

# Miconazole-loaded solid lipid nanoparticles: formulation and evaluation of a novel formula with high bioavailability and antifungal activity

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**Background and objective:** Miconazole is a broad-spectrum antifungal drug that has poor aqueous solubility (<1 µg/mL); as a result, a reduction in its therapeutic efficacy has been reported. The aim of this study was to formulate and evaluate miconazole-loaded solid lipid nanoparticles (MN-SLNs) for oral administration to find an innovative way to alleviate the disadvantages associated with commercially available capsules.

**Methods:** MN-SLNs were prepared by hot homogenization/ultrasonication. The solubility of miconazole in different solid lipids was measured. The effect of process variables, such as surfactant types, homogenization and ultrasonication times, and the charge-inducing agent on the particle size, zeta potential, and encapsulation efficiency were determined. Furthermore, in vitro drug release, antifungal activity against *Candida albicans*, and in vivo pharmacokinetics were studied in rabbits.

**Results:** The MN-SLN, consisting of 1.5% miconazole, 2% Precirol ATO5, 2.5% Cremophor RH40, 0.5% Lecinol, and 0.1% Dicetylphosphate, had an average diameter of 23 nm with a 90.2% entrapment efficiency. Furthermore, the formulation of MN-SLNs enhanced the antifungal activity compared with miconazole capsules. An in vivo pharmacokinetic study revealed that the bioavailability was enhanced by >2.5-fold.

**Conclusion:** MN-SLN was more efficient in the treatment of candidiasis with enhanced oral bioavailability and could be a promising carrier for the oral delivery of miconazole.

**Keywords:** miconazole, Precirol ATO5, solid lipid nanoparticles, encapsulation, Cremophor RH40, antifungal activity

## Introduction

Miconazole is a broad-spectrum antifungal drug that has an imidazole group.<sup>1,2</sup> Miconazole is a weak base and shows poor aqueous solubility (<1 µg/mL); as a result, a reduction in its therapeutic efficacy has been reported.<sup>3,4</sup> Miconazole has a dual mechanism of action: the inhibition of ergosterol biosynthesis and the inhibition of peroxidases, which causes the accumulation of peroxide within the cell, leading to cell death.<sup>5,6</sup> This antifungal drug is available in different dosage forms, including topical, oral, and parenteral, depending on the type and severity of infection.<sup>7-9</sup> Miconazole has been extensively used for the treatment of dermatophytosis, cutaneous mycosis, pityriasis, fungal vaginitis, and oropharyngeal candidiasis.<sup>10-13</sup>

Various approaches have been used to overcome its limitation of poor water solubility, such as the addition of surfactants, co-precipitation techniques, or by incorporating miconazole into colloidal carrier systems, including lipid nanoparticles.<sup>14-16</sup> These systems have been shown to enhance the antifungal activity of miconazole.<sup>4</sup> To date,

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few authors have attempted to enhance the oral bioavailability of miconazole, and the results are inconsistent.<sup>17,18</sup>

Solid lipid nanoparticles (SLNs) were developed at the beginning of the 1990s as an alternative particulate delivery system to liposomes, emulsions, microparticles, and polymeric nanoparticulate systems. SLNs combine the advantages of those systems, such as controlled release, biodegradability, biocompatibility, and the protection of the incorporated drug against chemical degradation.<sup>19</sup> However, SLNs simultaneously overcome the drawbacks of other colloidal carrier systems.<sup>20,21</sup> SLNs have drawn major attention as novel colloidal drug carriers for the administration of drugs by several routes, such as oral, topical, parenteral, ophthalmic, and rectal.<sup>22–25</sup> SLNs can be prepared using various methods: high-pressure homogenization, ultrasonication/high-speed homogenization, solvent emulsification–diffusion, solvent evaporation, double emulsion, and microemulsion.<sup>26–28</sup>

The aim of this study was to prepare and evaluate miconazole-loaded SLN (MN-SLN) formulations for oral administration to provide an innovative way to enhance the antifungal activity of this drug. Furthermore, *in vitro* antifungal activity and *in vivo* pharmacokinetic studies were conducted using the optimal formulations.

## Materials and methods

Miconazole base was received as a kind gift from Pfizer, Inc. (New York, NY, USA). Precirol ATO5, Compritol 888 ATO, Gelucire, and Labrasol were obtained from Gattefosse (St-Priest, France). Cholesteryl stearate was purchased from Fluka Chemical Company (Buchs, Switzerland). Cremophor RH40 and Poloxamer 188 were purchased from Sigma-Aldrich (St Louis, MO, USA). Lecinol was a kind gift from Nikko chemicals Co., Ltd (Tokyo, Japan). All other reagents and chemicals were of analytical grade.

## Methods

### Measurement of the solubility of miconazole in lipids

The method depends on the measurement of the partitioning behavior of the miconazole base in various lipids (Precirol ATO5, Cholesteryl stearate, Nikkomulose, Tri-fat, and Compritol 888 ATO). Miconazole base (25 mg) was dispersed in a mixture of a melted lipid (500 mg) and 0.5 mL of hot distilled water with continuous shaking for 5 minutes in a hot water bath at 75°C. After cooling and centrifugation at 15,000 rpm and 10°C for 30 minutes, an aqueous phase was separated. Then, the samples were analyzed for their miconazole base content by measuring the absorbance using ultraviolet spectroscopy at 274 nm, for the determination of the amount dissolved in aqueous phase.

The amount dissolved in lipid phase was determined indirectly by subtracting the amount dissolved in water from the total amount of miconazole used during the preparation. Then, the partition coefficient for miconazole in different mixtures was determined.

### Preparation of MN-SLNs

MN-SLNs were prepared by a hot emulsification/ultrasonication method. According to the partitioning results, Precirol ATO5 was selected as a solid lipid for the formulation of MN-SLNs. Miconazole powder (1.5%), Precirol ATO5 (2%), and Lecinol (0.5%) were dissolved in a mixture of chloroform and methanol (1:1) (20 mL). The solvent was then completely removed using a rotary evaporator. The drug-embedded lipid layer was melted by heating at 75°C. An aqueous phase was then formulated by dissolving one of the surfactants (2.5%), such as Gelucire, Poloxamer, Labrasol, or Cremophor RH40, in double-distilled water and adding it to the molten lipid phase. This was followed by homogenization for 3 minutes. Coarse hot oil in a water emulsion was obtained, which was then ultrasonicated using a probe sonicator. Finally, the obtained hot nanoemulsion was allowed to cool to room temperature to prepare MN-SLNs. The impact of varying the critical parameter variables on the preparation of different formulations is shown in the following sections.

### SLN preparation

SLNs were prepared by varying the surfactant types (Gelucire, Poloxamer 188, Labrasol, and Cremophor RH40) and ultrasonication time (3 and 7 minutes), while the surfactant concentrations remained constant at 2.5% and the homogenization time was 3 minutes.

### Particle size and zeta potential measurements

The hydrodynamic diameter and zeta potential of the resulting dispersions were measured by dynamic light scattering using a Zetatrac machine (Microtrac, Inc., PA, USA).

### Measurement of the entrapment efficiency

The SLN dispersion was centrifuged at 5,000 rpm for 30 minutes. The quantity of free drug in the dispersion medium was determined. The amount of miconazole in the aqueous phase was recorded at 274 nm.

Encapsulation efficiency was calculated as follows:

$$\text{Encapsulation efficiency (\%)} = 100 - (\text{Fs}/\text{Ts} \times 100) \quad (1)$$

where Fs is the free soluble drug and Ts is the initial amount of drug added during the preparation of MN-SLNs.

### Drug release study

A drug release study was carried out following the dialysis bag method.<sup>29</sup> An MN-SLN suspension was placed in dialysis bags that had a 12 kDa molecular weight cutoff (Sigma-Aldrich) and was then immersed in 250 mL of 0.1 N HCl (pH = 1.2) at 37°C as a dissolution apparatus with a paddle rotating at 50 rpm for 2 hours. Then, the pH was increased to 7.4 for the remaining 10 hours. An aliquot of the sample (5 mL) was taken from the dissolution medium at different time intervals (0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, and 12 hours) and analyzed for its miconazole content at 247 nm.

### Determination of the flow properties

The flow properties of pure miconazole and its SLN formulations were described by the following methods:

#### Bulk and tapped densities method

Two grams of tested powder was weighed and poured into a 10 mL graduated cylinder, and then, the cylinder was tapped three times at 3-second intervals from a height of 2.5 cm. The volume of the powder (bulk volume) was recorded, which was used to calculate the bulk density according to the following equation:

$$\text{Bulk density } (\rho_b) = \frac{\text{Weight in (g)}}{\text{Bulk volume (cm}^3\text{)}} \quad (2)$$

The tapped density of the drug was determined by tapping the cylindrical measure several times until a constant volume was achieved (tapped volume), which was used to calculate the tapped density of the drug according to the following equation:

$$\text{Tapped density } (\rho_t) = \frac{\text{Weight in (g)}}{\text{Tapped volume (cm}^3\text{)}} \quad (3)$$

After calculating the bulk and tapped density, two parameters indicating the flowability were determined: the Hausner ratio and Carr's index.

The Hausner ratio is the ratio between the tapped density and the bulk density, and Carr's index can be estimated from the following equation:

$$\text{Carr's index} = (\rho_t - \rho_b / \rho_t) \times 100. \quad (4)$$

The obtained value gives an idea of the flow characteristic of powder particles.

#### Angle of repose method

By using a fixed-base funnel method, the angle of repose was measured as follows: The powder sample, either miconazole alone or MN-SLN, was allowed to fall through a funnel that

was hung 2 cm above the surface until the apex of the pile reached the lower tip of the funnel. Then, the diameter and the height of the pile were measured and used to calculate the angle of repose according to the following equation:

$$\text{Tan } \theta = h/r \quad (5)$$

where  $\theta$  is the angle of repose,  $h$  is the pile height, and  $r$  is the radius of the formed pile.

Triplicate samples were carried out for each experiment.

### Assessment of antifungal activity

In vitro antifungal studies were conducted against *Candida albicans* in Sabouraud dextrose agar medium (SDA).

#### Inoculum preparation

Three to five colonies of standard strain *C. albicans* were suspended in 2 mL of sterile normal saline and simultaneously vortexed. McFarland standards (0.5 meq) were used to adjust the turbidity of the homogenous suspension. A sterile swab was dipped into the suspension and swabbed on dried plates containing SDA to obtain a lawn culture.

#### Disk diffusion method

Sterile filter paper disks (6 mm) were placed and inoculated on dried SDA plates. Then, 100  $\mu$ L of the MN-SLN suspension in sterile water was placed on the disk. The plates were incubated at 25 $\pm$ 1°C. The zone of inhibition was observed around the disk after 1 and 2 days, respectively. Ethanol (99.9%) was used as a positive control. Data were analyzed using one-way analysis of variance (ANOVA). The level of significance was set at  $P < 0.05$ .

#### In vivo pharmacokinetic study

An in vivo drug absorption study was conducted according to the institutional guidelines of the Animal Ethics Committee of the Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia. Twelve albino male rabbits weighing between 2 and 2.5 kg were used in this study. Based on in vitro and antifungal activity results, negatively charged MN-SLN formulations were selected for in vivo evaluation. These formulations were composed of 150 mg of miconazole, 200 mg of Precirol ATO5 as a solid lipid, 250 mg of Cremophor RH40 as a surfactant, 50 mg of Lecithin, and 10 mg of Dicylphosphate and were prepared by 3 minutes of homogenization followed by 7 minutes of an ultrasonication method.

The rabbits were kept in a fasting condition for 24 hours before the experiment was commenced. In this experiment, two groups of rabbits (six rabbits/group) were orally administered with either a miconazole capsule (as a control) or its

SLN formulation (10 mg/kg). Suspensions of formulations in 5 mL of normal saline were orally administered via gastric intubation.

Blood samples (2 mL) were collected before and after drug administration at different time intervals (0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours). The obtained serum samples were frozen at  $-20^{\circ}\text{C}$  until the analysis of high-performance liquid chromatography was performed.

### Statistical analysis for pharmacokinetic data

$C_{\max}$  and  $T_{\max}$  were calculated using the plasma concentration–time curve in the WinNonlin™ Nonlinear Estimation Program. ANOVA was employed to assess the significance of the difference between the  $T_{\max}$ ,  $C_{\max}$ , and area under plasma concentration–time curve from time zero to infinity ( $\text{AUC}_{0-\infty}$ ) data of the miconazole obtained from the control capsule and the MN-SLN formulations ( $P \leq 0.05$ ) using the statistical product and service solutions program. The area under plasma concentration–time curve from time zero to 24 hrs ( $\text{AUC}_{0-24}$ ) was calculated using the linear trapezoidal rule. In addition, the  $\text{AUC}_{0-\infty}$  and relative bioavailability ( $\text{BA}_R$ ) of the MN-SLNs were calculated using the following equation:<sup>30</sup>

$$\text{BA}_R = \frac{\text{AUC}_{\text{MN-SLNs}} \times \text{Dose}_{\text{capsule}}}{\text{AUC}_{\text{capsule}} \times \text{Dose}_{\text{MN-SLNs}}} \quad (6)$$

## Results and discussion

### Screening of lipid phase

The solubility of miconazole base in lipids was assessed by measuring the ratio of the amount of miconazole dissolved in the lipid phase to the amount of miconazole dissolved in the aqueous phase. The results indicated that the highest partition

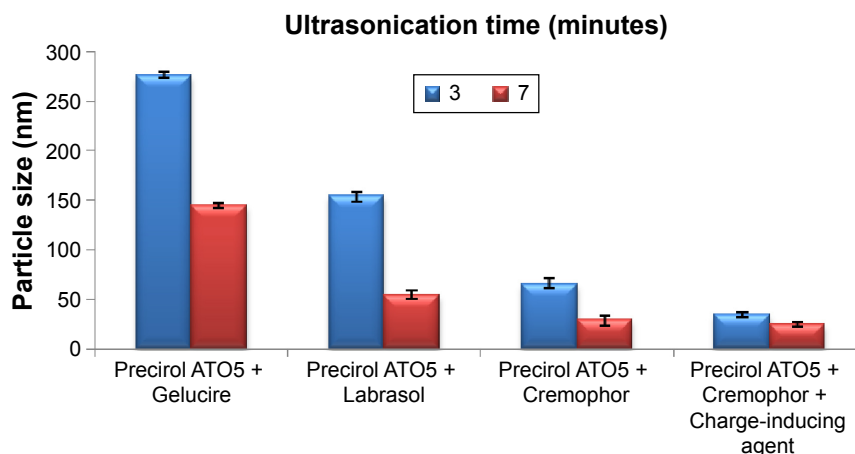
coefficient (14.6) was observed in Precirol ATO5 which was selected as a core lipid for the MN-SLN formulations, whereas it was 11.3, 8.6, 6.7, and 5.9 in cases of Cholesteryl stearate, Nikkomulse, Trifat, and Compritol 888 ATO, respectively. This could be attributed to the fact that Precirol ATO5 has a longer-chain fatty alcohol in its structure than the other lipids used, which results in the creation of a less ordered solid lipid matrix, leaving enough space to accommodate the drug molecule.<sup>31</sup>

### Preparation and characterization of miconazole SLNs

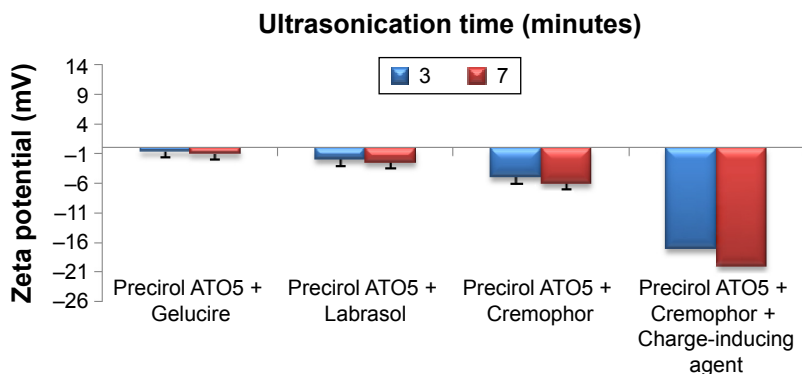
MN-SLNs were successfully produced by hot homogenization followed by ultrasonication. Figures 1 and 2 indicate that the ultrasonication time has a significant impact on the particle size, while the incorporation of a charge-inducing agent during the preparation of the MN-SLN has a significant effect on the zeta potential. Moreover, the results indicated that the hydrodynamic diameter of the MN-SLNs containing Cremophor RH40 as a surfactant was 22 nm. The reduction in particle size during the production of the SLNs leads to an increase in the attraction force between the particles, which increases the surface tension at the interface, leading to physical instability.<sup>32</sup> The incorporation of Cremophor RH40 as a surfactant in the formulation imparts a repulsion force between the nanoparticles and reduces not only the surface energy but also the interfacial tension of the system.<sup>33</sup>

### Drug release study

According to the particle size and entrapment efficiency, the release of the optimal MN-SLN formula containing 150 mg of miconazole, 200 mg of Precirol ATO5 as a solid



**Figure 1** Hydrodynamic diameter measurements of different miconazole-loaded solid lipid nanoparticle formulations.

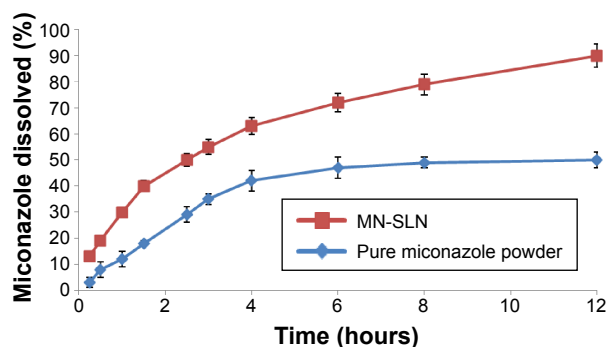


**Figure 2** Zeta potential measurements of different miconazole-loaded solid lipid nanoparticle formulations.

lipid, 250 mg of Cremophor RH40 as a surfactant, 50 mg of lecithin, and 10 mg of dicetylphosphate, which was prepared by 3 minutes of homogenization followed by 7 minutes of ultrasonication, was compared with the release of pure drug. MN-SLNs displayed 90% release at the end of the test, whereas the percentage of miconazole released in the case of the plain drug powder was only 50%, as shown in Figure 3. The release of miconazole from the MN-SLN formulations displayed a biphasic drug release pattern with a burst release within 2 hours (~45% of miconazole were released) followed by a sustained release.<sup>34</sup> The reason for the initial burst in the release profile may be due to the drug adsorbed on the surface of the SLNs. The slow release in the later stage was attributed to the fact that the solubilized or dispersed drug can only be released slowly from the lipid matrices through dissolution and diffusion mechanisms.

## Flow properties

The flow properties of the miconazole in its pure state and the MN-SLN formulations were confirmed by the values of the Hausner ratio, Carr's index, and angle of repose.



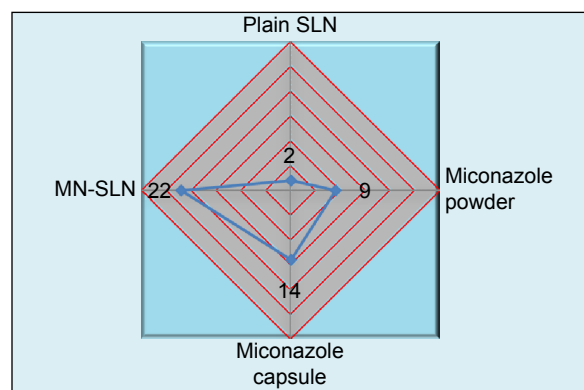
**Figure 3** In vitro release profile of miconazole from MN-SLNs and pure miconazole powder.

**Abbreviation:** MN-SLNs, miconazole-loaded solid lipid nanoparticles.

According to United States Pharmacopeia 29-National Formulary 24 (USP 29-NF24), materials that have Hausner ratios ranging from 1.26 to 1.34, Carr's index from 21 to 25, and angle of repose from 31° to 45° are likely to flow. This means that the miconazole powder has bad flowability as the Hausner ratio, Carr's index, and angle of repose were 1.6°, 35°, and 55°, respectively. On the other hand, the flow parameters for the MN-SLNs were 1.021 for the Hausner ratio, 15.21% for Carr's index, and 22.2° for angle of repose, which indicate an enhancement in all the flowability parameters. The SLNs have good flowability and can be incorporated during manufacturing processes without a need for the addition of a glidant, which has deleterious effects on the solubility and bioavailability of some drugs.

## Assessment of antifungal activity

The antifungal efficacies of miconazole SLNs against *C. albicans* were investigated. As shown in Figure 4, marketed miconazole capsules showed an inhibition zone that



**Figure 4** Inhibition zones for different formulations of miconazole against *Candida albicans*.

**Abbreviations:** MN-SLN, miconazole-loaded solid lipid nanoparticle; SLN, solid lipid nanoparticle.

**Table 1** Pharmacokinetic parameters of miconazole after oral administration of MN-SLNs and marketed capsules at a dose of 10 mg/kg (n=6)

Formulation	$T_{max}$ (hour)	$C_{max}$ (ng/mL)	$AUC_{0-24}$ (ng-hour/mL)	$K$ (hour <sup>-1</sup> )	$AUC_{0-\infty}$ (ng-hour/mL)
MN-SLN	4.05±0.6	13.71±2.15	231±20	0.05±0.03	294±24
Miconazole marketed capsules	1.54±0.3	8.72±1.23	94±11	0.28±0.06	121±15

**Note:** The significance level was set at  $P < 0.05$ .

**Abbreviations:** MN-SLN, miconazole-loaded solid lipid nanoparticle;  $T_{max}$ , time required to reach maximum plasma level;  $C_{max}$ , maximum plasma concentration;  $AUC_{0-24}$ , area under plasma concentration-time curve from time zero to 24 hrs;  $AUC_{0-\infty}$ , area under plasma concentration-time curve from time zero to infinity.

was better than miconazole powder alone at 14 and 9 mm; however, the MN-SLNs showed the maximum inhibition zone of 22 mm. These results indicated that the formulation of miconazole as MN-SLNs enhanced the antifungal activity. This could be due to the small particle size (nanoscale) of the SLNs, which enhances the permeation across the cell membrane of *C. albicans* fungus.

### In vivo pharmacokinetic study

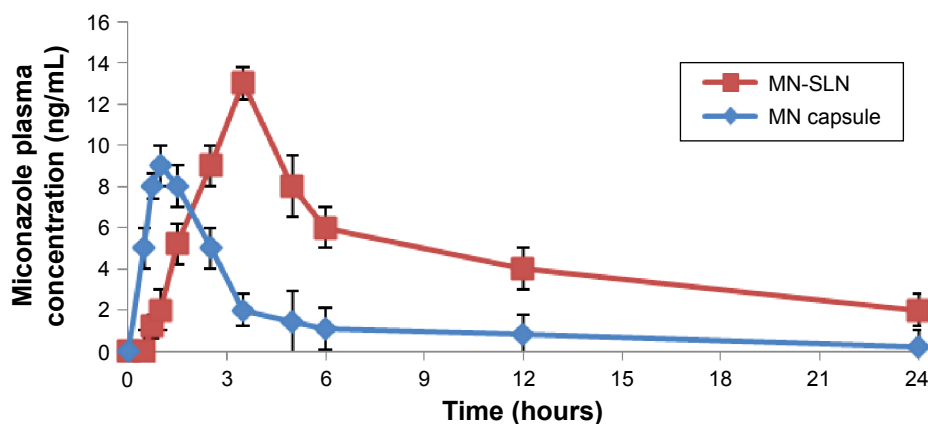
There was a statistically significant difference in the  $T_{max}$ ,  $C_{max}$ , and  $AUC_{0-\infty}$  data between the MN-SLNs and the marketed capsules (Table 1 and Figure 5) at  $P \leq 0.05$ . The mean  $AUC_{0-\infty}$  for the marketed capsules was significantly different from the  $AUC_{0-\infty}$  for the MN-SLNs. These results confirmed that the formulation of MN-SLNs increased the bioavailability of miconazole by >2.5-fold.

These results indicated that the MN-SLN formulation enhanced the miconazole absorption and permeation characteristics across the membrane of gastrointestinal tract. The results also revealed that MN-SLNs can significantly modify the pharmacokinetic profile and can increase the drug bioavailability by >2.5-fold in comparison with the marketed oral capsule formulation, which was because miconazole

possesses poor aqueous solubility. The preparation of this drug as an SLN enhanced not only its solubility but also its tissue permeability. Furthermore, the pharmacokinetic characteristics of the drug upon delivery in an SLN formulation are dictated by the properties of the SLN rather than by the physicochemical characteristics of the drug molecule. Additionally, the presence of Cremophor as a surfactant in the SLN formula causes a steric hindrance that helps reduce the tissue uptake by evading the reticuloendothelial system, which will improve the residence time of SLNs in the blood circulation.<sup>22</sup>

### Conclusion

The formulation of miconazole in oral SLNs, which is a novel drug delivery system, enhanced the bioavailability by >2.5-fold compared with the marketed capsules and was more efficient in the treatment of candidiasis. The optimum MN-SLN formula was composed of 1.5% miconazole, 2% Precirol ATO5, 0.5% Lecithin, 2.5% Cremophor RH40, 0.5% Lecinol, and 0.1% Dicetylphosphate. The usage of this formulation could eliminate the major drawbacks of the conventionally used capsules. MN-SLNs could be a promising carrier for the oral delivery of miconazole.



**Figure 5** Plasma concentration–time curve for miconazole after oral administration of MN-SLNs and marketed capsules to rabbits at a dose of 10 mg/kg.

**Abbreviations:** MN, miconazole-loaded; MN-SLNs, miconazole-loaded solid lipid nanoparticles.

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## Disclosure

The authors report no conflicts of interest in this work.

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