An-Najah National University

Faculty of Graduate Studies

Nanoemulgel Formulation for Topical Delivery of Miconazole Nitrate

By

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Dedication

For my great mother Nawal who raised seven brilliant and successful girls alone

For my beloved sisters: Iman, Aiat, Wafaa, Dr. Kholoud, Dr. Montaha and Salam.

For my father –Allah rest his soul-.

For my husband, for his love, assistance and encouragement.

For my granted three children, Maraim, Omar and Ibrahim.

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Lastly, I would like to thank everyone who loves me and assist me in any previous and present stages of my life.

الاقرار

أنا الموقعة أدناه مقدمة الرسالة التي تحمل العنوان:

Nanoemulgel Formulation for Topical Delivery of Miconazole Nitrate

أقر بأن ما اشتملت عليه الرسالة إنما هو نتاج جهدي الخاص، باستثناء ما تمت الإشارة إليه فيما ورد، وأن هذه الرسالة ككل، أو أي جزء منها لم يقدم من قبل لنيل أية درجة أو لقب علمي أو بحثي لدى أي مؤسسة تعليمية أو بحثية أخرى.

Declaration

The work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

اسم الطالبة:…… **Student's Name:……**

التوقيع:…… **Signature:…….**

التاريخ:…… **Date:……..**

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List of Abbreviations

Symbol	**Abbreviation**
MNZ	Miconazol Nitrate
SC	Stratum Corneum
MSS	Manufacturers Standardization Society
Jepharm Co.	Jerusalem Pharmaceuticals Co. Ltd.
Nm	Nanometer
µm	Micrometer
NR	Nile red
pH	potential of hydrogen
HLB	Hydrophile-Lipophile Balance
Carbopol 940	Carboxyvinyl Polymer 940
Gr	Gram
Ml	Millileter
UV spectrophotometer	Ultraviolet–visible spectroscopy
Mg	Milligram
Min	Minute
Rpm	Revolutions per minute
[M]	Molar
NaOH	Sodium Hydroxide
HCl	Hydro chlori acid
Hr	Hours
PBS	Phosphate-buffered saline
PDI	Polydispersity index
PDP	Potassium dihydrogen phosphate
DHP	Disodium hydrogen phosphate
NaCl	Sodium chloride
L	Liter
°C	Celsius
Log P	Partiton coefficient
Mm	Millimeter
SD	Standard deviation
mV	Milivolt
SNEDDS	Self Nano-Emulsifying Drug Delivery System
Cr	Cream
C. albicans	*Candida albicans*

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Nanoemulgel Formulation for Topical Delivery of Miconazole Nitrate

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Abstract

Miconazole is a synthetic derivative of imidazole, a broad-spectrum antifungal drug used in the local treatment of vaginal, skin and nail infections. It has poor aqueous solubility, so significant reductions in its therapeutic efficacy have been reported.

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; 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 attained for the MNZ nanoemulgel and the commercial cream, Daktazol, repectively.

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 [mm] ± 2.3, 25.4 [mm] ± 2.7 and 18 [mm], respectively.

In conclusion, a novel MNZ nanoemulgel showing superior antifungal activity compared to that of the commercial product has been developed.

Chapter 1

Introduction

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Introduction

1.1 Background of the Study

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 **(I. P. Kaur & Kakkar, 2010)**. It is generally applied topically as a treatment for various diseases of skin surface, such as ring worm, perioral candidiasis, jock itch and athlete's foot **(Aljaeid & Hosny, 2016; Fothergill, 2006)**.

However, poor capability of MNZ to penetrate skin poses a challenge for treatment of cutaneous diseases through topical application **(Gupta, Agrawal, & Vyas, 2012; Kenechukwu et al., 2018; Khalifa, 2015).**

The low solubility and high lipophilicity of MNZ and the vehicle used for administration greatly affects penetration of MNZ across layers of skin (Bhalekar, Pokharkar, Madgulkar, Patil, & Patil, 2009). Consequently, development of MNZ delivery systems will help to improve its solubility, thermodynamic stability, penetration and therapeutic activity **(Kenechukwu et al., 2018; Shahzadi et al., 2014).**

Nanoemulgels are an amalgamated formulation of two different systems, in which a drug-containing nanoemulsion is incorporated into a gel base **(Eid, El-Enshasy, Aziz, & Elmarzugi, 2014)**. This combination overcomes limitations of each system separately. However, nanoemulsions have low

viscosity, related to poor retention on skin and poor spreadability **(Arora, Aggarwal, Harikumar, & Kaur, 2014).**

Topical nanoemulgel delivery systems have been demonstrated to improve the systemic delivery, pharmacokinetics, pharmacodynamics and therapeutic profile of lipophilic drugs. In recent years, 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 **(Sengupta & Chatterjee, 2017; S. Sharma, Kumar, Sahni, Ali, & Baboota, 2012).**

Topical therapy reduces the risk of systemic side effects, making it the most favorable route of therapy for diseases affecting the skin **(Zakrewsky, Kumar, & Mitragotri, 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, Bhatt, Kothiyal, & Gupta, 2015).

1.2 Significance of the Study

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 **(Whitesides, 2005).** The administration of a compound through the skin has many advantages,

including easy, pain-free administration, low cost and avoidance of the hepatic first-pass **effect (Tanner & Marks, 2008)**. However, a significant barrier to this route is the stratum corneum, which is the outermost layer of the epidermis. Therefore, nano delivery systems are essential and highly effective, and they play important roles in drug delivery, biological products and cosmetic applications **(Parveen, Misra, & Sahoo, 2012; Pitaksuteepong, 2016; Suri, Fenniri, & Singh, 2007).**

Because approximately 40% of new chemical entities are lipophilic in nature, and therefore present poor solubility in water, nanoemulsions have attracted enormous attention as delivery **vehicles (V. Sharma, Singh, Gill, & Harikumar, 2012)**.

Nanoemulsions are a dispersion of two immiscible liquids that are isotropically and thermodynamically stable (**Jaiswal, Dudhe, & Sharma, 2015)**. These liquids, such as water and oil, are stabilized by an interfacial film of surfactant molecules. The main difference between emulsions and nanoemulsions is the shape and size of the particles, which are dispersed in the continuous phase **(Salvia-Trujillo, Rojas-Graü, Soliva-Fortuny, & Martín-Belloso, 2015)**. The particle size in conventional emulsions is 1–20 μm, while those in nanoemulsionsare 10–200 nm **(Eid, Elmarzugi, & Jaradat, 2019)**. Nanoemulsions are superior to emulsions for transdermal use due to their higher thermodynamic stability, which improves drug solubility and transdermal permeability **(Chellapa et al., 2015)**.

Nanoemulsions are able to increase the thermodynamic activity and the concentration gradient across the skin, in addition to improving the permeability of their components through the skin, which makes the system convenient and efficient for transdermal delivery. However, nanoemulsions have low viscosity, which limits their application in transdermal delivery because of their cumbersome **use (Eid et al., 2020)**.

The weak interaction of biocompatible gels with surfactants has previously been investigated to characterize the rheological behavior of nanoemulsions **(Arora et al., 2014)**. When comparing a nanoemulsion to a nanoemulgel, the inclusion of a nanoemulsion into a gel matrix results in a nanoemulgel, which his more appropriate for transdermal application **(Chellapa et al., 2015)**.

The barrier characteristics of the stratum corneum represent the greatest challenge to transdermal drug delivery. In the human body, it is considered one of the most impermeable epithelia to exogenous substances (**Ramteke, Dhole, & Patil, 2012)**.

By using chemical permeation enhancers, the challenges associated with permeation can be minimized. However, the use of those chemical enhancers may be hazardous and harmful, especially for chronic application, because many of them are irritants.

To facilitate drug permeation through the skin, it is preferable to develop a new transdermal vehicle system that does not require the use of chemical enhancers. Nanoemulsion is one of the most promising techniques to

enhance the transdermal permeation of drugs (**Dhawan, Aggarwal, & Harikumar, 2014)**.

1.2.1 Previous Studies

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 MCZ **(Shinde, 2013)**.

Later, Maha and Sinaga (2018) evaluated the profile of a miconazole nitrate nanoemulsion and a cream. The results of evaluation of miconazole nitrate nanoemulsion preparations were better than cream preparations **(Maha & Sinaga, 2018)**.

This study developed a superior topical formulation for application to the skin or mucous membrane to restore a fundamental function of the skin or pharmacologically alter the underlying tissues. In this study, an MZN 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.

1.3 Objectives

This study will focus on the preparation of a novel nanoemulgel delivery system for MNZ nitrate with enhanced solubility, permeability, spreadability, efficacy and safety to improve patient compliance.

The objectives were as follows:

1. To optimize and evaluate a MNZ nitrate nanoemulsion.
2. To prepare and evaluate a MNZ nitrate nanoemulgel.
3. To evaluate the antifungal activity of an MNZ nitrate nanoemulgel.

1.4 Hypothesis

The MZN nitrate nanoemulgel will be formulated with different ratio of surfactants (Tween 20 and Span 80), almond oil (20%w/w) and distilled water, prepared using a self-emulsifying technique.

The self-emulsifying technique will lead to a substantial reduction in particle size and will increase the stability of the nanoemulgel formulation. The optimum nanoemulsion formulation will be selected and incorporated with hydrogel (Carbopol) to produce a nanoemulgel.

Chapter 2

Literature Review

Chapter 2

Literature review

2.1 Dermatomycosis

Dermatomycosis is a fungal infection that affects the stratum corneum layer of the skin, as well as the nails, hair and mucosal surfaces. Mycological contamination presents a significant health risk **(Hube, Hay, Brasch, Veraldi, & Schaller, 2015; Nenoff, Krüger, Ginter-Hanselmayer, & Tietz, 2014)**. Recently, there has been a significant increase in cases, which can be attributed to a number of factors including the rapid growth of vulnerable populations, including the elderly and those with immunodeficiency, in addition to cultural and social practices related to sports and the utilization of public pools. In immune deficient individuals, injuries and wounds related to dermatomycosis are Serious and progressive in nature. Although they first appear as shallow sores, there is a high risk of progression to a lethal infection. The lethal nature of these infections can be explained by their toxicity, widespread resistance to antifungals, poor penetration of drugs and delayed diagnosis. Allylamine and azole medications are among the drugs used to treat various antifungal infections, including dermatomycosis **(Baran, Hay, & Garduno, 2008; Singal & Khanna, 2011)**.

There are several issues with dermatomycosis treatment, including the low residence time of drugs at the site of activity, side effects and variable permeability of medications **(Luiza Ribeiro de Souza et al., 2012)**. The

largest organ of the human body is the skin, which acts as a barrier to actively maintain homeostasis **(Walters & Roberts, 2002).**

The skin is responsible for preventing the uncontrolled loss of water and uptake of dangerous synthetic substances from the environment. It also plays important roles in the synthesis of vitamin D and in thermoregulation **(Ahmed, Mikail, Zamakshshari, & Abdullah, 2020; Buffenstein & Pinto, 2009**). The main functions of the skin are related to the prevention of boundary molecular diffusion, primarily due to the stratum corneum (SC) **(Menon, Cleary, & Lane, 2012)**.

In general, particles can infiltrate the skin through two diffusion pathways: the trans appendageal and epidermal pathways **(Dayan, 2005).** The appendageal pathway occurs over a restricted accessible surface zone (around 0.1%) and is associated with the dispersion of ions and polar compounds. Most medications diffuse over the greater part of the epidermis **(Cevc, 1997; Ramteke et al., 2012)**. The infiltration of drugs through the SC can occur through the intercellular or transcellular courses **(Magnusson, Walters, & Roberts, 2001**). Partition coefficients are normally used to determine the primary pathway taken by a penetrant (log K) **(Abraham & Martins, 2004)**. Hydrophilic medications primarily diffuse through intercellular spaces, whereas lipophilic substances cross the SC through the transcellular pathway **(Kong, Chen, Kweon, & Park, 2011).** The majority of molecules pass the SC by utilizing both pathways.

The infiltration course relies heavily on the medication used, especially its chemical attributes and molecule size (**Cevc, 1997)**.

It is possible for some tiny particles that are in contact with superficial junctions or furrows to remain for a few hours, taking into consideration a delayed medication discharge. Because of this, new topical medication conveyance frameworks have been created for antifungal treatments, including niosomes, liposomes, nanostructured lipid carriers, microemulsions (**Bhatt et al., 2020)**, silver nanoparticles, solid lipid nanoparticles and liquid crystals. The current study aimed to investigate and present an overview of nanotechnology-based medication conveyance frameworks for the treatment of dermatomycosis (**Luiza Ribeiro de Souza et al., 2012)**.

2.2 Miconazole Nitrate

Miconazole is an antifungal medication that can act on different fungal groups because it contains an imidazole group **(Luca, 2006).** This antifungal medication can be found in various dose structures, including oral, topical and parenteral delivery systems, depending on the infection itself as well as its various species. Miconazole has been broadly utilized for the treatment of dermatophytosis, pityriasis, cutaneous mycosis and oropharyngeal candidiasis, as well asparasitic vaginitis **(Aljaeid & Hosny, 2016; Ramos et al., 2018)**.

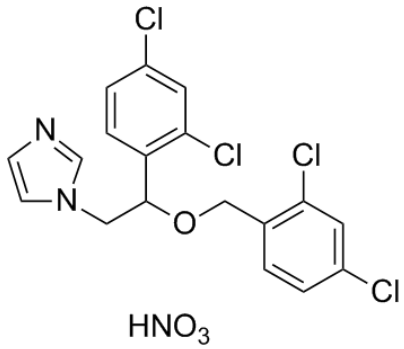


Figure 2.1 Synthetic chemical structure of Miconazole Nitrate.

2.2.1 Mechanisms of Activity

Azoles specifically prevent the synthesis of the basic ingredient and constituent of fungal cell membranes, ergosterol, by interacting with fungal Lanosterol 14α-demethylase, a cytochrome P450-dependentenzyme that changes lanosterol to ergosterol. By interfering in ergosterol synthesis, azoles lead to increased rigidity and/or permeability of the fungal cell membrane and disturb the bound to the fungal cell membrane. In this way, they prevent the growth and replication of the fungus. These molecules are generally fungistatic rather than fungicidal, unless they are present at a high enough concentration **(Luiza Ribeiro de Souza et al., 2012).**

2.2.2 Physicochemical Properties

Miconazole is typically classified as a Biopharmaceutical Classification System BCS class II drug. It is a weak base with poor aqueous solubility (1 μg/ml) and log P (partition coefficient) of 6.1. Accordingly, it displays a constrained antifungal effect and restricted dissolution characteristics and features **(Aljaeid & Hosny, 2016; Singh, Malviya, & Sharma, 2014).**

2.2.3 Topical Administration of Miconazole

Although MNZ nitrate is widely used as an antifungal agent, ordinary topical formulations of MNZ are not adequate for the topical therapy of deep-seated fungal infections **(Al-Maghrabi, Khafagy, Ghorab, & Gad, 2020; Bhalekar et al., 2009).**

Lotions, ointments and creams are likely to result in solidness and side effects, including a lack of spreadability, solidness and stickiness, among others, which may eventually result in patient noncompliance **(James et al., 2017).**

2.3 Nanotechnology

Drugs that are currently characterized as having poor solubility can be improved using nanotechnology. Nanotechnology involves the examination and utilization of materials and structures on the nanoscale, approximately 100 nanometers (nm) or less **(Mansoori & Soelaiman, 2005).** Chemical substances and elements with low solubility and oral bioavailability can be improved by micronization; however, this approach is in adequate as micronized particles have a small surface area for dissolution (**Khadka et al., 2014)**. Therefore, nanonization represents a superior approach **(Singh et al., 2014).**

2.4 Emulsions, Microemulsions, Nanoemulsions and Nanoemulgels

Emulsions consist of a dispersed and scattered framework comprised of small droplets that are incorporated into an immiscible vehicle. Emulsions are normally classified based on the size of their droplets. Macroemulsions are characterized by droplets of 1–100 μm in diameter, and are otherwise called a traditional emulsion/colloid. They are commonly unstable as the droplets of macroemulsions sediment, and also float during the dispersed phase and the medium phase. They tend to be unstable when they are absorbed by solid particles on the surface. Microemulsions (droplets between 10–100 nm), on the other hand, are considered an isotropic fluid framework with a uniform droplet size and favorable physiochemical properties. Moreover, nanoemulsions (droplet size 20–200 nm in diameter) are increasingly stable and, as a result, they do not require emulsifying agents to the same extent as macro- and microemulsions **(Eid et al., 2014)**.

A nanoemulgel typically refers to the creation of a hydrogel that contains a nanoemulsion. A nanoemulgel can be created by integrating a nanoemulsion framework into a hydrogel lattice, which is likely to have excellent skin penetration properties **(Chellapa et al., 2015).**

2.4.1 Nanoemulsions for Topical Application

According to many experts, nanoemulsions are a promising candidate for improving medication delivery. They are particularly well suited to medications with poor solubility, as this delivery system enhances

absorption of medications through skin and increases retention time of a medication in body, which will bring about fewer side effects in long run **(Rai, Mishra, Yadav, & Yadav, 2018; Sutradhar & Amin, 2013)**. Advantages of nanoemulsions, characterized by nanoscale-sized droplets, are not related to physical attributes or features of the emulsion itself, but rather the overall enhanced bioavailability of a medication **(Rai et al., 2018; Rehman et al., 2017).** A vast amount of research has been conducted to investigate bioavailability of lacidipine, with most studies finding that transdermal course had approximately 3.5-times higher bioavailability than oral course. This was attributed to avoidance of first-pass metabolism **(Fares, ElMeshad, & Kassem, 2018; Subramanian, Sharavanan, Chandrasekar, Balakumar, & Moulik, 2016).**

Nanoemulsion has also been found to improve penetration of medications within skin, which is a topic of great interest to many researchers **(Montenegro et al., 2016; Shah, Bhalodia, & Shelat, 2010)**. Research has found that the smaller the particles are, the greater the amount of medication that can fuse to them, which expands therapeutic activity towards skin. In addition, affinity of the medication for division or split can also increase its penetration into the skin. A recent study reported that a Nile red (NR) dye loaded in a lecithin nanoemulsion was able to permeate the skin 9.9-fold more efficiently than a NR-loaded general emulsion **(Chellapa et al., 2015; Zahin et al., 2019)**. Moreover, components used to formulate a structure consisting of ethyl oleate and propylene glycol were

found to enhance its permeation. The most well-known barrier to the permeation of transdermal medication is the stratum corneum, a 10–20 μm thick tissue layer with a well-organized lipid/protein matrix (**Kogan & Garti, 2006)**.

Another recent study reported that topical lipophilic flurbiprofen in a nanoemulsion has 4.4-times greater bioavailability than that of oral administration. Therefore, nanoemulsion is seen as a more spontaneous, unconstrained emulsifying technique that presents greater benefits over the other delivery systems. For example, polymeric nanoparticles and liposomes are characterized by a low-cost preparation procedure, high hydrophilic and lipophilic medication loading system to promotion the therapeutic efficacy thus saving the therapeutic agents **(Chellapa et al., 2015**).

2.4.2 Limitations of Nanoemulsions for Topical Application

The formulation of a nanoemulsion as a topical medication delivery system is limited by a number of barriers and obstacles that hinder the delivery and effective penetration of the drug through the skin. The rheological characteristics of nanoemulsions are important, especially for the formulation of small particles, which are critical for the efficient delivery of drugs through the skin. Current nanoemulsion formulations are not suitable for this purpose due to their low spreadability and viscosity, which has limited their clinical use. Therefore, the introduction of a nanoemulsion

alongside a gelling system could help overcome this obstacle **(Chellapa et al., 2015; B. Sharma, Iqbal, Kumar, Ali, & Baboota, 2019)**.

Despite the numerous benefits of nanoemulsions, their topical application is limited due to their low spreadability and viscosity. Thus, scientists have overcome the issues related to the use of nanoemulsions for transdermal delivery through the modification of nanoemulsions to nanoemulgels **(Arora et al., 2014; Choudhury et al., 2017).**

2.4.3 Nanoemulgels

Nanoemulgel is a process in which a nanoemulsion is created and combined with a hydrogel. This process requires a nanoemulsion system that can be intergraded into a hydrogel matrix, which may result in superior skin penetration **(Dhawan et al., 2014; Harwansh, Mukherjee, Bahadur, & Biswas, 2015)**. This type of nanoemulgel is of great interest to numerous researchers who seek to apply this delivery method to different types of medications to improve the topical treatment of various skin problems and/or deficiencies **(Elmataeeshy, Sokar, Bahey-El-Din, & Shaker, 2018; Harwansh et al., 2015)**.

Table 2.4.3.1 Cream and Gel Products Currently Available on the Market.

Product name	Manufacturer	Formulation
Daktarin 2% cream	MSS	Miconazole 2%, Cream
Daktarin oral gel	MSS	Miconazole 2%, oral gel
Pitrion cream	SYAM drug store	
Fungazole cream	Pharmacare company	Miconazole 2%, cream
Daktazol oral gel	Jepharm Co.	Miconazole 2%, gel

Table 2.4.3.2 Previous Studies on Miconazole Nanoemulsion or Nanoemulgel.

Authors (Reference)	Year	Formulation
(Shinde, 2013)	2013	Nanoemulsion
(Maha & Sinaga, 2018)	2018	Nanoemulsion

Emulgels are not likely to be novel formulations, as there are various manifestations and forms in the market, as shown in Table 2.4.3.1, while Table 2.4.3.2 lists many manifestations and forms of formulations of not only nanoemulgels, but also microemulgels, that have been previously produced and manufactured. The formulation of a nanoemulgel for topical delivery is, for many experts, considered a drug reservoir, which may impact the delivery of medications from the delivery system, and eventually inside the skin.

This delivery system relies heavily on the density of cross links and the structure of the polymer chains in the system. Furthermore, the ability of a medication to penetrate the skin and effectively free the therapeutic agent is affected by drug release from the carrier and the skin penetration. The nanoemulgel that is in contact with the skin likely to discharge the droplets that are impregnated with oil from the gel system of the network. At that

point, the droplets will infiltrate the outermost layer of the epidermis and legitimately take the medication particles without an exchange by means of hydrophilic period of nanoemulsions **(Chellapa et al., 2015; Naseema, Kovooru, Behera, Kumar, & Srivastava, 2020)**.

Nanoemulgels, whether they are oil-in-water or even water-in-oil, are nanoemulsions that have been converted into nanoemulgels through the use of a gelling agent. Nanoemulgels have jelly characteristics, with better nanoemulsion attributes for applications requiring absorption through the skin. The beneficial characteristics of nanoemulgels include minimal skin irritability, increased penetrability, and the ability to load a high concentration of medication for localized delivery, which is in contrast to other drug delivery systems such as microemulsions, liposomes or strong lipid nanoparticles **(Choudhury et al., 2017).**

2.4.4 Benefits of Nanoemulgels

The consistency of nanoemulsions can be improved through their conversion to nanoemulgels, which have decreased surface and interfacial pressure, thereby improving the consistency of the liquid phase **(Aithal, Narayan, & Nayak, 2020)**. Thickeners and emulsifiers are added to help counteract the gelling capability of the hydrogel to achieve an optimal solidness, saturation and consistency for topical drug-loaded nanoemulsions **(Chakraborty, Chaurasia, & Dutta, 2018)**. Within the nanoemulgel framework, the quality of the nanoemulsion is improved by the circulation of oil within the gel arrangement **(Gani & Benjakul,**

2018). These oil droplets carry various drugs, primarily lipophilic drugs. The effectiveness of solutions stacked within the framework is influenced by the solubility of the medication within the oil arrangement **(A. Kaur et al., 2017).**

Nanoemulgels achieve a decent union with the skin, which, along with their great solubility, prompts greater changes in the concentration gradient in relation to the skin, leading to enhanced skin penetration of the medication. In addition, the nanoemulgel approach is likely to improve the transportation of lipophilic and poorly soluble medications. In addition, the use of a nanoemugel also increases patient compliance as the formulation does not stick and spreads easily, unlike other localized drug delivery systems such as creams and ointments which are agitated upon use and have diminished the spread of the coefficient, thus they need to be rubbed onto the skin. Furthermore, nanoemulgels increase control over the delivery of medications as they enhance the impact of medications with a shorter half-life **(Chellapa et al., 2015; Eid et al., 2014)**. These colloidal transportation techniques can be used to fuse drug components to focus on improving the bioavailability, increasing the stability and decreasing the negative outcomes associated with delivery of the medications.

2.5 Self-emulsifying Technique

Low-energy emulsification techniques that are used to prepare nanoemulsions include the spontaneous method and the phase inversion method. They are generally considered better techniques and are preferred over high-energy emulsification techniques in terms of the thermodynamic capacity of the last formulation due to the joining of high energy during the assembly procedure **(Solans & Solé, 2012)**. The blending of surfactants, water and oil in an ideal proportion will help in forming a stable spontaneous emulsion under gentle agitation, that could produce the desired nano-size droplets dispersed in the continuous stage **(Jaiswal et al., 2015; Yukuyama, Ghisleni, Pinto, & Bou-Chacra, 2016).**

The addition of ingredients to the essential ingredients, the pH of the medium, and the features of the consolidated surfactant and the co-surfactant are all factors that influence the emulsification procedure **(Egito, Amaral-Machado, Alencar, & Oliveira, 2020; Pathania, Kaushik, & Khan, 2018).** In particular, the temperature-dependent solubility in Hydrophile-Lipophile Balance HLB differs for certain nonionic surfactants; therefore, polyethoxylated surfactants (e.g., Tween 80, Tween 60, Tween 20, Cremophor EL and Labrasol) are generally used for this strategy. The self-emulsification technique is generally suitable to combine the unstable parts (oil phase and water phase) that helps in producing stable nanoemulsion. Then again, the temperature-dependent automatic mingling of nonionic surfactants is used for phase progress during the phase inversion technique **(Morales, Solans, Gutiérrez, Garcia-Celma, &**

Olsson, 2006). This procedure is also limited by the use of thermolabile ingredients, even though this could be ameliorated by moving toward a lower phase inversion temperature through the choice of appropriate surfactant(s) **(Choudhury et al., 2017).**

Chapter 3
Materials and Methodology

Chapter 3

Materials and Methodology

3.1 Materials

Miconazole nitrate and a MZN nitrate product 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.

3.2 Methods

3.2.1 Wavelength Screening of a Miconazole-containing Medication Using UV Spectrophotometry

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

3.2.2 Calibration Curve for Miconazole

A standard stock solution was prepared according to European pharmacopoeia. 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 was diluted with up to 10 ml 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 & Gillella, 2012)**.

3.2.3 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 20and 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).**

3.2.4 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.

3.2.5 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 laser diffraction particle size analyzer (SALD-MS23and SALD-2300; Shimadzu Corp., Japan), which permitted the measurement of the diameter of the droplets and the polydispersity index **(Qushawy, Nasr, Abd-Alhaseeb, & Swidan, 2018)**.

3.2.6 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.

3.2.7 Hydrogel Preparation

Hydrogel was prepared by adding water to Carbopol 940, then the mixture was homogenized to achieve uniform dispersion. The pH of the hydrogel was adjusted to pH=6 using a few drops of 2 [M] sodium hydroxide (NaOH), which were added under constant stirring. Then the mixture was constantly stirred for 24 hrs to complete of the gelation. **(Sharma, S., Kumar, A., Sahni, J.K., Ali, J., & Baboota, S. (2012)).**

3.2.8 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.

3.2.9 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, then the zeta potential was graphed against the Carbopol concentration.

3.2.10 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 25°C. The viscosity shear rate values were between 0–100 rpm.

3.2.11 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 1.39 [mM], 16.77 [mM] and 136.75 [mM] 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 PBS, maintaining the temperature at37±1.0°C. Samples of the buffer solution were removed at 10, 20,30, 40, 50, 60, 90 and 120 min to determine how much of the drug was released from the nanoemulgel. 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, Istateyeh, Salhi, & Istateyeh, 2019).**

3.2.12 Antifungal Test

The antifungal activity was assessed by the agar well diffusion method using *Candida albicans*. A plate containing Muller–Hinton agar purchased from NutriSelect® Plus (Israel), 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, 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, Sadiki, & Ibnsouda, 2016).**

3.2.13 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) (purchased from JAX® Mice, Maine, US) 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). During the test, the diffusion cell was maintained at 37 ±1°C by heating in re-circulated 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).**

3.2.14 Statistical Assessment

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

Chapter 4

Results

Chapter 4

Results

4.1 Screening for the Miconazole Nitrate Wavelength

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

4.2 Calibration Curve for Miconazole Nitrate

To determine the MZN 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. Figure 4.1 shows the results of the MNZ calibration curve.

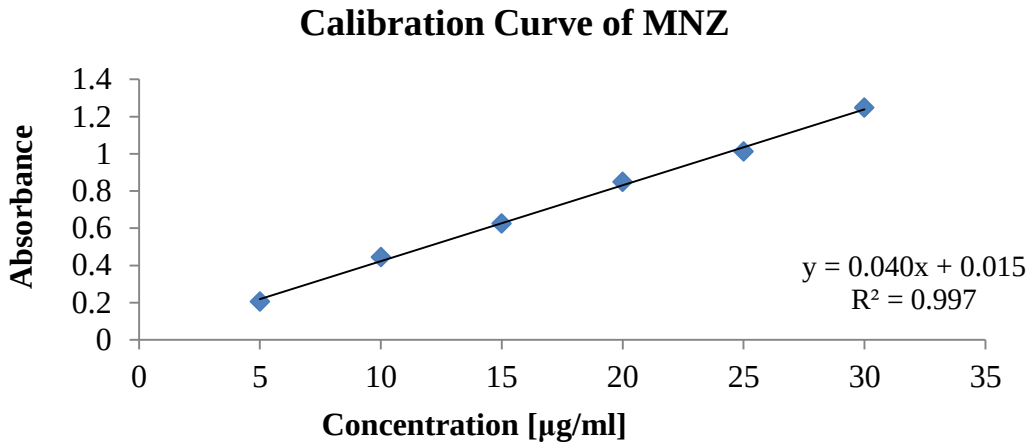


Figure 4.1: Miconazole nitrate calibration curve.

The calibration curve will be used along the research for calculating the concentrations through the getting results of the absorbance by the UV-spectrophotometer, by using the equation that connect between the absorbance and concentration y=0.040x+0.015.

4.3 Screening of Miconazole Nitrate Solubility in Several Oils and Surfactants

By dissolving MNZ in several oils and surfactants, the solubility of it was determined, then, the absorbance was measured using a UV spectrophotometer. The results apperceived are shown in the table 1 bellow.

Table 4.1: Represented the solubility results of MNZ 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

Based on the results presented in Table 1, the best solubilizing oils for MNZ were olive oil and almond oil, with concentrations of 53.375 and 53.125 mg/ml, respectively. Moreover, Tween80 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 cosurfactants, respectively. These oils and surfactants were used as the drug vehicle for the production of MNZ nanoparticles using the self-emulsifying technique.

4.4 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 Span80. The ternary phase diagrams are presented in Figure 4.2 The green area represents those compositions that produced nanoemulsion formulations with droplets smaller than 1 µm in size, while 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.

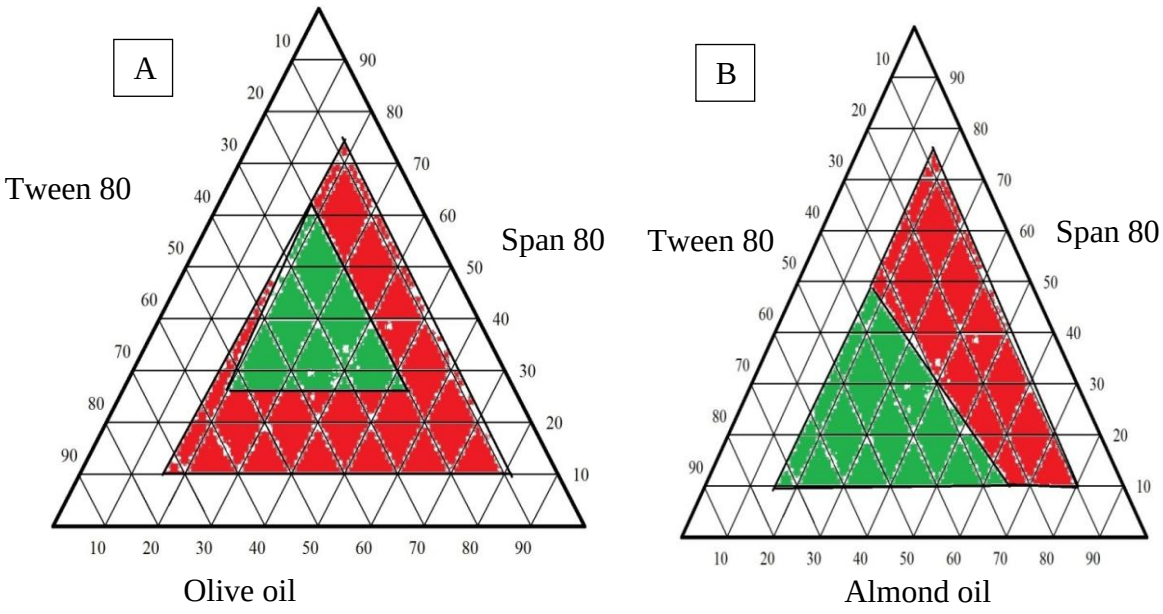


Figure 4.2: Ternary phase diagrams of (a) olive oil and (b) almond oil.

The green area represents nanoemulsion formulations and the red area represents macroemulsion formulations.

The results of the optimum nanoemulsion formulations are presented in Table 4.2.

Table 4.2: The Optimum Nanoemulsion Formulations for Both Oils.

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

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

4.5 Particle Size and Polydispersity Index of the Miconazole Nanoemulsion

The results showed no significant change after loading the MNZ in the selected nanoemulsion formulations, as shown in Table 4.3.

Table 4.3: Miconazole (MNZ) Nanoparticle Size and Polydispersity Index.

	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

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.

4.6 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 concentration of 0.4%, 0.6% or 0.8%). The results for MNZ particle size and polydispersity index are presented in Figure 4.3, while Figure 4.4 shows the zeta potential results for MNZ.

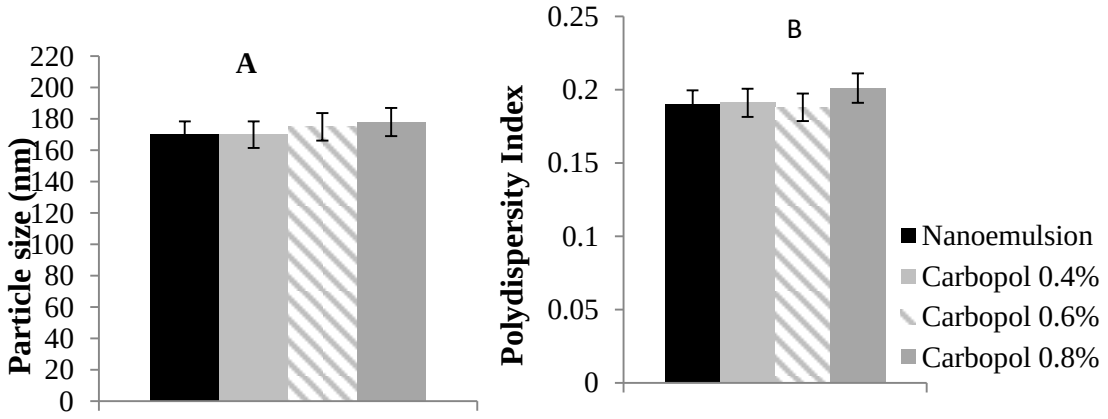


Figure 4.3: Miconazole (MNZ) (a) particle size and (b) polydispersity index.

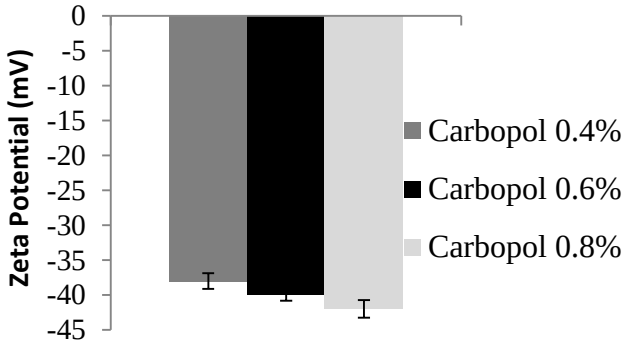


Figure 4.4: Miconazole(MNZ) zeta potential.

The drug particle size and PDI results did not significantly differ between the MNZ nanoemulsion form and when it was converted to the nanoemulgel. The results for the three different concentrations of Carbopol

were in 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 suggests that the formulations adequately prevented the agglomeration of particles, and therefore presented appropriate stability. **(Clogston & Patri, 2011).**

4.7 Rheological Properties of the Miconazole Nanoemulgel and Cream

Evaluation of the rheological properties is of great importance for semisolid forms, like that our formulated drug, as they indicate the efficacy and quality of the formulations. The results are shown in Figure 4.5.

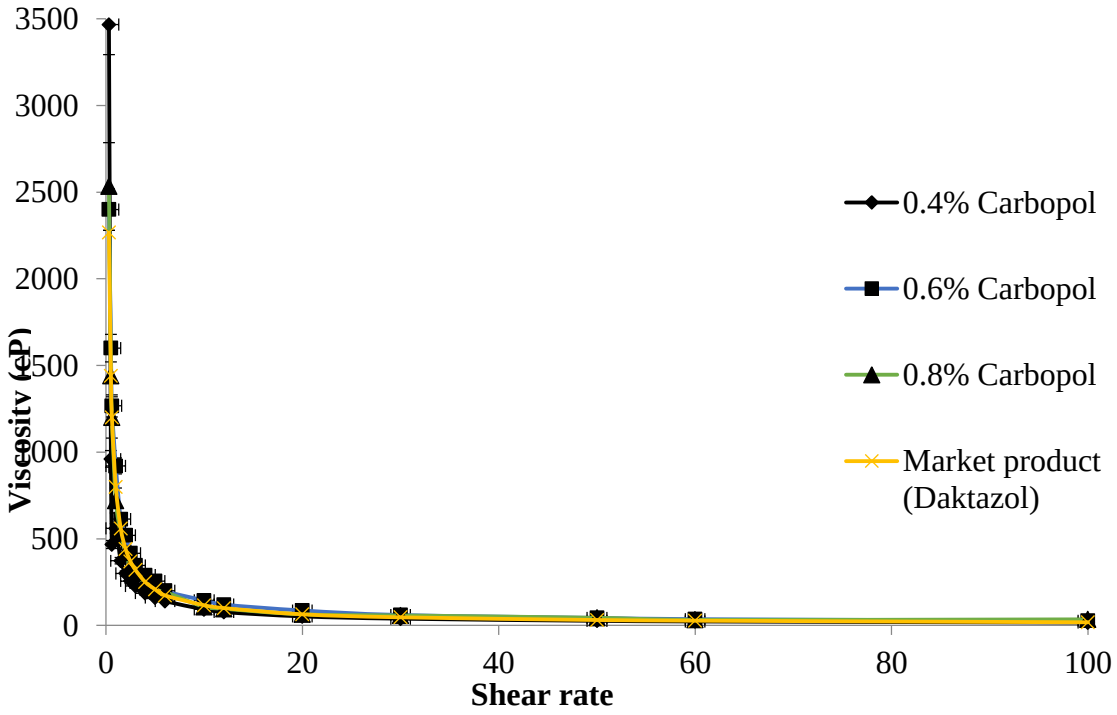


Figure 4.5: The rheological behavior of miconazole (MNZ) nanoemulgel formulations and MNZ market products.

As shown in Figure 4.5, 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.

4.8 Release of Miconazole (MNZ) From the Nanoemulgel Formulation

To study the release of MNZ from the nanoemulgel formulations, release tests were performed. This was also important 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 Figure 4.6.

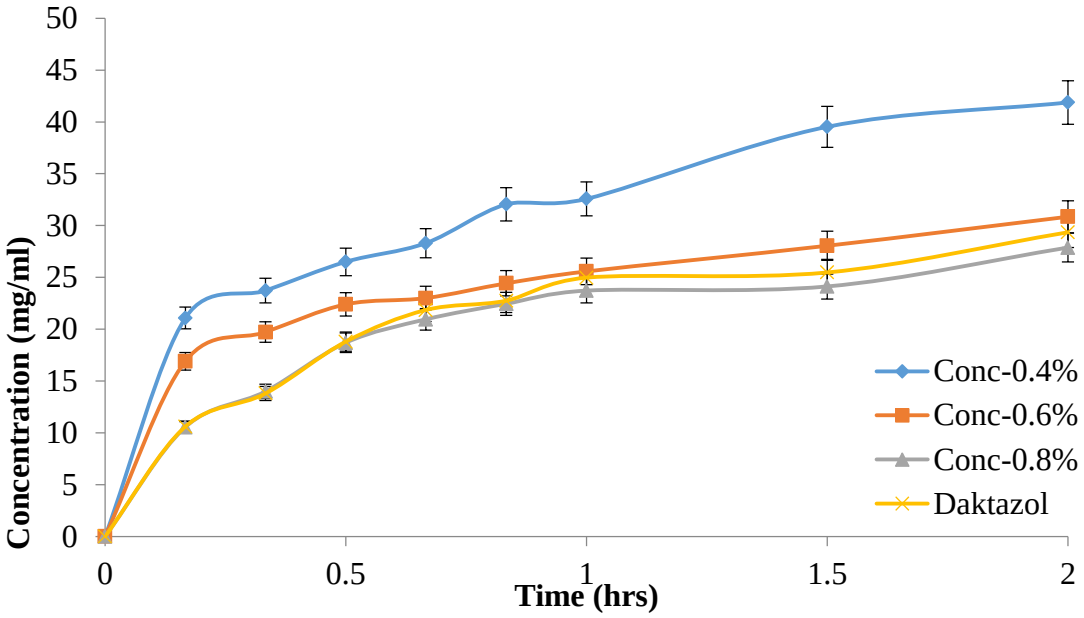


Figure 4.6: The release profile of miconazole (MNZ)from Nanoemulgels containing different Carbopol concentrations and from the market product.

The release profiles of the different formulations are presented in Figure 4.6 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.

4.9 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 presented in Figure 7 show the results of the diffusion cell test with the new MNZ nanoemulgel formulation and the market MNZ cream through the skin of a mouse.

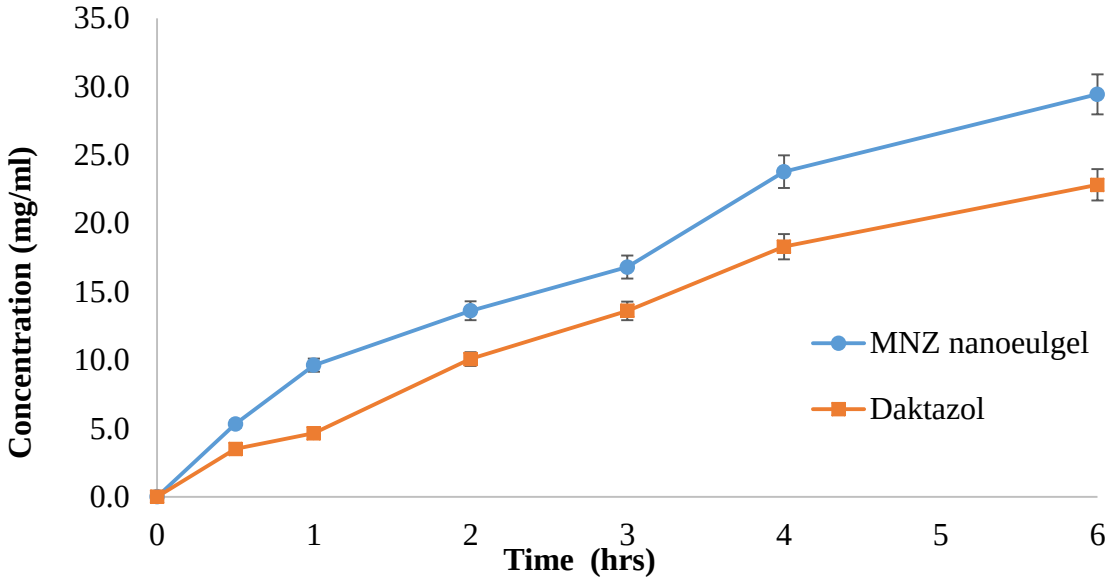


Figure 4.7: In vitro Franz difusion profile of the Miconazole (MNZ) Nanoemulgel and the MNZ market product.

A percentage cumulative drug release of 29.67% and 23.79% after 6 hours was attained for the nanoemulgel MNZ and the conventional Daktazol cream, repectively.

4.10 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. Table 4 presents the antifungal activity results, with the MNZ nanoemulgel showing the highest activity (40.9 ±2.3 mm).

Table 4.4: Antifungal Activity of the Miconazole (MNZ) Nanoemulgel, MNZ 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 ±2.4

Chapter 5

Discussion and Conclusion

Chapter 5

Discussion and Conclusion

5.1 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 the 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 an

amalgamation of a nanoemulsion containing the drug in a gel base **(Sengupta & 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, Patel, Raval, & Sheth, 2011)**.To enhance and improve the penetration and absorption of MNZ, as indicated by an increase in the amount of drug transported, we needed to identify the oil with the best solubilization of the lipophilic drug MNZ. 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 with the best solubilization potential 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 **(A. Kaur et al., 2017; G. Kaur, Bedi, & Narang, 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, Peng, Shi, & Wang, 2019).** This helps to reduce the surface tension of the water interface and oil and also reduces the droplet size, causing reduced dispersion of the self-nanoemulsifying drug delivery system (SNEDDS) (Weerapol, Limmatvapirat, Nunthanid, & Sriamornsak, 2014).Span 80was the chosen as co-surfactant as the HLB value was 4.3, indicating enhanced drug absorption and dispensability **(A. 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 the 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; while 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 SEDDS performance as it determines the extent of drug absorption and the rate of drug release **(Patel, Kevin, Patel, Raval, & Sheth, 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, Sahoo, & Sahu, 2016).** A droplet size smaller than 200 nm is an important criterion for achieving SEDDS, 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 **(A. 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, highly uniform emulsion and greater homogeneity, associated with improved physical stability **(Shinde, 2013).**

Almond oil was chosen because of its superior particles size and PDI results related to olive oil, 170±3.1 for almond oil compared to 201±4.2.

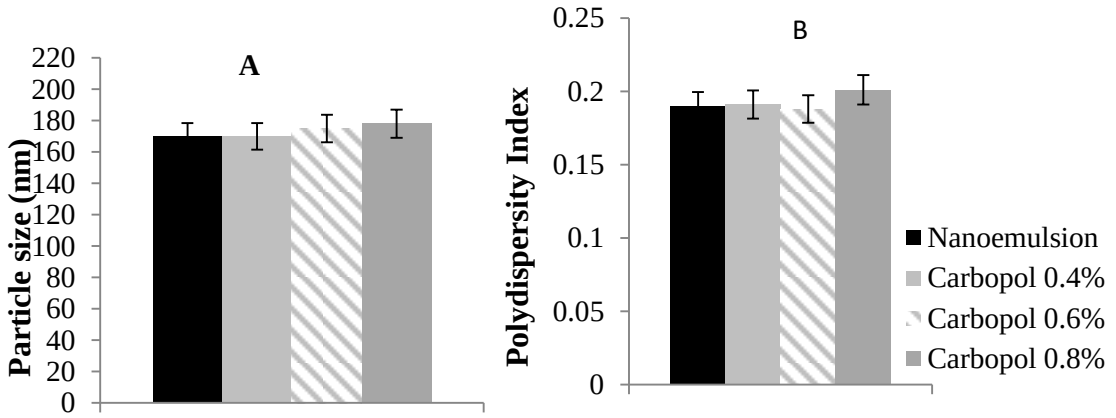


Figure 4.3: Miconazole (MNZ) (a) particle size and (b) Polydispersity index.

Measurement of the zeta potential is important because is it related to the physical stability and surface charge of the nano formulation. Ordinarily, the opportunity for aggregation is reduced as soon as the zeta potential value increases above 30 mV, either positive or negative, due to electrostatic repulsion within the particles. The nanoemulgel formulated in the current study presented an adequate negative value (-38 mV), indicating a stable nanoemulgel **(Paliwal, Kaur, & Arya, 2018).**

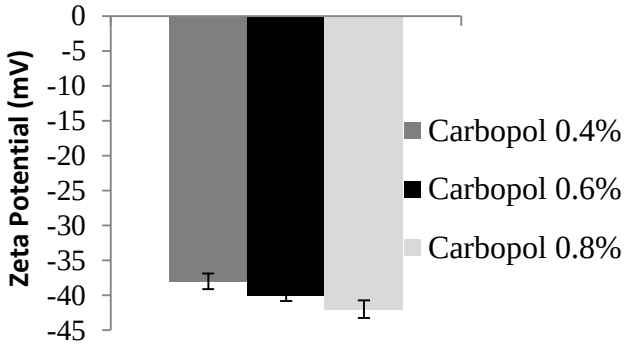
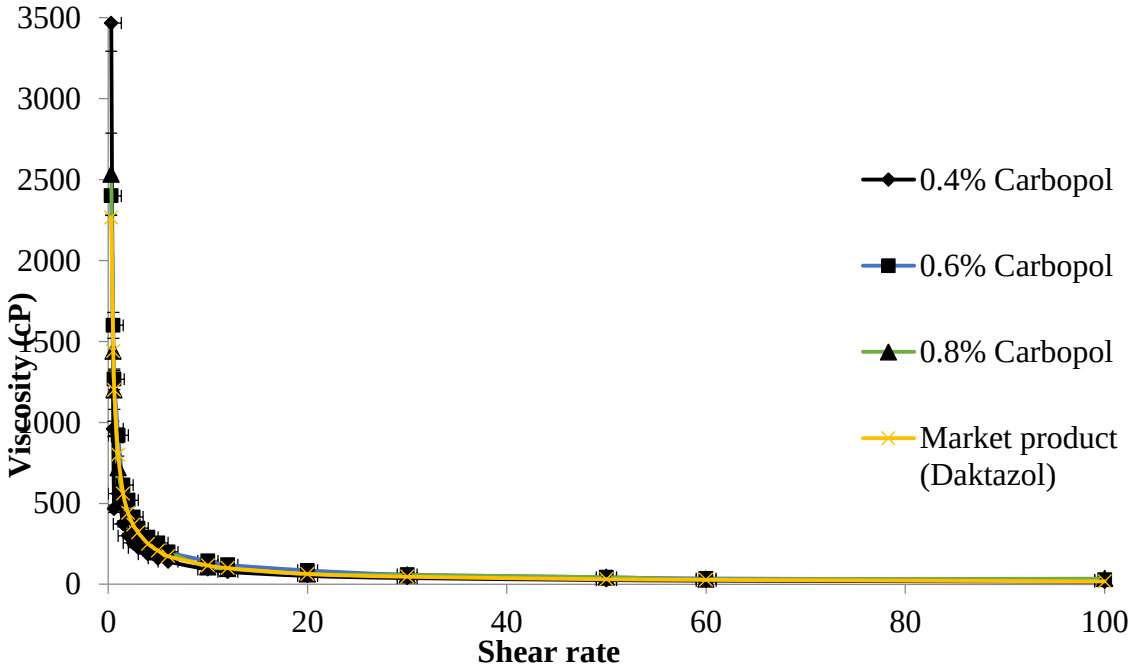


Figure 4.4: Miconazole(MNZ) zeta potential.

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 acceptability 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 based on the positive correlation observed between the Carbopol concentration and viscosity. Similar findings were previously obtained by Jadhao and his research team on the formulation of Miconazole Nitrate hydrogel **(Jadhao, Tekade, Patil, Patil, & Patil, 2017).**

The rheological behavior is presented in the next graph:



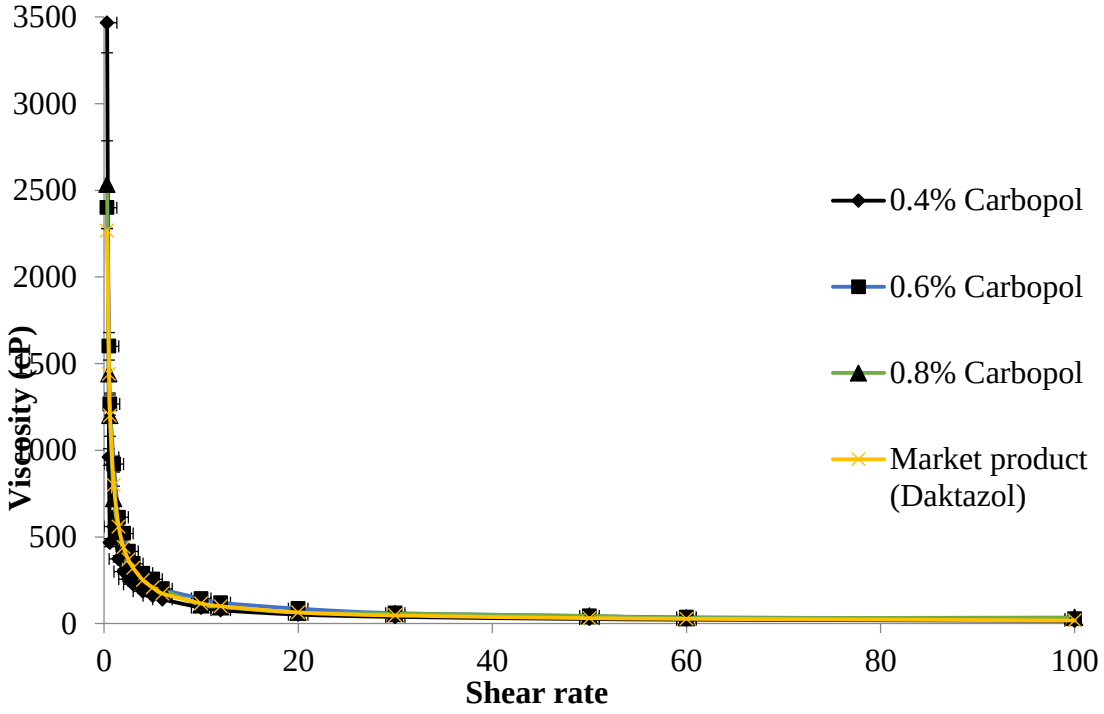


Figure 4.5: The rheological behavior of Miconazole (MNZ) Nanoemulgel formulations and MNZ market products.

Carbopol, as a rheological modifier, achieves excellent results in enhancing the physical appearance and stability of nano formulations. Similar results were reported by Eid et al. (2019), where good stability of the nanoemulgel was attributed to the presence of Carbopol as a thickening agent and the stability of the nanoemulsion **(Eid, Istateyeh, 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, Rath, Purazi, & Mudyahoto, 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 may be related to the decreased particle size, as smaller particles can easily penetrate the skin and over comethe barrier by squeezing betweenthe intracellular lipids of the startum 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).**

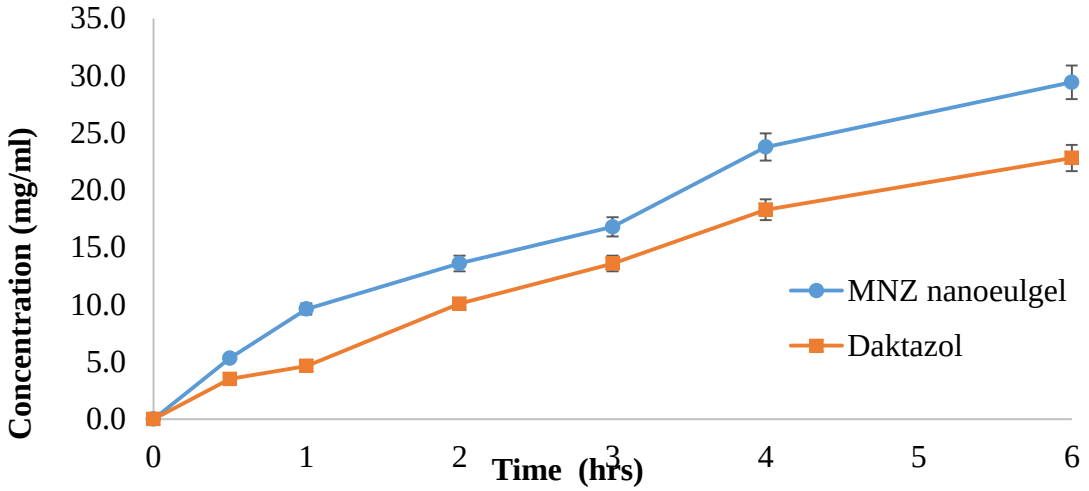


Figure 4.7: In vitro Franz difusion profile of the miconazole (MNZ) nanoemulgel and the MNZ market product.

A percentage cumulative drug release of 29.67% and 23.79% after 6 hours was attained for the nanoemulgel MNZ and the conventional Daktazol cream, repectively.

The antifungal activity against *Candida albicans*of Daktazol, the formulated nanoemulgel and almond oilwas investigated and compared. The zone of inhibition of the formulated MNZ nanoemulgel was significantly higher than that of the commercial product and almond oil.

Table 4.4: Antifungal activity of the Miconazole (MNZ) Nanoemulgel, MNZ 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 ±2.4

This improvement could be attributed to the decreased size of the particles (nanoscale), which increases the surface area and consequently increased 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 weredeveloped and evaluated **(Aljaeid & 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 18±2.4 mm zone of inhibition when testing the pure almond oil. This also supports the improvement in the zone of inhibition observed for the novel formulated nanoemulgel **(Kumar et al., 2012)**.

According to Kaur et al. (2017), the space between the cells of the skin is 70 nm. Conventional semi solid products, such as creams, penetrate the skin slower than nanoemulgels, which rapidly penetrate the skin and can deliver the active substances quicker and deeper **(A. 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. The residence time and the time of the contact of the nanoemulgel drug delivery system is prolonged, as previously reported by Sultana and his team **(Sultana et al., 2014).**

These findings support the improved antifungal activity of the MNZ formulation relative 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.

5.2 Conclusion

Based on the outcomes of the present study, we can conclude that the prepared stable MNZ nanoemulgel was superior to the Daktazole cream in all 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 formulationfor the nanoemulsion, composed of almond oil, Tween 80 and Span 80. This formulation presented the highest solubilizabiliy and improved nanoemulsion properties, including nanoscale droplet size, elevated negative zeta potential, 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 forumation will be able to overcome the skin barrier and increase the antifungal activity, leading to a shorter healing time and 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 the conventinal cream. Preparation ofMNZ nitrate in sucha dosage form enhanced MNZ solubility, skin penetration, drug loading and bioavailability. It also facilitated MNZ application, associated with improved patientcompliance, together with an increase intheefficacy of the drug and a decrease in side effects.

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جامعة النجاح الوطنية

كلية الدراسات العليا

تحضير ميكونازول نيترات ايملجل بتقنية النانو للاستخدام الموضعي

إعداد

دلال يوسف تايه

إشراف

الدكتور أحمد مصطفى عيد

قدمت هذه الأطروحة استكمالا لمتطلبات الحصول على درجة الماجستير في علوم صيدلانية من كلية الدراسات العليا في جامعة النجاح الوطنية في نابلس- فلسطين.

2021

تحضير ميكونازول نيترات ايملجل بتقنية النانو للاستخدام الموضعي

إعداد

دلال يوسف تايه

إشراف

الدكتور أحمد مصطفى عيد

الملخص

الميكونازول مشتق اصطناعي من الإيميدازول، وهو دواء مضاد للفطريات واسع الفعالية يستخدم في العلاج الموضعي لالتهابات المهبل والجلد والأظافر. لديه قابلية ضعيفة للذوبان بالماء، لذلك تم الإبلاغ عن انخفاضات كبيرة في فعاليته العلاجية.

هدف الدراسة هو تطوير تقنية مبتكرة لتحسين نفاذية وفعالية الميكونازول نترات الموضعية. ولهذا، قمنا بتصنيع نانومولجل لمادة الميكونازول نترات وذلك بدمج مستحلب مُصنع بتقنية النانو وهيدروجيل.

تم تحسين المستحلب المُصنع بتقنية النانو أولاً باستخدام تقنية الاستحلاب الذاتي ، ثم تم وضع الدواء في الصيغة المثلى التي وجدناها بعد الفحص وتقييمه قبل الخلط مع الهيدروجيل. تم تقييم تركيبات النانو امولجل للميكونازول نتراتت، وذلك بفحص خصائصها الفيزيائية ونشاطها المضاد للفطريات. بناءً على النتائج ، أظهرت التركيبة التي تحتوي على 0.4٪ كاربوبول أعلى نسبة إطلاق للمادة من التركيبة المُصنّعة، وبالتالي، تم اختيارها على أنها الصيغة المثلى.

تم إجراء اختبار *Cell diffusion* لفحص قدرة ميكونازول نترات نانومولجل على اختراق الجلد والوصول إلى مجرى الدم. النتائج التي توصلنا اليها لإطلاق الدواء التراكمي كانت بنسبة 29.67٪ للنانو امولجل الذي قمنا نحن بتصنيعه و 23.79٪ للمرهم التجاري (دكتازول) بعد 6 ساعات.

كذلك، تم اختبار النشاط المضاد للفطريات للتركيبة الجديدة المُصنعة (الميكونازول نانو امولجل) ضد فطريات "الكانديدا البيكانز" ومقارنتها بكريم الدكتازول (التجاري) وزيت اللوز. كانت النتائج: 40.9 [مم] ± 2.3 ، 25.4 [مم] ± 2.7 و 18 [مم] على التوالي.

في الختام ، تم تطوير مرهم جديد ميكونازول نترات بتقنية النانو امولجل والذي مقارنةً بالمنتج التجاري، أظهر نشاطًا مضادًا للفطريات أعلى.