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Original article

Development of miconazole nitrate nanoparticles loaded in nanoemulgel to improve its antifungal activity

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ABSTRACT

Miconazole is a synthetic derivative of imidazole, a medication with a broad-spectrum antifungal agent that is used to treat localized vaginal, skin, and nail infections. The aim of the study was to develop an innovative technique to improve the permeability and efficacy of topical miconazole nitrate. A nanoemulgel of miconazole nitrate was formulated by the incorporation of a nanoemulsion and a hydrogel. The nanoemulsion was first optimized using a self-emulsifying technique, and the drug was then loaded into the optimum formulation and evaluated prior to mixing with the hydrogel. Miconazole nitrate nanoemulgel formulations were evaluated for their physical characteristics and antifungal activity. Based on the results, the formulation with 0.4 % Carbopol showed the highest release profile (41.8 mg/ml after 2 h); thus, it was chosen as the optimum formulation. A cell diffusion test was performed to examine the ability of the Miconazole nitrate nanoemulgel to penetrate the skin and reach the bloodstream. Percentage cumulative drug releases of 29.67 % and 23.79 % after 6 h were achieved for the MNZ nanoemulgel and the commercial cream, Daktazol, respectively. The antifungal activity of the novel MNZ nanoemulgel formulation was tested against *Candida albicans* and compared to Daktazol cream and almond oil; the results were: 40.9 ± 2.3 mm, 25.4 ± 2.7 mm and 18 ± 1.9 mm, respectively. In conclusion, a novel MNZ nanoemulgel showing superior antifungal activity compared to that of the commercial product has been developed. This nanotechnology technique is a step toward making pharmaceutical dosage forms that has a lot of promise.

1. Introduction

Miconazole (MNZ) nitrate is a hydrophobic imidazole antifungal agent that has high efficacy as a topical treatment for superficial mycoses, cutaneous candidiasis, dermatophytosis, and other infections (Kaur and Kakkar 2010, Gwimo 2019). It is generally applied topically as a treatment for various diseases of the skin surface, such as ring worm, perioral candidiasis, jock itch, and athlete's foot (Aljaeid and Hosny 2016, Kandge et al., 2022). However, the poor capability of MNZ to penetrate the skin poses a challenge for the treatment of cutaneous diseases through topical application (Gupta et al., 2012, Khalifa 2015, Kenechukwu et al., 2018).

The low solubility and high lipophilicity of MNZ and the vehicle used for administration greatly affect the penetration of MNZ across the layers of the skin (Bhalekar et al., 2009, Polat et al., 2022). Consequently, the development of MNZ delivery systems will help to improve its solubility, thermodynamic stability, penetration, and therapeutic activity (Shahzadi et al., 2014, Kenechukwu et al., 2018, Hosny et al., 2019). Nowadays, nanotechnology has attracted considerable interest. It is defined as the methods, processes, and techniques used to generate nanoscale structures with a size range below 100 nm (Bayda et al., 2019). Nanoemulgels are an amalgamated formulation of two different systems in which a drug-containing nanoemulsion is incorporated into a gel base (Eid et al., 2014). This combination overcomes the limitations of each system separately. However, nanoemulsions have low viscosity, related to poor retention on the skin and poor spreadability (Arora et al., 2014).

Topical nanoemulgel delivery systems have been demonstrated to improve the systemic delivery, pharmacokinetics, pharmacodynamics, and therapeutic profile of lipophilic drugs. In recent years,

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the use of nanoemulgels has increased due to the higher compliance of patients. This can be attributed to the advantages of nanoemulgels, as this drug delivery method is noninvasive, avoids gastrointestinal side effects, has an excellent therapeutic, and safety profile and is easy to apply (Sharma et al., 2012, Sengupta and Chatterjee 2017).

Topical therapy reduces the risk of systemic side effects, making it the most favorable route of therapy for diseases affecting the skin (Zakrewsky et al., 2015). The compartmentalization of nanostructured drug delivery systems is restricted to specific environments; consequently, the drug is concentrated at its site of action. Topical nanoparticle drug delivery has emerged as one of the most promising strategies for site-specific drug delivery (Basera et al., 2015).

In prior studies, nanoemulsion has been used as a delivery system for the transdermal delivery of MNZ. In 2013, Shinde compared the *in vitro* antifungal efficacy of a novel MNZ nanoemulsion and a MNZ cream for treating *Candida albicans* infection. The new formulation presented a significant increase in the percentage of inhibition, highlighting nanoemulsion as a promising vehicle for enhancing the vaginal delivery of MNZ (Shinde 2013). Later, Maha and Sinaga (2018) evaluated the profiles of a miconazole nitrate nanoemulsion and a cream. Miconazole nitrate nanoemulsion preparations showed superior results when compared with cream preparations (Maha and Sinaga 2018).

In this study, an MNZ nitrate nanoemulgel was prepared and characterized to provide an agent with good permeability for topical use. An advantage of nanoemulgel delivery systems is their stable formulation, which could improve patient compliance. The aim of the present study was to formulate a novel MNZ nanoemulgel to improve the applicability and permeability of MNZ through the skin. This study will focus on the preparation of a novel nanoemulgel delivery system for MNZ nitrate with enhanced solubility, permeability, spreadability, efficacy, and safety.

2. Materials and methods

2.1. Materials

Miconazole nitrate and a MNZ nitrate product (Daktazol cream) currently available on the market were kindly gifted to the researchers by Jerusalem Pharmaceuticals Co. ltd., Palestine. Almond oil was gifted by professional-super pharm company, Israel. Tween 80, Span 80, glycerol, propylene glycol 400, ethanol, and carboxyvinyl polymer (Carbopol 940) were purchased from CBC Co., ltd., Japan. Crystal oil, olive oil, castor oil, and paraffin oil were obtained from the Al-Shams company, Palestine.

2.2. Wavelength screening of a miconazole using UV spectrophotometry

A sample of the medication, which consisted of 0.02 g of the active ingredient MNZ, was dissolved in 10 ml of methanol so that the optimum wavelength could be identified. The solution was mixed with a vortex mixer to ensure a homogenized solution, then the absorbance was measured using a UV spectrophotometer (7315; Jenway, United Kingdom) within a wavelength range of 200–600 nm (Reddy and Gillella 2012).

2.3. Calibration curve for miconazole

A standard stock solution was prepared according to the European Pharmacopoeia. The stock solution was prepared by dissolving 10 mg of MNZ in 100 ml of methanol (100 μg/ml). From this stock solution, 0.5–3 ml were diluted with up to 10 ml of methanol (5–30 μg/ml) and examined using a UV spectrophotometer. To generate the calibration curve, the absorbance results were plotted against the prepared concentrations (Reddy and Gillella 2012).

2.4. Solubility of miconazole in different surfactants and oils

The solubility of MNZ in different oils and surfactants was determined in order to select the most suitable oil and surfactant as the drug vehicle, which would then be used to prepare the nanoemulsion. By dissolving the active ingredient MNZ at a concentration of 2 % in different oils (castor oil, paraffin oil, olive oil, crystal oil, almond oil, and pine oil) and surfactants (propylene, Span 80, Tween 80, Tween 20, and glycerol), the solubility could be determined. The mixtures were prepared and centrifuged for 5 min at 6000 rpm, then the supernatants were collected to measure the absorption using a UV spectrophotometer (Hosny et al., 2019).

2.5. Preparation of olive and almond oils in self-nanoemulsifying systems

To optimize the nanoemulsion formulation, the drug vehicles (surfactants and oils) were selected based on the results of the MNZ solubility test. The self-nanoemulsifying technique was chosen for the preparation of the nanoemulsion. In order to generate a ternary phase diagram to optimize the nanoemulsion formulation, different compositions of olive oil, almond oil, Span 80, and Tween 80 were tested. The different formulations were weighed and vortexed for 1 min with delicate agitation to self-emulsify the formulations in distilled water.

2.6. Index analysis, polydispersity, and droplet size analysis of the almond and olive oil nanoemulsions

The size distribution and droplet size of the almond and olive oils and the surfactant emulsion were measured using a sampler and a laser diffraction particle size analyzer (SALD-MS23 and SALD-2300; Shimadzu Corp., Japan), which permitted the measurement of the diameter of the droplets and the polydispersity index (Qushawy et al., 2018).

2.7. Miconazole loading in the almond oil nanoemulsion formulation

Based on the droplet size results, the optimal emulsion formulation was chosen, and MNZ was loaded into it. The loading process was performed by dissolving MNZ in Tween 80, Span 20, and almond oil.

2.8. Hydrogel preparation

Hydrogel was prepared by adding water to Carbopol 940, and then the mixture was homogenized to achieve uniform dispersion. The pH of the hydrogel was adjusted using a few drops of 2 M sodium hydroxide (NaOH), which were added under constant stirring. Then the mixture was constantly stirred for 24 h to complete the gelation.

2.9. Preparation of the miconazole nanoemulgel

The optimized MNZ-loaded nanoemulsion formulation was incorporated into the Carbopol 940 hydrogel at several concentrations (0.4 %, 0.6 %, and 0.8 % Carbopol). Polydispersity index, particle size, and zeta potential analyses were performed for the attained nanoemulgel formulations.

2.10. Measurement of the zeta potential of the miconazole nanoemulgel formulations

The Omni (Brookhaven Instruments Corporation, New York, USA) was used to measure the zeta potential of the formulations. Measurements were performed in triplicate, and the average was calculated. The zeta potential was determined for each sample, and then the zeta potential was graphed against the Carbopol concentration.

2.11. Measurement of the rheological behavior of the miconazole nanoemulgel

There were several differences in the behavior of nanoemulgel formulations with different concentrations of Carbopol (the thickening agent). The temperature was measured using a rotational viscometer (DVI; Brookfield, USA) at the same value of 25 °C. The viscosity shear rate values were between 0 and 100 rpm.

2.12. Assessment of the release of miconazole from nanoemulgel systems containing different concentrations of Carbopol

The dialysis test was used to study the release of the MNZ from the nanoemulgel system. Five grams of MNZ were added to each sample, consisting of three different concentrations of Carbopol (0.4 %, 0.6 %, and 0.8 %). One liter of phosphate-buffered saline (PBS) was prepared by dissolving 0.19, 2.38, and 8 g of potassium dihydrogen phosphate (PDP), disodium hydrogen phosphate (DHP), and sodium chloride (NaCl), respectively, in distilled water, then making it up to 1 L. The pH of the PBS stock was adjusted to 7.4 pH with 1 M HCl.

The next step was to add the sample to a dialysis bag and place it in an isothermal shaker containing 40 ml of PBS, maintaining the temperature at 37 ± 1.0 °C. To determine the amount of the drug released from the nanoemulgel, samples from the buffer solution were taken at 10, 20, 30, 40, 50, 60, 90, and 120 min At a wavelength of 230 nm, UV spectrophotometry was used to measure the MNZ absorbance. The release test was also performed on the market product (MNZ cream). Lastly, the results of the formulated MNZ nanoemulgel were compared to those of the market MNZ cream (Eid et al., 2019).

2.13. Antifungal test

The antifungal activity was assessed by the agar-well diffusion method using *Candida albicans*. A plate containing Muller–Hinton agar was used for the inoculation of a standard inoculum of fungal culture. Two wells (A and B) with a diameter of 6 mm were punched into the agar: A was filled with the market MNZ cream, and B was filled with the formulated MNZ nanoemulgel. The plates were incubated for 48 h at 37 °C. The diameter of the zone of inhibition was measured to evaluate the antifungal activity (Balouiri et al., 2016).

2.14. Skin penetration study using the Franz cell diffusion test

A cell diffusion test was performed to examine the ability of the MNZ nanoemulgel to penetrate the skin and reach the blood stream. This is essential to determine whether the drug is suitable for topical use. Mice (10–12 weeks old) were sacrificed with carbon dioxide when the full thickness of their skin was reached. The media for the Franz cell diffusion test was PBS (pH 7.4). The diffusion cell was kept at 37 ± 1 °C during the test by heating recirculated water with oscillating (electromagnetic) stirring. Samples (1 ml) were taken from the receptor compartment at specified time intervals (0.5, 1, 2, 3, 4, 6, and 24 h) and replaced with fresh medium. The MNZ absorbance was assessed by ultraviolet (UV) spectrophotometry at a wavelength of 230 nm. The concentration was then calculated using the calibration curve. The release profile was determined by plotting the cumulative amount of MNZ released (mg/ml of the acceptor media) versus time (h) (Qushawy et al., 2018).

2.15. Statistical assessment

Each of the experiments was performed in triplicate, and the values were expressed as mean ± standard deviation (SD). Statistical significance was considered when the p-value was ≤ 0.005.

3. Results

3.1. Screening for the miconazole nitrate wavelength

To find the optimum wavelength for MNZ, screening was carried out by UV spectrophotometry. The optimum absorbance was achieved at 230 nm.

3.2. Calibration curve for miconazole nitrate

To determine the MNZ nitrate concentration in an unknown sample, a calibration curve was prepared with standards of different concentrations. The unknown samples were compared to a set of known values. Fig. 1 shows the results of the MNZ calibration curve.

The calibration curve will be used in the research to calculate concentrations from the UV-spectrophotometer absorbance results using the equation that correlates absorbance and concentration, y = 0.040x + 0.015.

3.3. Screening of Miconazole nitrate solubility in several oils and surfactants

By dissolving MNZ in several oils and surfactants, its solubility was determined, and the absorption was measured using a UV spectrophotometer. The results achieved are shown in Table 1 below.

Based on the results presented in Table 1, the best oil for dissolving MNZ were olive oil and almond oil, with concentrations of 53.375 and 53.125 mg/ml, respectively. Moreover, Tween 80 and Span 80 showed the highest solubilizing capability for MNZ amongst the surfactants, with concentrations of 53.150 and 52.450 mg/ml, respectively. Hence, they were chosen as the surfactants and co-surfactants, respectively. These oils and surfactants were used as the drug vehicle for the production of MNZ nanoparticles using the self-emulsifying technique.

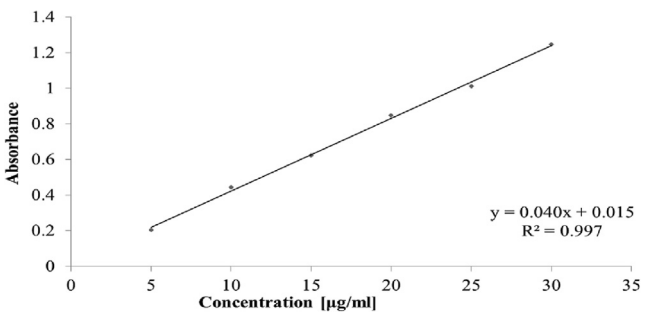

Fig. 1. Calibration curve of Miconazole nitrate.

Table 1
The solubility results of Miconazole nitrate in different oils and surfactants.

Oil/surfactant	Concentration (mg/ml)
Almond oil	53.125
Span 80	52.450
Tween 80	53.150
Olive oil	53.375
Crystal oil	2.725
Paraffin oil	1.550
Tween 20	35.350
Pine oil	28.000
Propylene	30.050
Glycerol	0.2750
Castor oil	12.425

3.4. Optimization of olive and almond oil nanoemulsion formulations

Olive and almond oil nanoemulsion formulations were optimized using the self-emulsifying technique. A ternary phase diagram was constructed to determine the optimum nanoemulsion formulations using several concentrations of oils (olive and almond oils), Tween 80, and Span 80. The ternary phase diagrams are presented in Fig. 2. The green area represents those compositions that produced nanoemulsion formulations with droplets smaller than 1 μm in size, whereas the red area represents the compositions that were able to produce macroemulsions with droplets between 1 and 20 μm in size. The optimum nanoemulsion formulations were chosen according to the droplet size and polydispersity index (PDI) of the two oil formulations. Those formulations with droplets smaller than 200 nm were chosen.

The results of the optimum nanoemulsion formulations are presented in Table 2.

The best formulations were those that obtained the smallest particles and were loaded with MNZ. The obtained formulations were measured for their particle size and polydispersity index in triplicate.

3.5. Particle size and polydispersity index of the miconazole nanoemulsion

The results showed no significant change after loading the MNZ into the selected nanoemulsion formulations, as shown in Table 3.

By comparing the formulations, it can be seen that the formulation loaded in almond oil presented the smallest particle size (170 nm) and polydispersity index (0.193). Thus, the formulation with almond oil was chosen for further experiments.

3.6. Miconazole nitrate nanoemulgel particle size, polydispersity index, and zeta potential

Nanoemulgel formulations of MNZ were prepared after preparing the drug nanoparticles using the self-emulsification technique and incorporating them into Carbopol hydrogel (Carbopol concentrations of 0.4 %, 0.6 %, or 0.8 %). The results for MNZ particle size and polydispersity index are presented in Fig. 3, whereas the zeta potential results for MNZ can be seen in Fig. 4.

The drug particle size and PDI results did not significantly differ between the MNZ nanoemulsion form and when it was converted to a nanoemulgel. The results for the three different concentrations of Carbopol were in the range of 170–180 nm. A slight increase was observed at higher concentrations of Carbopol, but generally the behavior of the three tested concentrations was similar.

The zeta potential results for the nanoemulgel formulations were below −30 mV for both drugs. This fact suggests that the formulations adequately prevented the agglomeration of particles, and, therefore, presented appropriate stability.

3.7. Rheological properties of the miconazole nanoemulgel and cream

Evaluation of the rheological properties is of great importance for semisolid forms, like that of our formulated drug, as they indicate the efficacy and quality of the formulations. The results are shown in Fig. 5.

As shown in Fig. 5, the behavior of the nanoemulgel formulations was similar for all three Carbopol concentrations tested; however, the viscosity increased as the Carbopol concentration increased. Furthermore, the viscosity decreased with an increase in the shear rate, which indicates that the drug nanoemulgel formulations presented pseudoplastic behavior.

3.8. Release of miconazole (MNZ) from the nanoemulgel formulation

To study the release of MNZ from the nanoemulgel formulations, release tests were performed. This study was also important

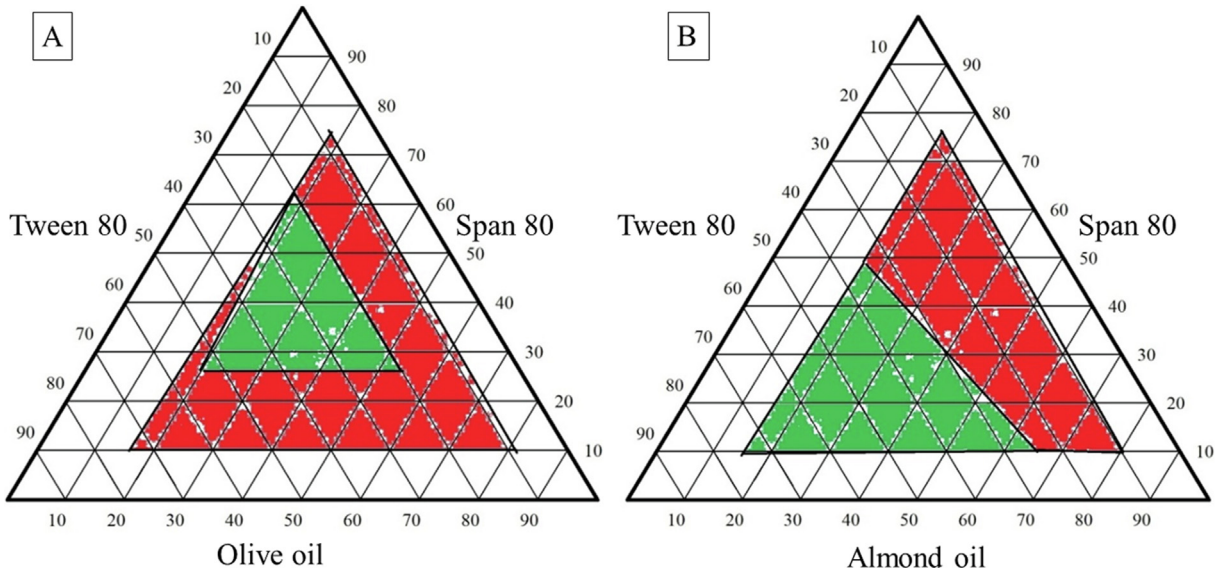

Fig. 2. Ternary phase diagrams of (a) Olive oil/Tween 80/Span 80 and (b) Almond oil/Tween 80/Span 80 nanoemulsions.

Table 2
The selected nanoemulsion formulations for both oils nanoemulsion.

Tween 80	Span 80	Olive oil	Particle size (nm)	PDI
64 %	16 %	20 %	190 ± 3.7	0.27 ± 0.03
Tween 80	Span 80	Almond oil	Particle size (nm)	PDI
72 %	8 %	20 %	175 ± 2.2	0.182 ± 0.06

Table 3
The particles size and polydispersity index of Miconazole nitrate nanoparticle.

	Tween 80	Span 80	Oil	MNZ	Particle size (nm)	PDI
Almond	72 %	8 %	20 %	0.02 g	170 ± 3.1	0.193 ± 0.06
Olive	64 %	16 %	20 %	0.02 g	201 ± 4.2	0.300 ± 0.04

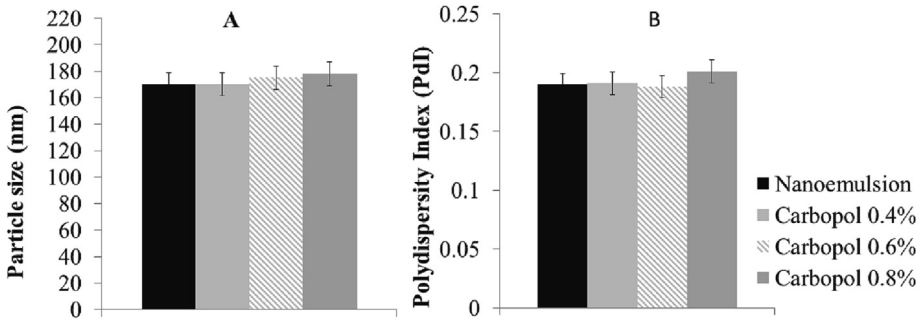

Fig. 3. The results of Miconazole nitrate nanoemulgel formulations (a) particle size and (b) polydispersity index.

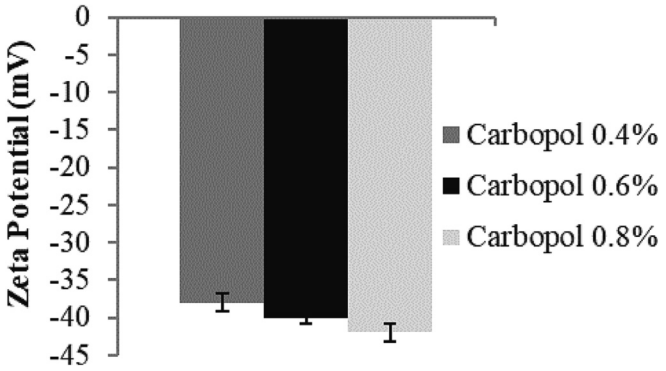

Fig. 4. Zeta potential of Miconazole nitrate nanoemulgel formulations.

for selecting the optimum Carbopol concentration for use as a thickening agent for the preparation of the hydrogel used in the nanoemulgel formulations. The release of the drug from the nanoemulgel formulations was tested using the dialysis method and compared to the market product. The results of the release study are shown in Fig. 6.

The release profiles of the different formulations are presented in Fig. 6. It is notable that there was an inverse relationship between the Carbopol concentration and the release profile, where the formulation with the lowest concentration of Carbopol (0.4 %) presented the highest release profile.

3.9. Skin penetration study using the Franz cell diffusion test

An *in vitro* Franz cell diffusion test was performed to determine the percentage cumulative drug release from the MNZ nanoemulgel and from the conventional Daktazol cream. The results pre-

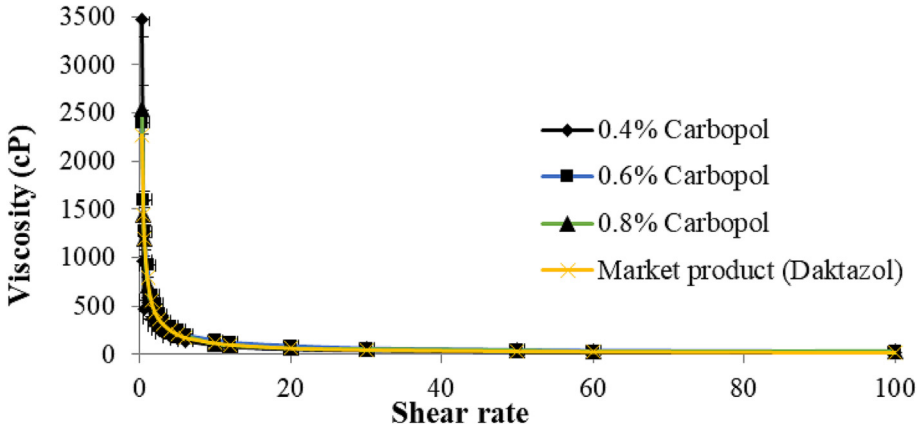

Fig. 5. The rheological behavior of Miconazole nitrate nanoemulgel formulations compared to Dektazol (market products).

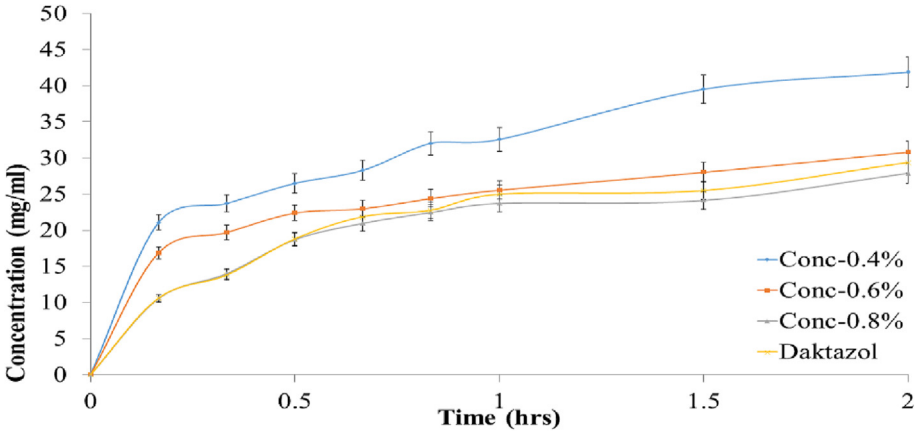

Fig. 6. The release profile of Miconazole nitrate nanoemulgels contains different Carbopol concentrations compared to the market product.

sented in Fig. 7 show the results of the diffusion cell test for freshly prepared MNZ nanoemulgel formulation and market MNZ cream through the skin of a mouse.

A percentage of cumulative drug release of 29.67 % and 23.79 % after 6 h was acheived for the nanoemulgel MNZ and the conventional Daktazol cream, respectively.

3.10. Evaluation of the antifungal effect of the miconazole nitrate nanoemulgel

An antifungal test was performed on *C. albicans* grown in agar media on Petri dishes to assess the antifungal activity of the MNZ nanoemulgel and compare it to the market product. This was achieved by measuring the inhibition zone. The antifungal activity results, with the MNZ nanoemulgel showing the highest activity (40.9 ± 2.3 mm), are presented in Table 4.

Table 4
Antifungal activity of Miconazole nitrate nanoemulgel, compared to market product and almond oil.

Daktazol cream (mm) mean ± SD	MNZ nanoemulgel (mm) mean ± SD	Almond oil (mm) mean ± SD
25.4 ± 2.7	40.9 ± 2.3	18 ± 1.9

4. Discussion

In this study, we investigated a novel nanoemulgel formulation for the topical delivery of MNZ nitrate, with the aim to improve its solubility, therapeutic activity, thermodynamic stability, and penetration, and consequently improve patient compliance. To accomplish this aim, the self-nanoemulsifying technique was used to prepare a MNZ nanoemulgel, which was later integrated into a Carbopol hydrogel. Tests of the drug release profile and antifungal activity were performed for the novel MNZ nanoemulgel in comparison to Daktazol, the market product.

Miconazole nitrate is a lipophilic imidazole antifungal drug (Shahzadi et al., 2014). The skin penetration of MNZ is limited, presenting a challenge for the topical application of MNZ for the treatment of cutaneous fungal diseases. To provide efficient treatment, the concentration of the drug that is delivered to the site of infection must be sufficient (Shinde, 2013). One of the modern solutions for improving the therapeutic profile and systemic delivery of hydrophobic drugs is the use of a nanoemulgel drug delivery system. This delivery method has been shown to substantially improve the pharmacodynamic and pharmacokinetic profiles of lipophilic drugs, in addition to their skin permeability. Nanoemulgels are a drug-containing nanoemulsion in a gel base (Sengupta and Chatterjee 2017).

A self-emulsification technique was used to formulate a novel nanoemulsion with suitable physiochemical properties. The ingredients of the system, whether inactive or active, needed to be carefully selected to ensure the optimum combination of oil, surfactant, and co-surfactant. Firstly, the solubility of MNZ in various oils, surfactants, and co-surfactants was evaluated to determine the optimum components of the self-emulsification system to achieve the desired MNZ solubility.

To achieve this goal, we tested this technique with different oils, surfactants, and co-surfactants (Patel et al., 2011). To enhance and improve the penetration and absorption of MNZ, as indicated by an

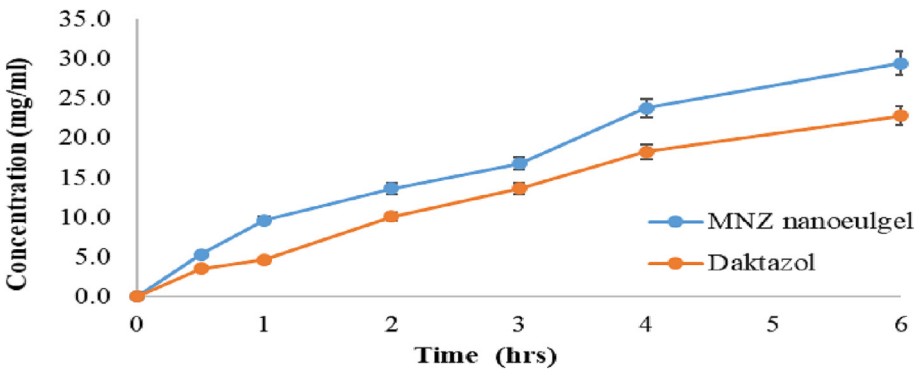

Fig. 7. *In vitro* Franz diffusion profile of the Miconazole nitrate nanoemulgel compared to the market product.

increase in the amount of drug transported, we needed to identify the oil with the best solubilization of the lipophilic drug MNZ. The selection of the oil phase is the most important parameter when attempting to achieve a stabilized nanoemulsion with the maximum amount of solubilized drug. In general, the oil (Almond oil) with the best solubilization potential (53.125 mg/ml) for the selected drug candidate is selected as the oily phase for the nanoemulsion formulation. This helps to achieve the highest drug load in the nanoemulsion (Kaur et al., 2017, Kaur et al., 2017).

In a study conducted in 2012, almond oil was found to show considerable antifungal activity (Kumar et al., 2012). Accordingly, these findings support the high antifungal activity of the novel formula, as illustrated by the marked inhibition zone for this oil in the antifungal assay.

The hydrophilic–lipophilic balance (HLB) value is another significant criterion for the selection of a surfactant. Hydrophilic surfactants are considered to give priority to the interface and reduce the energy required to form the nanoemulsion, thereby improving its stability. Nonionic surfactants are usually chosen because they have been found to be least affected by changes in ionic strength and pH, and they are also known to be safe and biocompatible. Based on toxicological concerns, ionic surfactants were excluded (Shinde 2013).

The hydrophilic Tween 80 surfactant was chosen as the nonionic surfactant for this formulation, as it had an elevated emulsifying activity with a HLB value of 15 (Lian et al., 2019). This helps to lower the surface tension at the water–oil interface and makes the droplet size, causing reduced dispersion of the self-nanoemulsifying drug delivery system (SNEDDS) (Weerapol et al., 2014). Span 80 was chosen as a co-surfactant as the HLB value was 4.3, indicating enhanced drug absorption and dispensability (Kaur et al., 2017).

The self-emulsifying technique was used to prepare the nanoemulsion. In order to find the optimum nanoemulsion components, pseudoternary phase diagrams were constructed for almond oil and olive oil with different surfactants and co-surfactants. Two ternary phase diagrams were constructed: ternary phase diagram A was composed of almond oil, Tween 80, and Span 80; whereas - ternary phase diagram B consisted of olive oil, Tween 20, and Span 80. Plotting these diagrams allowed us to determine which formulation obtained the desired droplet size (smaller than 200 nm), representing the optimum formulation.

The droplet size is a decisive factor for SNEEDS performance as it determines the extent of drug absorption and the rate of drug release (Patel et al., 2011). Furthermore, the interfacial surface increases as the particle size decreases, which improves the extent and speed of absorption and the bioavailability of the drug (Senapati et al., 2016). A droplet size smaller than 200 nm is an important criterion for achieving SNEDDS, which is the main advantage of developing a formulation with nanotechnology.

Achieving a suitable mix of surfactant and co-surfactant leads to a smaller globule size and helps to prevent aggregation of the formed globules through the creation of a strong mechanical barrier (Kaur et al., 2017). An additional important parameter in the SNEDDS formulation is the PDI, also known as the droplet size distribution, which measures the homogeneity of the particles. The PDI is the proportion of the standard deviation to the mean droplet size. To achieve more homogeneous particles, the PDI value should be as close to zero as possible, which indicates a narrow particle size distribution, a highly uniform emulsion, and greater homogeneity, which are associated with improved physical stability (Shinde 2013).

The measurement of the zeta potential is important because it is related to the physical stability and surface charge of the nanoformulation. Ordinarily, the opportunity for aggregation is reduced as soon as the zeta potential increases above 30 mV, either positively or negatively, due to electrostatic repulsion within the particles. The nanoemulgel formulated in the current study presented an adequate negative value (below −35 mV), indicating a stable nanoemulgel (Paliwal et al., 2018).

The rheological behavior is an important criterion for topical products, as it is related to the release of the drug from the formulated nanoemulgel. The spreadability, flowability, and rheology are all important to ensure consumer acceptance of the product. The flow behavior of the formulation in the current study presented a nonlinear relationship between the shear rate and viscosity; hence, the behavior of the nanoemulgel is considered pseudoplastic. This result was expected on the basis of the positive correlation observed between Carbopol concentration and viscosity. Similar findings were previously obtained by Jadhao and his research team on the formulation of Miconazole Nitrate hydrogel (Jadhao et al., 2017).

Carbopol, as a rheological modifier, achieves excellent results in enhancing the physical appearance and stability of nanoformulations. Similar results were reported by Eid et al. (2019), where the good stability of the nanoemulgel was attributed to the presence of Carbopol as a thickening agent and the stability of the nanoemulsion (Eid et al., 2019).

To assess the speed of drug release from the novel formulation, a drug release test was performed. The results of this test showed a remarkably higher release of MNZ compared to the commercial product. The reduced droplet size of the formulation enhanced the drug release rate, as evidenced by increased permeation of the active ingredient through the membrane, indicating higher bioavailability compared to the commercial product. Moreover, the amount of drug released from the nanoemulgel decreased as the concentration of Carbopol was increased. Accordingly, the best formulation in terms of drug release was the formulation containing 0.4 % Carbopol. Similar results were presented by Eid et al. (2019), who developed sodium fusidate and fusidic acid nanoemulgels. For both of these nanoemulgels, the highest release and pseudoplastic behavior were observed for formulations containing 0.4 % Carbopol.

Franz diffusion vertical cells (FDVC) provide a reproducible and reliable means of *in vitro* drug release (IVDRT) testing for different dosage forms (Kanfer et al., 2017). The cumulative percentage of MNZ released from the nanoemulgel was 29.67 %, which was significantly higher than the amount released from the conventional Daktazol cream (23.79 %, $p < 0.05$). The improved permeation of MNZ in the nanoemulgel can be related to the decreased particle size, as smaller particles can easily penetrate the skin and overcome the barrier by squeezing between the intracellular lipids of the stratum corneum. Comparable results were previously presented by Qushawy et al. (2018), who prepared transfersomes of MNZ to overcome the skin barrier function (Qushawy et al., 2018).

The antifungal activity against *Candida albicans* of Daktazol, the formulated nanoemulgel, and almond oil was investigated and compared. The zone of inhibition of the formulated MNZ nanoemulgel was significantly higher (40.9 ± 2.3 mm) than that of the commercial product (25.4 ± 2.7 mm) and almond oil (18 ± 1.9 mm). This improvement could be attributed to the decreased size of the particles (nanoscale), which increases the surface area and consequently increases the penetration of the drug through the *C. albicans* cell membrane, where it inhibits ergosterol synthesis. The same findings were reported in a study by Aljaeid et al. (2016), in which MNZ-loaded solid lipid nanoparticles were developed and evaluated (Aljaeid and Hosny 2016). These authors confirmed that the smaller the particle size, the better the antifungal activity. Similar results were presented by Shinde (2013) in a study that investigated the nanoemulsion formulation potential for vaginal MNZ delivery (Shinde 2013). The antifungal activity of almond oil was supported by the findings

of Kumar et al. (2012), as we got an 18 mm zone of inhibition when testing the pure almond oil. This also supports the improvement in the zone of inhibition observed for the novelly formulated nanoemulgel (Kumar et al., 2012).

According to Kaur et al. (2017), the space between the cells of the skin is 70 nm. Conventional semisolid products, such as creams, penetrate the skin slower than nanoemulgels, which rapidly penetrate the skin and can deliver the active substances quicker and deeper (Kaur et al., 2017). Moreover, the nanoemulgel delivery system is associated with improved solubility of lipohilic drugs, such as MNZ, which improves drug loading and increases the bioavailability of the drug. As Sultana and his team have reported earlier in 2014, the nanoemulgel drug delivery system has a longer residence time and time of contact with cells (Sultana et al., 2014). Parasuraman and his team (2019) reported that the use of methylene blue carbon nanotubes enhanced the antimicrobial activity against gram negative and positive bacteria as a result of the accumulation of the photosensitizer in the cell membrane, which causes critical damage to the bacteria (Parasuraman et al., 2019). Another research study was conducted by Anju et al. (2019). highlighted that the loading capacity and entrapment efficiency of carbon nanotubes are two important parameters in antimicrobial photodynamic inactivation (Anju et al., 2019).

These findings support the hypothesis that the antifungal activity of the MNZ nanoemugel formulation was improved when compared to the conventional MNZ cream, as seen in the inhibition zone test, as well as an improvement in all the outcomes reported in the study.

5. Conclusion

Based on the outcomes of the present study, we can conclude that the stable MNZ nanoemulgel was superior to the Daktazole cream in the studies performed. The nanoemulgel was prepared by incorporating a nanoemulsion and hydrogel base, with the inclusion of Carbopol as a thickening agent. Using the self-nanoemulsifying technique, we obtained the optimum MNZ formulation for the nanoemulsion, composed of almond oil, Tween 80, and Span 80. This formulation presented the dissolving power and improved nanoemulsion properties, including nanoscale droplet size, elevated negative zeta potential a narrow PDI, and improved permeation through the skin of mice, indicating better cumulative drug release. Moreover, we observed excellent antifungal activity against *Candida albicans* when compared to the marketed Daktazole cream. In conclusion, the preparation of MNZ as a nanoemulgel has the potential to overcome the challenge posed by the poor solubility of MNZ. Hence, this formulation will be able to overcome the skin barrier and increase the antifungal activity, leading to a shorter healing time and the maximum activity of the drug with the minimum frequency and dose, which will improve patient compliance.

The nanoemulgel drug delivery system has many advantages over conventional cream. The preparation of MNZ nitrate in such a dosage form enhanced MNZ solubility, skin penetration, drug loading, and bioavailability. It also facilitated MNZ application, associated with improved patient compliance, together with an increase in the efficacy of the drug and a decrease in side effects. This dosage form will play a major role in formulating more effective novel dosage forms for pharmaceutical companies.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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