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Ketoconazole carriers for topical delivery

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**Abstract**

Skin’s superficial fungal infections are diseases that affect most people worldwide. About 20\% to 25\% of world’s population is infected and the incidence continues to increase. There are a number of clinical presentations usually resulting from an infection by one of the dermatophyte species, notably *Trichophyton rubrum*. A number of modern treatment strategies are available and are generally well tolerated and effective. However, a significant proportion of patients, 20-30\%, can expect treatment failure and/or relapse following treatment. The search for new treatment modalities and drugs is hampered by our lack of understanding of the basic pathophysiological mechanisms that underlie these frequently encountered infections. Ketoconazole (KTZ) is a synthetic, broad-spectrum antifungal drug. It is a potential inhibitor of ergosterol (a main lipid membrane of fungi) synthesis. It is poorly soluble in water and unstable, specially in aqueous media. The purpose of this work was to develop new systems for the percutaneous delivery of KTZ. A nanoemulsion with 0.13\% (w/w) and liposomes with 0.094\% (w/w) of KTZ were developed and fully characterized. Although the percentage of ketoconazole incorporated was quite low (0.13\% and 0.09\% for the nanoemulsion and liposomes, respectively when compared with traditional formulations (2\%), the results obtained showed high values of microbiologic efficacy. These results are likely associated with dissolution of ketoconazole and the presence of a skin enhancer, ethoxydiglycol. Although liposomes presented higher efficacy they also showed higher skin permeation and they were retained in the deeper layers of the skin while nanoemulsion was mainly retained in SC, where retention of KTZ in the SC is essential. These innovative formulations (nanoemulsion and liposomes) showed promising results.
**Introduction**

The skin fungal infections are classified as: superficial or cutaneous and mucocutaneous, subcutaneous and systemic or deep [1], [2]. Superficial infections of skin are diseases that affect more people worldwide. They are believed to affect 20% to 25% of the world’s population, and the incidence continues to increase [3], [4], [5]. These infections vary with age, gender, ethnic and socio-cultural habits. Superficial mycoses, affecting some areas of the body as the top layer of skin, the hair, the nails and mucous membranes [1], [6]. The mycoses are dermatophytooses, diseases usually caused by *Malassezia spp* ( pityriasis versicolor and seborrhoeic dermatitis) and *Candida albicans* (candidiasis) [1], [7]. For treatment of these superficial infections, the topical administration of antifungals present advantages, compared to oral administration, as: exposure to the drug is limited to the affected skin and the drug entry into the blood flow is limited or minimized, which limit the adverse effects of the drug [6], [8]. In this type of infection, wherein the pathogenic microorganism acts inside the outermost layer of the skin, the antifungal must achieve the stratum corneum (SC) in sufficient concentration to inhibit the growth of pathogenic agent [9].

Ketoconazole (KTZ) is a synthetic, broad-spectrum antifungal drug. It inhibits the ergosterol synthesis (the fungi main lipid membrane). It is poorly soluble in water (\(-\log P = 4.34\)) and it is a weak base with two pK values 6.75 and 3.96. It is unstable (oxidation and hydrolysis), if not properly formulated, specially in aqueous media [10].

The currently marketed products may not be ideal for successful therapy. The development of alternative approaches for treatment of fungal skin infections by topical treatment, includes new vehicles systems for antifungal agents such colloidal systems, nanoparticles and vesicular transporters [8]. The aim of this study was the development of innovative systems applying nano technology and micro encapsulation as an alternative for topical delivery of KTZ and elucidate the underlying mechanism of permeation enhancement. New topical formulations with good adhesion providing the shortening of the treatment period, high penetration of the drug in the SC, nails and hair in order to maintain a high concentration of the drug in the affected area are the requirements established for a new topical medicine [6]. Nanoemulsions present superior properties compared to macroemulsions: small droplet size, uniform distribution on the skin, high surface area, better occlusivity and pleasant sensation when applied topically [11]. Liposomes have been used as drug carriers for the topical treatment of dermatological diseases [12]. The liposomes can incorporate hydrophilic or hydrophobic active substances, allow a sustained and/or controlled release as well as higher drug retention in the skin. The incorporation of KTZ in these vehicles, may cause a prolonged drug delivery and minimize side effects [12]. A nanoemulsion with 0.13% (w/w) and liposomes with 0.094% (w/w) of KTZ were developed and fully characterized. In vitro studies (release, permeation and retention) and microbiologic efficacy against *Candida albicans* were assessed.

**Materials and Methods**

**Materials**

KTZ was obtained from Edol, Portugal. The Sucrose Stearate (Sisterna® SP 70-C), Lecithin, glycerin and alcohol (Pro-lipo™ Duo) and Ethoxydiglycol (Transcutol® CG) were kind gifts from Sisterna (Roosendaal, Netherlands), Lucas Meyer Cosmetics (Champlan, France) and Gattefossé (Saint Priest Cedex, France), respectively.

Hidroxipropilmetilcelulose (HPMC) was obtained from Hercules, USA. Propylene glycol, phosphate buffer and methanol were purchase from Sigma Aldrich, USA.

All other reagents were of HPLC. Deionized water was obtained by inverse osmosis (Millipore, Elix 3).

**Nanoemulsion and liposome development**

It was intended to introduce 2% of KTZ in to nanoemulsion and liposomes since, this is the amount used in current topical pharmaceutical. The nanoemulsion development showed that only 0.13% of KTZ was dissolved in 5% (w/w) of ethoxydiglycol (solubilizer). The
Nanoemulsion was prepared with 5% of surfactant and 5% (w/w) of solubilizer in water. In the case of liposomes, Lecithin, glycerin and alcohol (L+G+A) – 0.094% of KTZ (72.4% ± 0.4%). The final formulations are represented in Table 1.

- **Nanoemulsion Formulation**

  The surfactant (Sucrose stearate) was mixed to purified water, then, the KTZ already dissolved in ethoxydiglycol, were added, mixed and homogenized using a Ultra-Turrax® Basic 10 at 30000 rpm, during ten minutes, at room temperature (25 ± 2°C). HPMC was added to this system and stirred using magnetic stirrer (250 rpm) for 12h.

- **Liposome Formulation**

  Liposome formulation composition is described in Table 1. KTZ was previously dissolved in ethoxydiglycol. L+G+A was mixed with KTZ solution under agitation (homogenizer Heidolph, at 800-1000 rpm). Water was added dropwise and liposome formulation was left to agitate for additional twenty minutes, at the same speed.

### Table 1 - Qualitative and quantitative composition (%, w/w) of final innovative formulations.

<table>
<thead>
<tr>
<th>Raw ingredients</th>
<th>Nanoemulsion Quantitative Composition (%, w/w)</th>
<th>Liposome Quantitative Composition (%, w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucrose stearate</td>
<td>5.00</td>
<td>L+G+A</td>
</tr>
<tr>
<td>Ethoxydiglycol</td>
<td>5.00</td>
<td>Ethoxydiglycol</td>
</tr>
<tr>
<td>HPMC</td>
<td>1.00</td>
<td>Purified Water for liposomes</td>
</tr>
<tr>
<td>Purified water</td>
<td>88.87</td>
<td>Purified Water residual</td>
</tr>
<tr>
<td>Drug</td>
<td>Drug</td>
<td>Drug</td>
</tr>
<tr>
<td>KTZ</td>
<td>0.13</td>
<td>KTZ</td>
</tr>
</tbody>
</table>

**Particle size**

The size distribution was measured by laser diffraction using Malvern Mastersizer 2000 equipment (Malvern Instruments Ltd, Worcestershire, UK) in conjunction with the accessory 2000 Hydro S. The parameters used for the analysis of samples were: an obscuration range of 10 - 20 %, water as dispersant, stirring 750 rpm without ultrasound. The sample size used was the enough to get an obscuration in the selected range. The data are expressed in terms of relative volume distribution of particles in the size range class (mean ± SD, n = 5).

The size distribution was measured by dynamic light scattering using the equipment Zeta sizer Nano S (Malvern Instruments Ltd., Worcestershire, UK). This equipment has a measuring range of 3 nm to 10 µm in diameter. The liquid used for dispersing the particles was water, in appropriate cells. The sample (20 µl) was diluted in 2 ml of water. The results were presented as (mean ± SD, n = 3).

**TEM analysis**

Particle morphology analysis was performed by transmission electron microscopy (TEM) Briefly, the suspension sample was applied to the cooper grid, dried at room temperature and analysed on Hitachi 8100 with ThermoNoran light elements EDS detector and digital image acquisition.

**Determination of pH**

The pH was determined for all formulations developed using a potentiometer (Mettler Tolero®: Electrode: InLab® Expert Pro pH, Mettler Toledo®), at (25 ± 2°C).

**HPLC method for the determination of KTZ**

High performance liquid chromatography (HPLC) with UV detection was used to determine the KTZ concentration in the formulation. A chromatograph Beckman (detector, pump, autosampler and software) with a column Lichrospher 100 RP-18 5 μm (250 mm x 4 mm) was used. The analysis was
performed at room temperature. Test conditions were: mobile phase - acetonitrile:phosphate buffer (55:45, v/v), flow rate - 1.5 mL/min, injection volume - 20 µL, UV detection at 254 nm.

**Incorporation efficiency (IE)**

The amount of KTZ incorporated into liposomes, non-incorporated fraction was separated from the loaded one by ultracentrifugation. Samples were centrifuged in a ultra-centrifuge (Optima XL90, Beckman) at 180 000 xg for 2 hours, at 15° C. After centrifugation, the supernatant was removed and the pellet was suspended in water. The quantification of the drug was performed after extraction with methanol under vigorous stirring. Samples were analyzed by UV spectrophotometry at 242.6 nm (U-2001 Spectrophotometer, Hitachi). Samples were analyzed in duplicate.

**In vitro release of KTZ**

KTZ release profile was measured using Franz diffusion cell of 2.5 cm². The synthetic membrane used was 0.45 µm membrane of cellulose nitrate. Propylene glycol/ethanol (1:1) was used as the receptor phase. The cells were immersed in a bath system at 32 ± 2°C under stirring (200 rpm). The formulations samples were applied (about 2 g) on the membrane surface in the donor compartment further sealed by Parafilm®. Samples were collected from the receptor fluid at predetermined time points - 0.5, 1, 2, 3, 5, 6 hours and replaced with an equivalent amount (200 µl) of fresh receptor medium. The KTZ content in the withdrawn samples was analyzed by HPLC. Six replicates were used.

The cumulative amount of KTZ permeated (Qt) through excised human skin was plotted as function of time and determined based on the following equation:

\[ Q_t = V_r \times C_t + \sum_{i=1}^{t-1} V_s \times C_i - \frac{S}{t=0} \]

where, \( C_t \) is the drug concentration of the receiver solution at each sampling time, \( C_i \) the KTZ concentration of the sample applied on the donor compartment, and \( V_r \) and \( V_s \) the volumes of the receiver solution and the sample, respectively. \( S \) represents the skin surface area (1 cm²).

**In vitro tape stripping of KTZ**

**In vitro skin retention or penetration study** was performed by tape stripping according to the method described by OECD Guideline 428 48. The formulations (0.2 to 0.4 g) were spread over the newborn pig’s skin (1 cm²) in contact
with 4 ml of receptor phase as described before. 24 h later, the skin samples were rinsed to remove the excess formulation and dried with filter paper. After the skin samples had been attached and fixed on a smooth surface, the SC was removed using 20 adhesive tapes (Scotch® 3M, UK). In order to improve the reproducibility of the tape stripping technique, a cylinder (2 kg) on foam and an acrylic disk were used and the pressure was applied for 10 sec for each tape. All the tapes (excluding the first one) with the SC removed and the remaining skin (viable epidermis and dermis, ED) were cut into small pieces used for the extraction process previously validated. In this extraction process, 3 ml of mobile phase and 0.5 ml of methanol was added to the SC tapes and ED pieces. Both samples were vigorously stirred for 2 min in a vertical mixer (Kinematica AG), and sonicated for 20 minutes in order to obtain the cell lysis. The final solution was centrifuged (30000rpm, 10 min) and the supernatant was filtered (0.2 μm) and injected in HPLC to quantify the amount (%) of KTZ retained in these skin layers (SC + ED).

Data analysis

The data were expressed as mean and standard deviation (mean ± SD) of experiments. Statistical evaluation of data was performed using one-way analysis of variance (ANOVA), p < 0.05 was considered to be statistically significant.

Microbiological efficacy of formulations

For this study, were used two types of methods: Etest® method and Disk Diffusion Susceptibility Test, which is generally used in in vitro assays for the determination of microbial sensitivity. The Kirby-Bauer method was performed in diffusion disks and also in newborn pig skin, obtained from a local slaughterhouse. For both methods, Candida albicans (ATCC 10231) was inoculated on Sabouraud Dextrose agar plate. Concerning Etest®, after the inoculation, the Etest® tape impregnated with KTZ was added to plate, and incubated at 37°C for 24 h and then observed the minimum inhibitory concentration (MIC). Concerning Kirby-Bauer method the skin adapted agar diffusion test, the last one is an adaptation of a well-known in vitro assay to verify the effectiveness of antibiotic product contained in topical formulations (Kirby-Bauer method or disc diffusion antibiotic sensitivity method). Briefly, small impregnated paper discs with KTZ are dropped in different zones of the culture on an agar plate. The diameter of the inhibition zone is proportional to the sensitivity of the microorganism and the efficacy of the antifungal agent. In the adapted test, instead of antifungal impregnated discs, newborn pig dermatomed skin discs, on which 15 µL of test formulations were applied on the SC, were incubated on Sabouraud Dextrose agar plate (Thermo Scientific™ Oxoid™, UK) inoculated with Candida albicans (ATCC 10231) 24 h at 37°C. Skin discs were made with 13 mm biopsy punches. After incubation time, efficacy of tested formulation was determined by measuring the inhibition zone diameter from back of plate using a caliper.

Results

Organoleptic characteristics

The nanoemulsion showed white and homogeneous appearance while. Liposomal formulation presented a yellow color and homogeneous aspect and translucent.

Particle size

The particle size of gelified nanoemulsion formulation was about 91 ± 3 µm. However, the mean particle size for the same formulation without HPMC was about 375 ± 5 nm. Liposomes average size obtained (213 ± 3 nm) is suitable for skin drug delivery by means of nanocarriers.

TEM analysis

The formulation with liposomes, was examined in the TEM equipment, in order to get a clear image of the liposomes (Figure 1).

![Figure 1 - Morphology of the liposomes.](image)
Liposomes present a multilamellar structure and the vesicles diameter appears to be smaller than that measured by dynamic light scattering.

pH measurement
The formulations in study, exhibited different pH, about 7.16 and 5.97 for the nanoemulsion and liposomes, respectively. Both formulations indicated adequate pH for topical application.

KTZ Assay
The initial percentage of KTZ assayed was 94 and 90 % for nanoemulsion and liposome respectively. For every evaluation time points the KTZ assay is within the pre-established limits - 90 - 110 %.

Incorporation efficiency (IE)
The amount of KTZ incorporated into the liposomes was 72.4 ± 0.9 %, the initial 0.094 % of KTZ.

In vitro release of KTZ
The results of the amount of KTZ released from nanoemulsion and commercial cream through the cellulose nitrate membrane are shown in Figure 2.

In vitro permeation of KTZ
The results, for study systems and commercial cream, of the amount of KTZ permeated through the newborn pig’s skin are shown in Figure 3.

After 24 hours, nanoemulsion, liposomes and commercial cream permeated 0.20 ± 0.22 %, 0.02 ± 0.03 % and 0.19 ± 0.07 % of the drug, respectively.

ANOVA statistical analysis, showed no significant differences between the final formulations and the commercial formulation (p> 0.05). The fluxes, permeability coefficients and lag time, for three formulations are presented in Table 3.

Table 2 - Kinetic parameters obtained from zero-order model and the Higuchi model for the final formulation and reference (mean ± SD, n=3).

<table>
<thead>
<tr>
<th></th>
<th>Zero Order</th>
<th></th>
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<th>Higuchi Model</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>k</td>
<td>b</td>
<td>R²</td>
<td>k</td>
<td>b</td>
<td>R²</td>
</tr>
<tr>
<td>Nanoemulsion</td>
<td>119.22</td>
<td>277.19</td>
<td>0.58</td>
<td>426.21</td>
<td>-42.81</td>
<td>0.68</td>
</tr>
<tr>
<td>Commercial cream</td>
<td>683.12</td>
<td>391.54</td>
<td>0.97</td>
<td>2264.37</td>
<td>-1163.53</td>
<td>0.97</td>
</tr>
</tbody>
</table>

For kinetic parameters, Table 2, was clear that the Higuchi model describes a statistically better drug release mechanism, since, presented the best value of R².

Figure 2 - In vitro release profile of KTZ in nanoemulsion and commercial cream, (mean ± SD, n=3).
Table 3 - The permeation parameters of final innovative formulations and the commercial formulation (mean ± SD, n=6).

<table>
<thead>
<tr>
<th></th>
<th>Flux (µg/cm²/h)</th>
<th>Kp (cm/h)</th>
<th>Lag time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanoemulsion</td>
<td>0.050 ± 0.050</td>
<td>2.9x10⁻⁵ ± 3.3x10⁻⁵</td>
<td>4.75 ± 0.00</td>
</tr>
<tr>
<td>Liposome</td>
<td>0.002 ± 0.004</td>
<td>2.5x10⁻⁶ ± 4.4x10⁻⁶</td>
<td>4.75 ± 0.01</td>
</tr>
<tr>
<td>Commercial cream</td>
<td>0.570 ± 0.180</td>
<td>2.9x10⁻⁵ ± 8.9x10⁻⁶</td>
<td>1.55 ± 0.71</td>
</tr>
</tbody>
</table>

In vitro tape stripping of KTZ

The results in KTZ retention in the SC layer and the viable layers, for formulations in study and reference cream, are shown in Figure 4.

![Figure 4 - Percentage of KTZ retained on SC and viable skin layers in nanoemulsion, liposome and commercial cream, (mean ±SD, n= 3).](image)

The results obtained for SC were: 0.8 % (4.0 µg/ml), 0.4 % (1.1 µg/ml), and 0.1 % (6.1 µg/ml) for nanoemulsion, liposome and commercial cream, respectively. For viable skin layers, the results were: 0.3 % (1.8 µg/ml), 1.0 % (3.1 µg/ml), and 0.04 % (2.6 µg/ml) for nanoemulsion, liposome and commercial cream, respectively.

Microbiological efficacy of formulations

Etest® allowed to determine the MIC that inhibits microbial growth of the yeast Candida albicans. The MIC obtained was 0.047 µg/ml.

For the Kirby-Bauer method were used three standards with KTZ concentrations of 5 µg/ml (P1), 15 µg/ml (P2) and 38 µg/ml (P3). These standards were selected according to the concentration of innovative formulations, liposomal formulation (5 µg/ml) and nanoemulsion (35 µg/ml).

In the paper discs, the results obtained in terms of the inhibition zone for the standards was approximately 25 mm, 28 mm and 32 mm for the P1, P2, and P3, respectively. In the case of pharmaceutical preparation, the inhibition zone obtained was: 32 mm, 35 mm and 39 mm for nanoemulsion, commercial cream and liposomes, respectively. Concerning placebos, the yeast growth inhibition occurred only in the commercial cream placebo, probably related to the presence of a preservative.

Given that the standard P1 has a KTZ concentration similar to liposomes (5 µg/ml), comparing the inhibition halos is perceptible that there was a higher diffusion in the formulation with liposome. Nanoemulsion, presented the same inhibition halo that P3 standard. Commercial cream, which has 421 µg/ml of KTZ, only obtained a 35 mm inhibition zone, being very similar to the result that the nanoemulsion with a much lower concentration of KTZ.

The adapted diffusion test revealed drug skin retention and no inhibition zone was detected for standards, placebos, commercial cream
and nanoemulsion however, for liposomes the growth inhibition occurred.

## Discussion

The nanoemulsion presented white color and homogeneous aspect. The addition of polymer on nanoemulsion increased the particle size the 375 nm for 90 µm [11]. Liposomes were tested as innovative carriers for KTZ and the formulation obtained presents yellow color and homogeneous and translucent aspect. In terms of morphology (Figure 1), liposomes present the aspect of multilamellar structures. This result is in accordance to the L+G+A manufacturer liposome description. “Pro-liposome” used in this work is a preparation able to form spontaneously liposomes with only an addition of water. These instantaneous liposomes presented mean size of 213 nm, also in accordance to the mean size proposed by the manufacturer. In terms of IE, the maximum concentration of KTZ that these liposomes were able to incorporate was 5.5 µg/ml. KTZ liposomes were prepared with this initial concentration and IE obtained was 72 %. Gunjan Tiwari (2013) formulated liposomes with various concentrations of KTZ. For 5 µg/ml KTZ initial concentration author could only reach 16.4 % IE [13]. Guo, et al. (2015) developed various types of liposomes with the purpose of incorporating 3 mg/g KTZ and concluded that conventional liposomes were the vehicle where IE is lower, approximately 50.3 % [14]. Patel, et al. (2009) formulated liposomes with 2% active substance, and was able to incorporate approximately 54.41 % KTZ in liposomes [15]. The last two authors, have shown that conventional KTZ liposomes can be prepared with higher incorporation efficiency. Variability between studies is probably related to the use of different phospholipids. However, manufacturing process used for the preparation of liposomes with L+G+A was found not to be a limitation factor (data not shown), and can be easily scalable and adapted for industry.

The in vitro release assay, allows to evaluate the ability that the drug has for to free of the vehicle, allowing then find the best vehicle for drug delivery. Through Figure 2, it is observed that the best vehicle for the release of ketoconazole was nanoemulsion. This result can be related with presence of cutaneous promoter, ethoxydiglycol, in formulation and also in the fact the active substance to be dissolved in formulation, and not suspended as in the commercial cream, being more promising the entrance of drug in skin. The ethoxydiglycol beyond solubilize the hydrophilic and hydrophobic excipients is also described as one promoter that can increase the solubility of drug in the skin [16], [17]. The permeation study, allows acquiring the knowledge about the drug behavior when applied in the skin. Through Figure 3, was observed that amount permeated over time was very reduced, about 0.20 %, 0.19 % and 0.02 % for nanoemulsion, commercial cream and liposomes, respectively. These results indicate that addition of cutaneous promoter (ethoxydiglycol) and the drug dissolution at the innovative formulations allowed obtain the same or better results that the commercial cream. In relation to permeation parameters (Table 3), was verified that the innovative formulations presented lower flux that commercial cream allowing that KTZ on these formulations had more difficulty in permeate the SC. This conclusion features larger relevance with the results obtained for lag time, that was in these formulations where the KTZ lingered more time to be detected in receptor phase of Franz cellules, that the indicated that drug remains during more time retained in SC, permitting a more lasting action for skin superficial infections. Liposome formulation that presented the lower flux value. Patel, et al. (2009) refer that these systems allow a high drug skin accumulation, with relatively low permeation flow, comparatively to conventional topical forms. Furthermore, the authors associated the lower flux to prolonged drug release caused by several lipid bilayers present in multilamellar liposomes [12].

Concerning the results obtained in drug retention in the SC layer and the viable skin layers (Figure 4), it was found that the formulation with liposomes showed higher amount of drug in the epidermis and dermis. The remaining formulations showed greater amount of KTZ in the SC. Probably, the results obtained in liposome formulation is associated to high amount of cutaneous promoter existing...
in this preparation, once, conventional liposomes do not penetrate deep into the skin, but remain confined to the upper layer, SC, with minimal penetration into the deeper tissues [14].

All formulations studied have a KTZ concentration above the MIC obtained in Etest® assay for Candida albicans, which may indicate that the formulations studied were effective against the yeast used. The results obtained in the Kirby-Bauer method in the paper discs, indicated that liposomes, despite being the preparation with less KTZ in their composition, was the one with a higher zone of inhibition. In the case of the nanoemulsion, this system showed a similar zone of inhibition to the commercial cream, however, there is a significant difference in the amount of KTZ, which is significantly lower in the nanoemulsion. Thus, innovative formulations, although having less amount of antifungal agent, showed better results. These results proved that the use of a skin enhancer, ethoxydiglycol, and the total dissolution of KTZ influence the efficacy of the formulation, when compared to the commercial cream.

Concerning the drug retention in the SC for effective treatment for superficial skin infections, the liposomes despite having a higher inhibition zone, is not the best vehicle for the treatment of such infections. This is because, in this formulation has occurred absence of growth of Candida albicans in skin discs, indicating that the drug permeated all the skin layers and was not retained in SC. Thus, the best formulation is the nanoemulsion, due to the fact that this nano system was effective against Candida albicans, although the lower amount of KTZ incorporated in this system, when compared to the commercial cream. The overall results suggest that a suitable developed nanoemulsion formulation of KTZ can be of actual value for improving its clinical effectiveness in topical treatment of fungal infections.

Conclusion
The results obtained showed that nanoemulsion enhanced drug release when compared to commercial formulation being a promising approach for skin targeting delivery of KTZ. In case of liposomes formulation, although the percentage of encapsulation was 0.094%, the KTZ loaded liposomes enhanced its stability and delivery suggesting its use in skin topical therapy. These favorable results obtained from the innovative formulations are due to the fact that the innovative systems presented KTZ dissolved and a skin enhancer in its composition, which allows the drug becomes more available to be effective. Although liposomes presented higher microbiologic efficacy against Candida albicans, they also showed higher permeation and they were retained in the deeper layers of the skin while nanoemulsion was mainly retained in SC.

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Declaration of Interest section
The authors declare no conflicts of interest.

References


