl, 68.8 g, 25%, w/w, water solution, Sigma–Aldrich Chemical). Then, ethyl acetate (30 mL) was quickly added under vigorous stirring. After 2 h at room temperature, the mixture was heated for 40 h at 80°C. The resulting solid was filtered, abundantly washed with water and ethanol, dried at room temperature, and at last calcined at 600°C for 20 h in order to eliminate the surfactant.

ECO-Loading Procedure

Appropriate amounts of ECO and MCM-41 (weight ratio 1:3, that is, 25% of drug in final loaded MCM-41) were mixed together until a homogeneous dispersion was obtained. The mixture was heated at 161–165°C under stirring for 30 min, then was cooled rapidly by using dry CO_2.

The final product (MCM-41–ECO) underwent XRPD, surface area, TGA, and DSC analyses.

Preparation of ECO and MCM-41 Physical Mixture

The physical mixture was prepared by mixing crystalline ECO and MCM-41 (1:3 weight ratio) with a spatula.

Preparation of Formulations A, B, and C

These formulations were prepared by mixing appropriate amounts of the ingredients (Tab. 1) with mortar and pestel and Pevaryl® powder (Janssen-Cilag) was taken as a reference (formulation D).

Table 1. Composition of Formulations A, B, C, and D

Ingredients	Formulation A (g)	Formulation B (g)	Formulation C (Physical Mixture) (g)	Formulation D (Commercial Formulation) (g)
ECO			1.0	1.0
ZnO	5.0	5.0	5.0	5.0
Talc	88.8			91.6
Colloidal silica	2.2	2.2	2.2	2.2
MCM-41		88.8	91.8	
MCM-41–ECO	4.0	4.0		
Fragrance				0.2

ECO In Vitro *Release*

The *in vitro* drug release was performed by using the rotating paddle method at 60 rpm according to Farmacopea Ufficiale Italiana XII ed. (F.U. XII) at 37 ± 0.5°C and in sink conditions (samples corresponding to 70 mg of free ECO in 1000 mL of deionized water). Four milliliters of dissolution fluid was removed from the vessel at predetermined intervals and replaced by the same volume of fresh dissolution medium preheated at 37°C. The samples were centrifuged (Centrifuge ALC 4218) at 4000 rpm for 5 min and the ECO content was determined by second derivative UV spectroscopy ($\lambda_{max} = 278.0$ nm). All experiments were performed in triplicate and the error was expressed as standard deviation.

In Vitro *Antifungal Activity Evaluation*

Formulations A, B, and C were suspended in low-melting-point agarose water solution maintained at 37°C at a 1.25 mg/mL final concentration and were compared to formulation D taken as a reference control.

C. albicans ATCC 10231 strain was used in this study by applying the diffusion test on Mueller–Hinton agar, basically following the procedure described by the National Committee for Clinical Laboratory Standards (NCCLS) document M44-A (NCCLS, 2004) with minor modifications. Microorganisms were grown and maintained aerobically at 35–37°C on Sabouraud Dextrose Agar with chloramphenicol (Panreac, Barcelona, Spain). Candidal cells were prepared by transferring a single colony from the agar plates into Sabouraud Dextrose Broth (Biolife, Milan, Italy) and by incubating it in aerobic conditions overnight at 35°C. Cultures were then centrifuged at 1000*g* for 10 min and the cells resuspended in 0.9% NaCl to match the 0.5 McFarland turbidity standard (yeast suspensions containing $\sim$1 to 5×10^6 cells per milliliter).

Within 15 min, after adjusting the turbidity of the inoculum suspension, the dried surfaces of Müeller-Hinton plus 2% glucose agar plates (90.0 mm diameter Petri dishes containing agar at a depth of 4.0 mm) were seeded with *C. albicans* test strain. A sterile cotton swab was dipped into the adjusted suspension and the agar plates were inoculated by streaking the swab over the entire agar surface (the procedure was repeated by streaking two more times, rotating the plate approximately 60° each time to ensure an even distribution of inoculum).

After seeding, 4 mm diameter cavities were punched out and 50 μL aliquots of the formulation under study suspended in agarose were transferred into each cavity. The plates were kept at room temperature for about 2 min to allow the agarose to solidify and then were incubated under air at 35°C for 24 h. Zone diameter endpoints were measured with calipers from the point where there was a sharp decline in the density of growth.

Moisture Adsorption Studies

Pyrex desiccators containing appropriate saturated salt solutions (Tab. 2) in distilled water were used to create chambers with different levels of relative humidity. All desiccators were kept at ca. 20°C to maintain the desired relative humidity level. The tested samples (0.500 g) were placed in Petri dishes (14 cm diameter) and kept in desiccators for 30 days. After 1, 2, 3, 7, 14, 25, and 30 days, the samples were again accurately weighted and the adsorbed moisture was determined by means the following formula:

$$\frac{M - M_i}{M_i} \times 100 = \%\ \text{of adsorbed water}$$

where M is the weight at predetermined interval and M_i the initial weight.

Table 2. Saturated Salt Solutions Used for Different Relative Humidity Levels

Salt	Relative Humidity at 20°C
Magnesium chloride	33
Potassium carbonate	44
Sodium bromide	59
Sodium nitrite	65
Sodium chloride	75
Potassium chloride	85
Potassium nitrate	93

 DOI 10.1002/jps

Experiments were performed three times in order to evaluate their reproducibility.

Storage Stability Studies

Physical stability tests were performed by storing MCM-41–ECO at 40°C in a dessicator over $CaCl_2$ for 30 days. Samples were monitored by XRPD after 1, 7, 15, and 30 days.

RESULTS AND DISCUSSION

ECO Loading

As a first attempt, the preparation of inclusion compound was performed according to the classical method[8,17] by equilibrating a drug solution with MCM-41, followed by filtration of the suspension. As ECO is sparingly soluble in ethanol, but shows good solubility in methanol and dichloromethane, several attempts were done in these solvents and in their mixture with ethanol. Since by this procedure only a very poor ECO loading was obtained, the melting procedure was performed. This method is normally applied to obtain solid dispersion[18] or to get cyclodextrin complexes[19] or adsorption compounds on porous calcium silicates.[20] Recently, it has been proposed for loading drugs on SBA-15[21] as well.

Thermal stability of ECO was immediately checked. Unfortunately the drug, whose melting point is 165°C, decomposes by slightly increasing the temperature (Fig. 1). Therefore, drug loading was performed at 165°C. In these temperature conditions no decomposition products were detected by ^{1}H-NMR (data not reported).

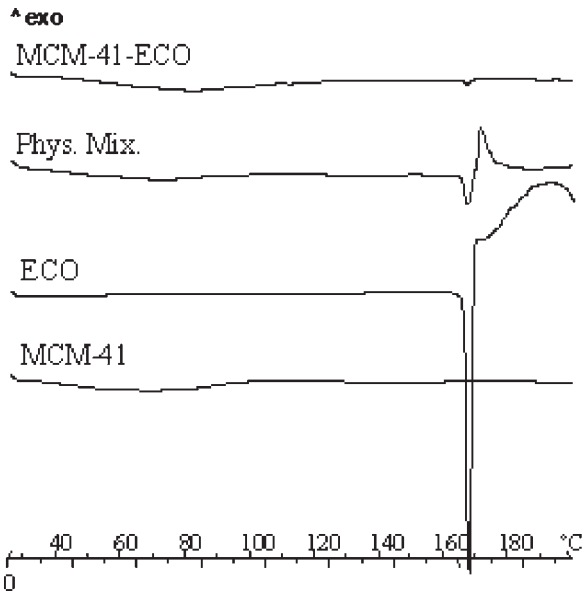

Figure 1. Thermal behavior of MCM-41, ECO, physical mixture, and MCM-41–ECO.

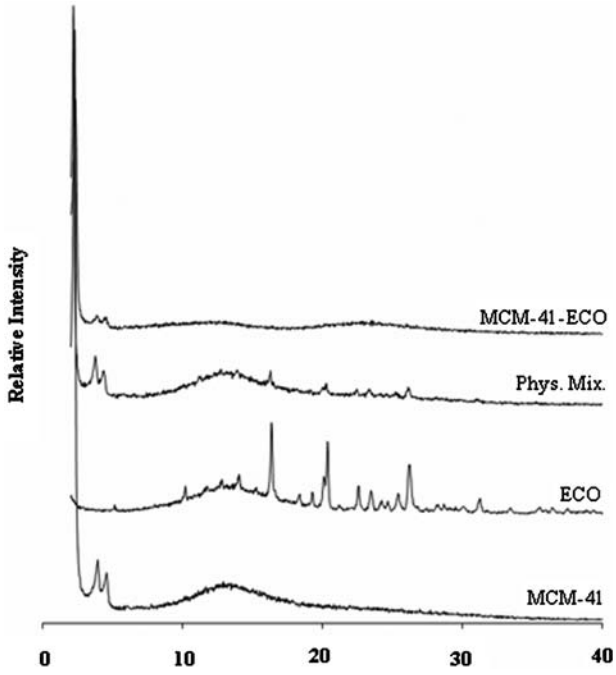

Figure 2. XRPD patterns of MCM-41, crystalline ECO, physical mixture, and MCM-41–ECO.

MCM-41–ECO Characterization

ECO complex was characterized by XRPD and DSC to investigate the physical state of the drug. XRPD diffractogram showed the presence of typical peaks of MCM-41 (Fig. 2) and no peaks relative to crystalline ECO as observed for the physical mixture. These data were partially confirmed by DSC. In fact, thermal profile of crystalline ECO (Fig. 1) showed an endothermic peak at 165°C ($\Delta H = -134.5$ mJ/mg) relative to drug melting. On the other hand, the drug-loaded MCM-41 sample showed a very little peak at this temperature, with very low fusion enthalpy change ($\Delta H = -4.3$ mJ/mg of drug). This was a proof that ECO was mostly dispersed and that only crystal traces were present.

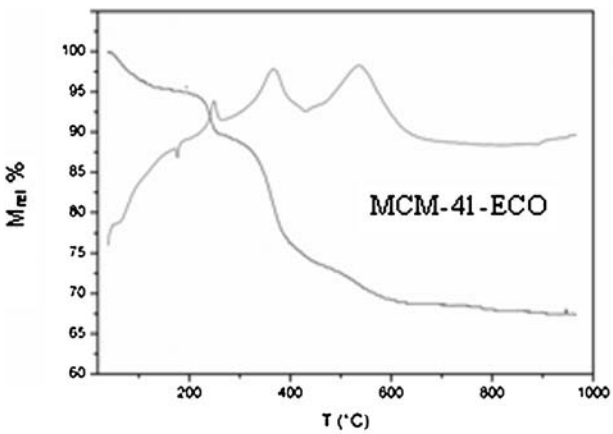

Figure 3. Thermogravimetric analysis of MCM-41–ECO.

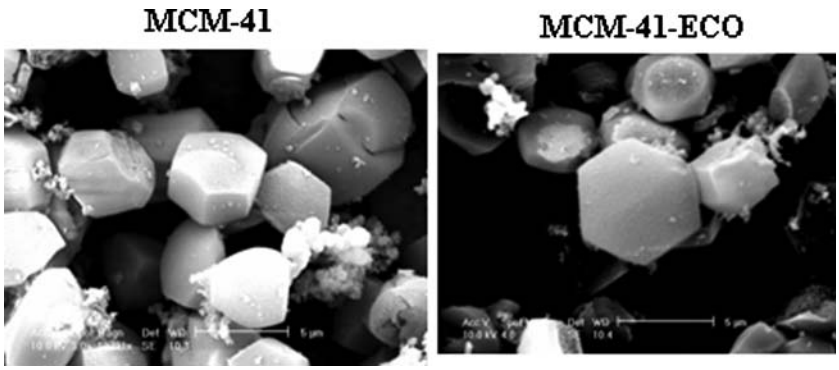

Figure 4. Scanning electron micrographs.

Thermogravimetric analysis (Fig. 3) gave a profile characterized by four steps. A first reduction of mass at ca. 100°C due to the loss of moisture (ca. 5%), the following gradual reductions in mass between 200 and 600°C are due to the included drug.

As shown by SEM micrographs (Fig. 4), MCM-41 and MCM-41–ECO are constituted by quite homogeneous and near hexagonal microcrystals whose diameter is between 3 and 6 μm. It is noteworthy to point out that the drug-loading process does not modify the morphology and the size of microcrystals, and that the presence of separate drug crystals was not observed in loaded MCM-41 samples.

MCM-41, MCM-41–ECO nitrogen adsorption–desorption isotherms are reported in Figure 5, while the calculated BET-specific surface areas are shown in Table 3. By comparing the adsorption isotherms, it is possible to note that the adsorbed nitrogen volume at p/p_0 values around 0.3 decreases after ECO loading. Consequently, the calculated mesopore volume decreases from 0.62 cm^3/g for MCM-41 to 0.33 cm^3/g for the loaded sample. Accordingly, a specific surface area decrease was found.

From the pore size distribution, calculated by the BJH–KJS method and shown in Figure 6, it is possible to notice that the mesopore volumes have an average dimension of 3.25 nm. ECO molecules are probably inserted into some MCM-41 mesopores causing their complete filling while the others were not involved in drug inclusion.

A computer model was performed in order to evaluate the ECO molar volume (Fig. 7). The approximate dimensions of ECO molecules are 13.11 Å × 9.88 Å × 3.95 Å which corresponds to an estimated molar volume of 308 cm^3/mol.

Table 3. BET Surface Area and Pore Volume Calculated for MCM-41, MCM-41–ECO

	MCM-41	MCM-41–ECO
BET surface area (m^2/g)	789	477
Pore volume (cm^3/g)	0.62	0.33

Taking into account the determined mesopore volume of MCM-41 (0.62 cm^3/g), the pore volume of loaded sample can be calculated as follows: 1.0 g contains 0.25 g of ECO and 0.75 g of MCM-41, thus the pore volume of the sample can be evaluated by: $0.75 \times 0.62 - 308 \times (0.25/444.6) = 0.29\ cm^3/g$.

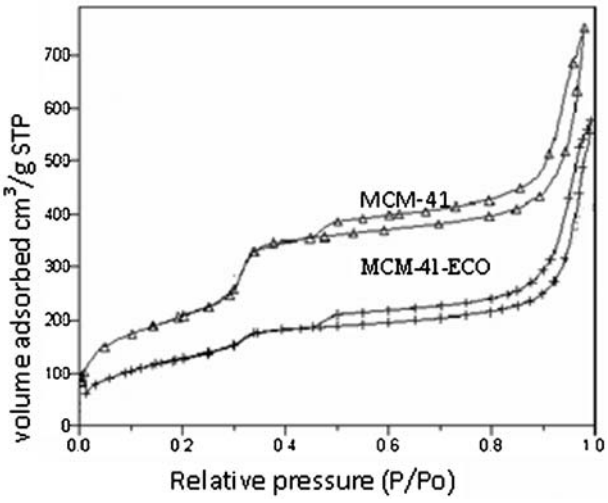

Figure 5. Nitrogen adsorption–desorption isotherms of MCM-41 and MCM-41–ECO.

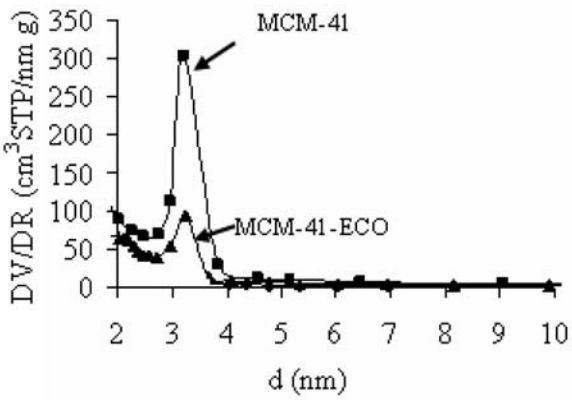

Figure 6. Pore distribution average of MCM-41 and MCM-41–ECO.

 DOI 10.1002/jps

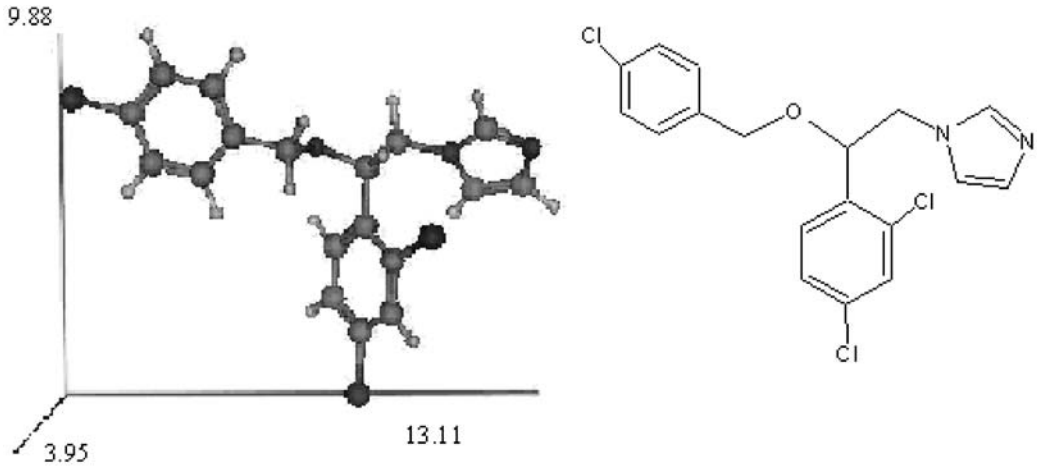

Figure 7. Virtual imagine of ECO and relative dimensions.

The calculated pore volume is similar to that experimentally measured and reported in Table 3. This proves that ECO molecules are inserted into the MCM-41 mesopores.

In Vitro Drug Release Studies

Formulation A was prepared (Tab. 1) and compared to the commercial product. The *in vitro* dissolution tests revealed that only a small amount of ECO was released from both samples; however, formulation A showed a higher release than D.

In order to improve drug release, a new formulation was prepared on the following rational. Since formulation D contains, besides ECO, talc, zinc oxide, and colloidal silica and the presence of zinc oxide is important because it may interact with many enzymatic and cellular functions,[22] while talc, usually used to minimize friction between skin fold, may be a drug release retardant agent,[23] a new formulation B was designed (Tab. 1) where talc is entirely substituted by MCM-41 because of its excellent moisture adsorptive characteristics.[13] Formulation B dissolution test was performed and its release profile was compared to those coming from formulations A, C, and D (Fig. 8). Drug release from formulation B, even if low and incomplete, was indeed much higher than that from all other tested formulations; in fact, it reached a value of 11% after 6 h, almost four times higher than that from D. These data confirmed the negative influence induced by the presence of talc and the positive effect produced by including ECO in MCM-41.

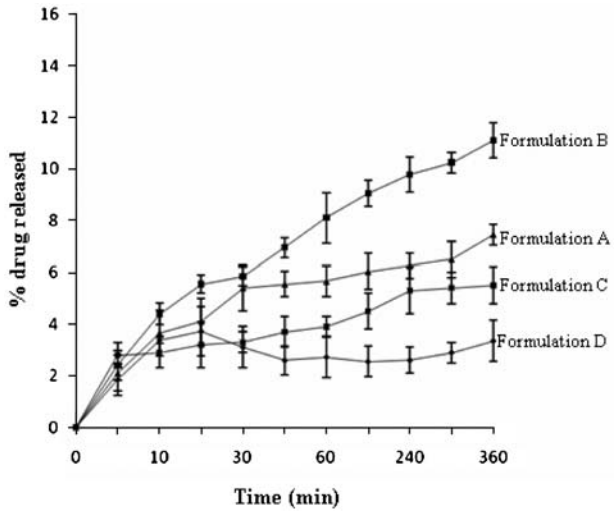

Figure 8. ECO release profile from the four different formulations.

In Vitro Antifungal Activity

The inhibition zone diameters obtained by the tested formulations (formulations A–D) are summarized in Table 4. The data were analyzed for significance by one-way analysis of variance (ANOVA) followed by *post hoc* analysis (Scheffé test) for pair-wise comparisons. Statistically significant differences were found between inhibition zone diameters of formulations A and B compared to formulations C and D. The difference between formulation A and B was also statistically significant, formulation B being the most

Table 4. Inhibition Zone Diameters Obtained With the Tested Formulations

	Disk Diffusion (mm)[a]	
	Range	AM
Formulation A	22.5–23.5	23*
Formulation B	24.5–25.5	25*
Formulation C	19.5–20.5	20
Formulation D	19.5–20.5	20

AM, arithmetic mean of the inhibition zone diameters.
[a]Test organism: *Candida albicans* ATCC 10231 strain.
*$p < 0.05$ versus formulation D: multiple pair-wise comparisons (Scheffé test).

Table 5. Moisture Uptake of MCM-41, Formulation B, and Formulation D at Different RHs after 1 and 7 Days

	MCM-41		Formulation B		Formulation D	
RH	1 Day	7 Days	1 Day	7 Days	1 Day	7 Days
33	−0.32 ± 0.80	1.06 ± 0.15	−0.2 ± 0.41	0.98 ± 0.43	−0.42 ± 0.06	−0.34 ± 0.39
59	4.65 ± 0.12	9.08 ± 0.25	4.20 ± 0.32	8.01 ± 0.23	0.06 ± 0.02	0.07 ± 0.03
65	11.61 ± 0.14	38.54 ± 0.25	10.13 ± 0.40	33.78 ± 0.76	0.20 ± 0.10	032 ± 0.13
75	16.2 ± 0.52	57.43 ± 0.29	15.06 ± 0.13	51.65 ± 0.12	0.27 ± 0.03	0.30 ± 0.03
85	20.18 ± 0.20	60.52 ± 0.21	18.07 ± 0.65	55.02 ± 0.34	0.26 ± 0.07	0.12 ± 0.08
93	24.44 ± 0.73	61.01 ± 0.48	21.99 ± 0.56	54.98 ± 0.23	0.57 ± 0.03	0.52 ± 0.03

effective against the test organism (i.e., *C. albicans* ATCC 10231 strain).

Moisture Adsorption Studies

MCM-41 has an abundant number of silanol groups because of the amorphous surface structure, and, since one silanol group is able to adsorb three water molecules through hydrogen atom and the lone pairs oxygen electrons,[13] this material can sorb on the surface of silica, via formation of hydrogen bonds, a large amount of water molecules, followed by capillary condensation. Therefore, MCM-41 is able to adsorb exudates and moisture. In order to prove this, moisture adsorption studies on MCM-41 and formulations B and D were performed according to literature.[24]

From moisture adsorption studies (Tab. 5), MCM-41 proved to be a very hygroscopic material. Formulation D did not show any water sorption properties, whereas B showed the best adsorbent characteristics.

Storage Stability Study

Storage stability studies were conducted in order to verify the physical stability of MCM-41–ECO. In fact, since the higher dissolution rates were due to drug adsorption on material with high surface area and to the lack of the drug in a crystalline form, it was considered appropriate to verify if adsorbed ECO is converted in time into its crystalline form. The eventual presence of crystals was monitored by XRPD after 30-day storage at 40°C. The spectra, data not reported, showed reflections in the range of 2–8°, typical of MCM-41, and no peaks relative to crystalline ECO.

CONCLUSIONS

The present study revealed that: (i) formulation B showed better release and antifungal activity than the commercial formulation D, (ii) storage stability studies proved that the drug included in MCM-41 pores maintains its physical state in the tested condition, (iii) MCM-41 resulted to possess good moisture adsorbent capacity, which is very useful in retaining moisture present in skin–skin fold, responsible for maceration and microorganism growth.

In conclusion, from *in vitro* tests, formulation B has better performances than the commercial formulation toward skin mycotic infections.

ACKNOWLEDGMENTS

The authors wish to thank Mr. Marco Marani for the precious collaboration and technical assistance. This work was supported by Ministero dell'Università e della Ricerca (Italy, PRIN 2007).

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