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Formulation and characterization of Miconazole Nanoemulgel for Topical Delivery by Using Natural Oils

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Abstract

The prevalence of pharmaceutical formulations referred to as nanoemulgels (NEG) is increasing due to their inherent capacity to operate as both a nanoemulsion and a gel. These products are widely recognised for their ability to distribute easily, deliver controlled release, offer ease of application, and effectively moisturise dry skin. Numerous studies have provided evidence to support the notion that the use of natural essential oils can enhance the permeability of topical formulations on the skin, hence augmenting the safety and efficacy of medication delivery. In this study, we employed the gelling agents carbopol 943 and hydroxypropyl methylcellulose (HPMC) to create nanoemulsion gels (NEG) with the aim of enhancing the permeation of micronazole for the treatment of candidiasis. Two variations of NEG were prepared, namely Soybean oil-based nanoemulsion gel (Soybean-oil-NEG) and Sunflower oil-based nanoemulsion gel (Sunflower-oil-NEG). In order to enhance the solubility of micronazole and facilitate the formation of a nanoemulsion (NE), a series of excipients were investigated in our experimental study. The size, shape, entrapment efficacy, and drug release of NE droplet particles were assessed in our study. Furthermore, the physicochemical features of the improved nanoemulsion formulation were characterised using techniques such as Fourier transform infrared (FT-IR) spectroscopy and X-ray diffraction (XRD) analysis. In order to generate negative ions (NEGs), the neutral entities (NEs) were introduced into gel matrices. The properties of NEGs encompassed drug

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content, homogeneity, rheology, spreadability, and antifungal activity against Candida albicans, demonstrated by both in vitro and in vivo studies. The optimised micronazole non-ionic emulsion gel (NEG) formulations included either 15% Soybean oil or 20% Sunflower oil. The polydispersity indices and droplet diameters of the optimised nanoemulsions (NEs) were determined to be 0.24 and 0.26, respectively. The quantities of micronazole that were released from the Sunflower-oil and Soybean-oil nanoemulsion gels (NEGs) after a duration of 24 hours were found to be 91% and 4.5%, and 89% and 7%, respectively. Scanning electron microscopy (SEM) was employed to elucidate the internal structural structure and consistent, uniform shape of the NEGs. Both Soybean oil and Sunflower oil exhibited drug concentrations of 98.5 ± 2.2% and 98.8 ± 3.4%, respectively. The penetration values of micronazole were found to be 117 ± 7 g cm^2 when using Soybean oil and 108.34 ± 6 g cm^2 when using Sunflower oil. Furthermore, when compared to a commercial formulation, the micronazole NEG formulations exhibited higher levels of inhibition in fungal growth. Finally, it should be noted that in vivo studies have demonstrated that NEGs do not induce skin irritation. The combination of micronazole with either 15% Soybean oil or 20% Sunflower oil exhibits enhanced dispersion, drug dissolution, and permeability properties. This stability and increased efficacy compared to micronazole alone make it a viable option for the effective and safe treatment of candidiasis.

Keywords: nanoemulgels, topical delivery, miconazole, natural oils

Introduction

Tinnitus is a widely seen disease that affects persons globally, mostly associated with the pathogenic fungus referred to as trichophyton rubrum. The subject matter under consideration pertains to a particular kind of fungal infection that selectively affects keratinized tissue, distinguished by its filamentous form. The current agreement recognizes that this subject is a public health concern with substantial consequences for individuals' holistic well-being and quality of life. The reoccurrence of the illness is frequently seen as a result of the emergence of resistance to traditional treatment modalities.The user's text has a scholarly tone and style. Minor skin or subcutaneous infections possess the potential to spread and, in rare cases, lead to mortality. Dermatophytosis, often known as dermatophyte infection, is a frequent fungal illness that mostly affects the skin, hair, and nails. According to epidemiological research, it has been demonstrated that dermatophytosis, a fungal infection, is predicted to impact around 25% of the worldwide population, leading to an annual occurrence of severe cases ranging from one million to one billion.The user's text lacks sufficient depth and detail to undergo a complete academic editing.[1] The management of dermatophytosis presents difficulties as a result of the restricted accessibility of efficacious antifungal agents targeting dermatophytes, as well as the evolution of drug resistance to these pharmaceuticals. The phenomenon of antifungal medicine resistance has been documented in several countries around the globe, including the United States, Europe, Asia, and Australia. This resistance has been detected at various levels, spanning both interregional and intraregional dimensions. This finding highlights the variability in the effectiveness of antifungal treatments in diverse geographic areas. [2] The emergence of resistance may be ascribed to many mechanisms, encompassing the upregulation of genes linked to multidrug resistance, the increased

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functionality of efflux pumps, and modifications in the composition and configuration of enzymes. Moreover, the high occurrence of resistance observed in Candida glabrata isolates poses a substantial concern linked to the use of azole antifungal drugs. [3]

The major medical approach for managing localised, simple dermatophyte infections, also known as dermatophytosis, is the use of topical antifungal therapy. In instances of more pronounced infections, it is frequently advised to provide systemic treatment. The persistent and recurrent nature of dermatophyte infections increases the likelihood of toxicity and the emergence of treatment resistance, notwithstanding their rare occurrence of causing death. Thus far, the documentation of azole resistance has been restricted to a small number of instances. [4] The user's text lacks the necessary expansion to meet the academic standards and requires further elaboration for appropriate academic adaptation. A significant issue related to the therapeutic use of azole antifungals is the widespread understanding of systemic and ocular toxicity. The user has supplied a numerical input of 6. In addition to the conventional, transient side effects, individuals utilising micronazole have also reported the manifestation of serious adverse events such as anaphylaxis, hepatotoxicity, endocrine dysregulation, and lengthening of the QTc interval. In the United States, the use of micronazole is restricted due to prevailing conditions. Its application is specifically designated for instances where alternative antifungal therapies have shown to be unsuccessful or are considered inappropriate. As a result, its occurrence is rare in several nations. Micronazole is a commercially accessible antifungal agent utilised for the therapeutic treatment of cutaneous fungal infections. It is marketed in several forms, such as shampoo, solution, and lotion. [5] Numerous studies have shown evidence that the utilisation of oils obtained from diverse sources broadens the range of antifungal activity and augments the effectiveness of antifungal medications, such as micronazole, against fungal species that have acquired resistance. Numerous botanical species are frequently employed for the purpose of oil extraction, such as Schinus lentiscifolius Marchand, Otacanthus azureus (Linden) Ronse, Carum copticum, Thymus vulgaris, Hirtellina lobelii DC, Cryptocarya aschersoniana, Schinus terebinthifolia, Cinnamomum amoenum, and Hirtellina lobelii DC. The book makes mention of several plant species, such as Allium sativum, Melaleuca alternifolia, Agastache rugosa, Ligusticum chuanxiong, Pancalieri, and M. alternifolia. There has been a suggestion regarding the possible effectiveness of essential oils when used alongside antifungal medicines. This combination aims to improve permeability, mitigate the harmful effects of free radicals, and boost the anti-inflammatory qualities of the treatments. [5] Topical medications, including lotions and ointments, are associated with various limitations. These factors encompass a lower spreading coefficient, reduced capacity to penetrate the stratum corneum, and diminished patient adherence resulting from stickiness or the necessity of rubbing the treatment. One of the difficulties inherent in the use of gels is to their inefficiency in facilitating the delivery of hydrophobic pharmaceutical compounds. The possible enhancement of a topical formulation's efficacy can be achieved by the usage of an emulgel, which consists of a blend of emulsifiers and certain oils. The proposed formulation has the potential to address the challenge of pharmaceutical solubility by enhancing the permeation of treatments over the stratum corneum. In the current context, administering a lower dosage of the medication may result in a heightened pharmacological reaction. Emulgels, which possess characteristics of both gels and emulsions, are frequently suggested for the transdermal delivery of hydrophobic medicinal substances.

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These formulations possess several benefits, including their ease of diffusion, application, and removal, a prolonged time of viability, and a diminished impression of oiliness. In comparison to creams, emulgel formulations offer a more consistent and progressive release of the active therapeutic constituents. The composition of a multi-stage emulgel may display significant changes among its constituent components. The oil droplets being examined have a significant level of concentration as a result of their dense arrangement, occupying approximately 74% of the internal phase's volume. Emulsions possess intrinsic qualities that contribute to their semi-solid texture, hence simplifying their application onto the skin. Microgels play a pivotal role in several activities, including the storage of bioactive compounds, regulation of active molecule release, serving as templates for other particles, and filling hydrogel beads. The addition of a gelling agent to the emulsion leads to the transformation of its structure into a gel matrix, hence improving the emulsion's mucoadhesive qualities. [6] As a result, this gives rise to a prolonged period of the medication's contact with the skin. The potential for improved effectiveness of micronazole formulations lies in the enhancement of cutaneous permeability and enhanced skin moisture. In addition, the drug is applied to the skin for a prolonged period of time, hence promoting improved patient compliance. Both Soybean oil and Sunflower oil have demonstrated the potential to improve permeability. These oils have been seen to participate in interactions with proteins inside cellular structures, modify the lipid content of the outermost layer of the skin (known as the stratum corneum), and eventually promote improved absorption. As a result, the combination has a synergistic effect, hence enhancing the antifungal capabilities of micronazole. To boost the transdermal penetration and therapeutic efficacy of micronazole, a nanoemulsion gel (NEG) was developed by including Sunflower oil and Soybean oil as enhancers. The droplet size, surface charge, and drug release percentage of the nanoemulsion were assessed by the use of transmission electron microscopy. A comprehensive investigation was performed on the organoleptic features of micronazole nanoemulsion gels (NEGs) to ascertain their physicochemical qualities, homogeneity, viscosity, pH, spreadability, drug content, and ex vivo permeation. The present work aimed to investigate the skin irritancy potential of Micronazole NEGs by in vivo testing, while also evaluating their antifungal activity against Candida albicans. The improved efficacy in the therapy of fungal infections has been attributed to the pharmacological features of micronazole nanoemulsion gels (NEGs). [7]

RESULTS

Identification of Drug, Calibration Plot, Melting Point, and Solubility Study:

To identify the most suitable solvent for micronazole, we determined its solubility in a number of different solvents. We found decreasing solubility in the following order: Soybean oil > Sunflower oil > Tween 20 > PEG 200 > span 80 > transcutol > labrasol > Cotton seed oil > olive oil > castor oil > paraffin oil > water. A calibration curve obtained with ethanol had linearity in the range of 0−25 μg mL−1. A regression of this calibration curve yielded a regression coefficient of r 2 = 0.997, slope of 0.0273, and intercept of 0.0166 (Figure 1). [8]Based on these solubility profiles of the drug in different solvents, Sunflower oil and Soybean oil were selected for further use in NE formation due to having the highest solubility (Figure 2). Drug solubilities in Tween 20 (66 ± 4.5 mg mL−1) and span 80 (56 ± 5 mg mL−1) were used as a surfactant and a cosurfactant in the NE formulation. Micronazole was

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identified on the basis of its appearance, and it appeared as a white, odorless powder, and the melting point was recorded at 146 °C using a melting point apparatus.[9]

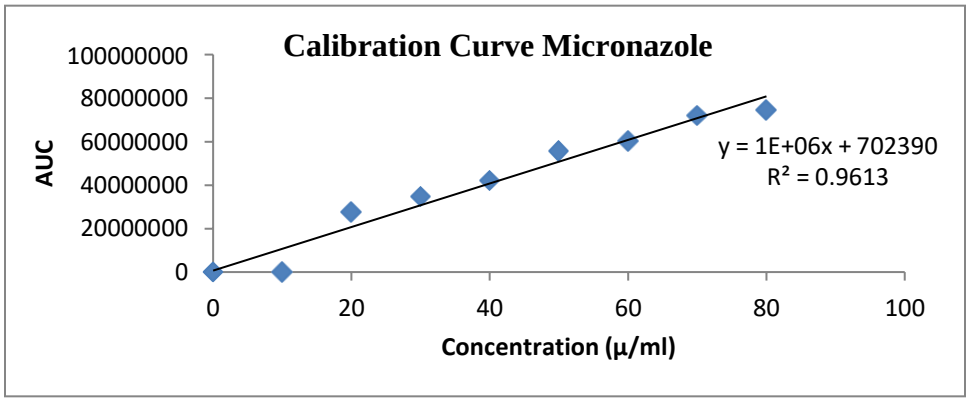

Figure 1. Calibration plot of micronazole in phosphate-buffered saline (PBS).

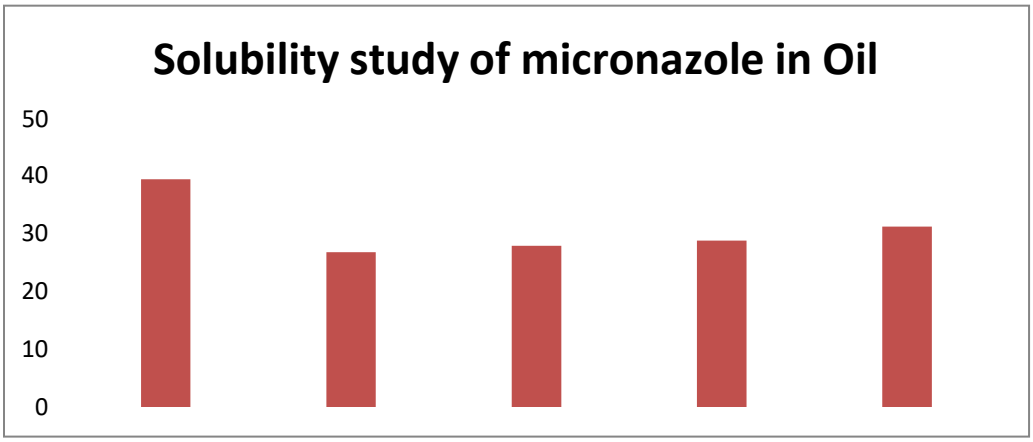

Figure 2. Solubility of micronazole in different solvents. Data are expressed as mean ± standard deviation (SD) (n = 3)

Pseudoternary Phase Diagram.

A pseudoternary phase diagram was constructed for the %oil, %Smix, and %water components. The most stable NE region was found for an Smix ratio of 3:1 (Figure 3A,B). At other ratios of Smix, unstable NE was produced due to opacity, turbidity, or phase separation during freeze−thaw cycles, centrifugation, and dilution test or storage. For an Smix ratio of 3:1, with a high surfactant concentration, improved thermodynamic stability of the NE occurs, probably due to a lowering of the interfacial tension, resulting in small globules possessing surface charge. [10] The optimized formulation comprised 20% Soybean oil, with an Smix ratio of 3:1 (45%) and 35% water. A second preparation of NE comprised 15% Sunflower oil, with an Smix ratio of 3:1 (35%) and 50% water [11](Table 1).

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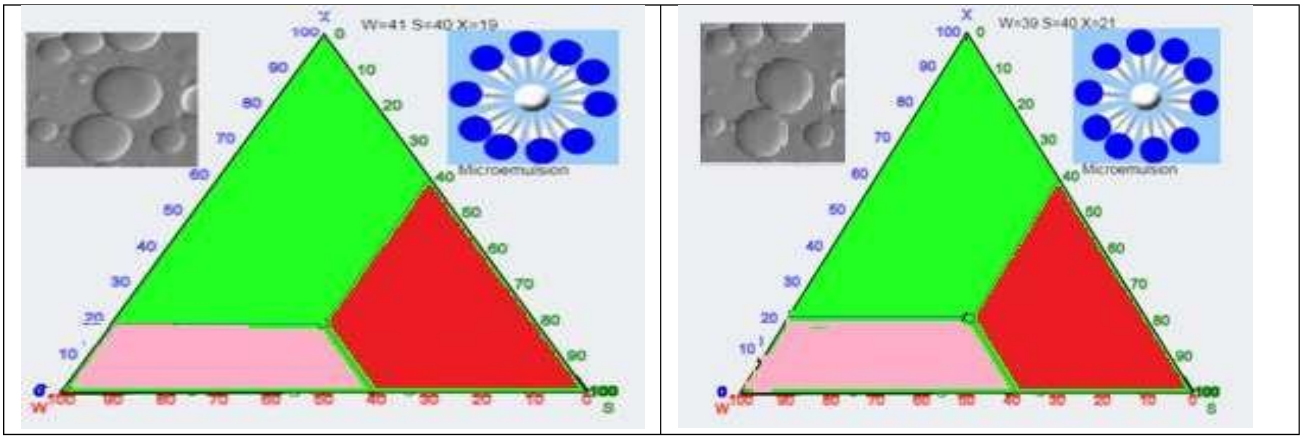

Figure 3: Pseudoternary phase diagram showing apices of the triangle of % Soybean oil, % Smix (3:1), and % water (A); and % Sunflower oil, % Smix (3:1), and % water (B). Black dot point indicates the NE region.

S.No	Formulations	Amphiphilic Region %	Smix %	Aqueous Region %
1	Soybean oil	**25**	**45**	**30**
2	Sunflower oil	**20**	**35**	**45**

Table 1: Optimized NE Formulation Composition

Determination of Globule Size:

The average sizes of the lipid droplets in the optimised formulations of nanoemulsions (NEs) containing 20% Soybean oil and 15% Sunflower oil were measured to be 67 ± 3.4 nm and 78 ± 5.2 nm, respectively, as seen in Figure 4A and Figure 4B. The polydispersity indices (PDI) of the NEs were 0.24 and 0.26, respectively. As per the International Union of Pure and Applied Chemistry (IUPAC), the term "polydispersity" pertains to the degree of heterogeneity in the distribution of particle sizes within a given sample. The PDI value often falls between the range of 0.01 to 0.7. On the other hand, a Polydispersity Index (PDI) score of 0.05 is often considered to indicate a high level of monodispersity. A PDI value over 0.7 indicates a higher degree of particle dispersion, which may render it unsuitable for size analysis with the Malvern Zetasizer. Insights into the stability of the nanoelectrospray (NE) were obtained by the measurement of the droplet surface charge, quantified as the potential. The voltage readings obtained were 19 mV when using a 20% concentration of Soybean oil and 22 mV when using a 15% concentration of Sunflower oil. [12] Transmission electron microscopy (TEM) was employed to conduct a detailed examination of the size of the NE globules (Figure 5A,B). The globules exhibited a spherical shape, uniformity, homogeneity, and a state of dispersion. The dimensions of the globules observed by transmission electron microscopy (TEM) were found to be similar to those observed using the Malvern Zetasizer.

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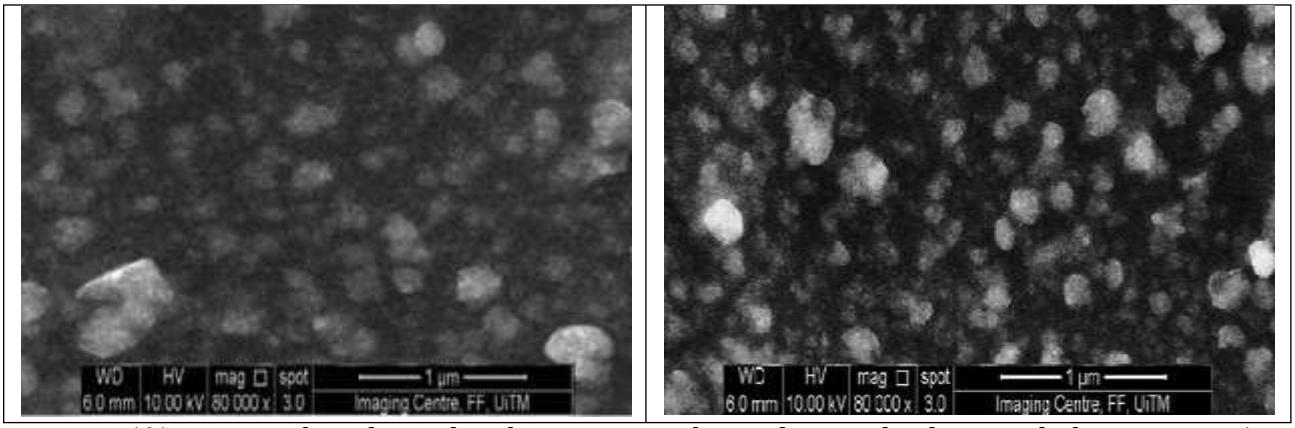

Figure 4: (A) Intensity-based size distribution curve obtained using the dynamic light scattering (DLS) technique of 20% Soybean-oil−NE. (B) Intensitybased size distribution curve of the nanoemulsion containing 15% Sunflower-oil−NE.

Drug Gel Content: Micronazole was analyzed at 225 nm using a UV−visible pectrophotometer, and the drug content was obtained as a percentage. Spectrophotometric analysis was performed for a standard curve of the drug. The curve was plotted between the concentration (µg mL−1) and absorbance. The total drug content of micronazole in the formulations was estimated from a reference standard curve ($y = 0.0273x + 0.0166$, $r^2 = 0.997$) (Figure 1). The drug contents in the optimized NEG formulations containing 20% Soybean oil and 15% Sunflower oil were 98.5± 2.2 and 98.8± 3.4%, respectively. [13]

Determination of Viscosity: The viscosity results of blank and drug-loaded preparations are listed in Table 6. All formulations (including blank and drug loaded) appeared to be less viscous, which is a characteristic hallmark of NE demonstrating Newtonian type flow pattern.32 According to Tukey -HSD tests, the viscosity results of all NE formulations (blank NE, DIF-loaded and DIF-IC-loaded NE formulations) were divided into four distinct subsets. Drug-loaded NEs expressed higher viscosity than the blank NE formulae. The pH values for all nanoemulgel formulations ranged from 5.63–6.42 (Table 7). The pH, viscosity and conductivity values of all nanoemulgel formulations generated statistically significant results ($p < 0.05$). [14]

Homogeneity and Spreadability: The NEG homogeneity was inspected visually by placing it in a settled position in a container. It was of uniform consistency and homogeneous, with no aggregates.17 The spreadability values of 20% Soybean-oil−NEG and 15% Sunflower-oil−NEG were between 4.12 ± 0.23 and 4.32 ± 0.17 cm. [15]

X-ray Diffraction (XRD): Micronazole had a strong peak at 2 angles of 17.5, 19.8, 23.2, and 27.1°, demonstrating the substance's crystallinity.33 Both formulations had much less crystallinity, indicating that the medication had changed into an amorphous state that was highly soluble and capable of being dissolved and absorbed into the systemic circulation. [16]

Scanning Electron Microscopy (SEM): The surface topography of the NEGs was assessed using an EVO LS 10 transmission electron microscope (TEM) manufactured by Carl Zeiss in Brighton, Germany.

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The nanoemulgels formulated with Soybean oil and Sunflower oil exhibited consistent, dense, and homogeneous structures without any discernible pores. [17]

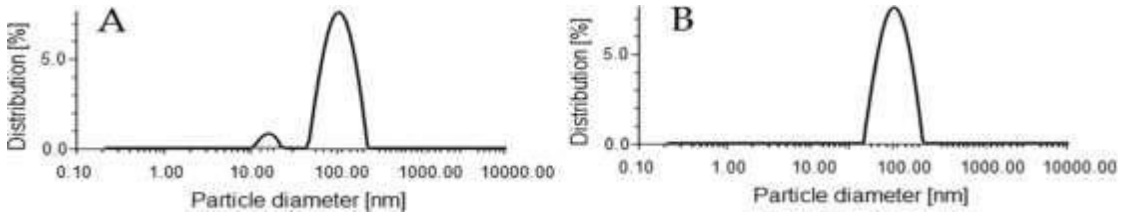

Figure 5. TEM size analysis of NE droplets. (A) TEM of 20% Soybean-oil−NE; and (B) TEM of 15% Sunflower-oil−NE.

Fourier Transform Infrared (FT-IR) Analysis: Fourier Transform Infrared (FT-IR) spectra of micronazole and NEGs loaded with micronazole. The drug exhibits an infrared (IR) absorption peak at 1646.12 cm-1, which can be attributed to the vibrational characteristics of a carbonyl group (stretch CO). Another IR absorption peak is observed at 1505 cm-1, which corresponds to the stretching vibration of an aliphatic ether group (C-O). Additionally, a peak at 1245.12 cm-1 is observed, indicating the stretching vibration of a cyclic ether group (C-O). Another notable peak is observed at 1200 cm-1, which can be attributed to the presence of a tertiary amine. Lastly, an IR absorption peak is observed at 810 cm-1, indicating the stretching vibration of the C-Cl bond. Sunflower. [18]

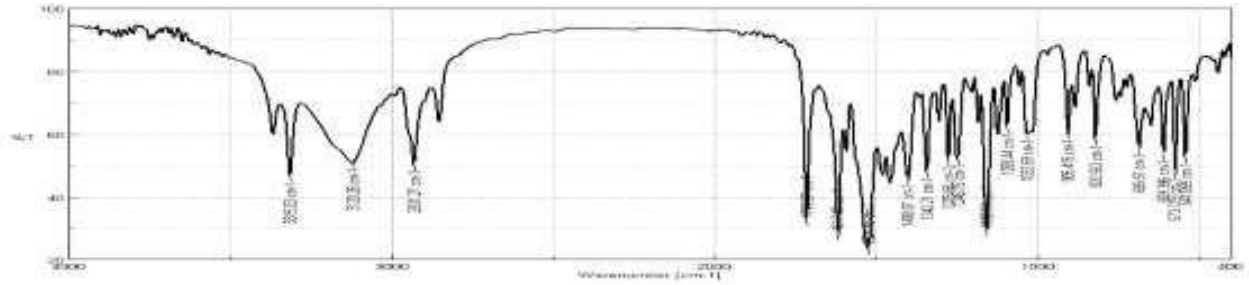

Figure 8. (A) FT-IR spectra of micronazole

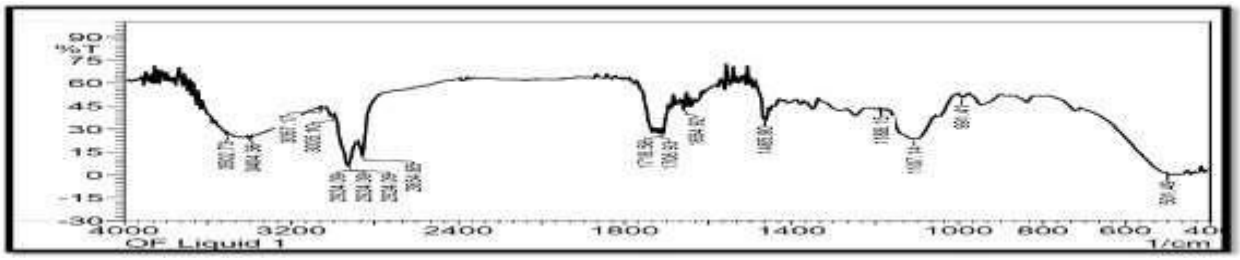

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Figure 8. (B) FT-IR spectra Soybean oil -containing

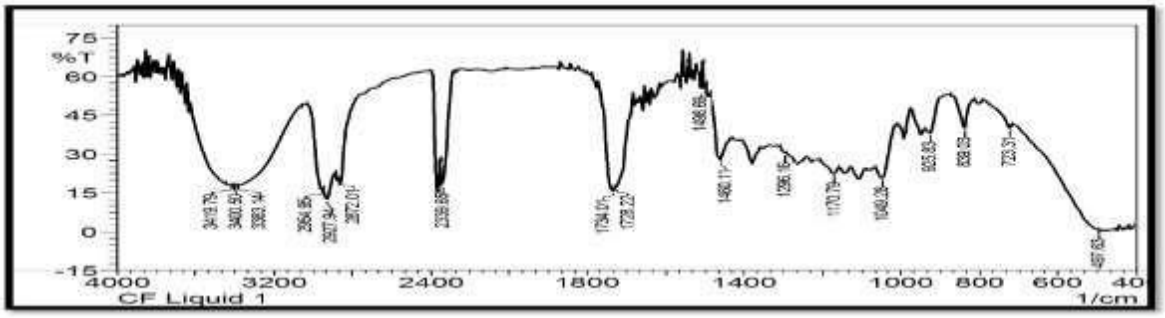

Figure 8. (C) FT-IR spectra Sunflower oil -containing NEG.

Drug Release and Kinetic Profile: Percentage drug release from the nanoemulsion was compared to a pure drug. The percentage cumulative micronazole release from retention of micronazole may be ascribed to the poor permeation and solubility of keto-gel. No significant differences were observed between the two formulations when comparing drug retention in the different skin layers ($p > 0.05$). [19]

Formulation Code	**Zero-order kinetic**		**First Order Kinetics**		**Higuchi Model**		**Korsmeyer-Peppas Model**			**Hixson Crowel Model**	
	R2	**K_0(h^{-1})**	**R2**	**K_1(h^{-1})**	**R2**	**K_H(h-1/2)**	**R2**	**N**	**K_K**	**R2**	**K_{HC}(h-1/3)**
Soybean oil	0.988	0.200	0.827	-0.004	0.952	4.786	0.919	0.368	10.186	0.927	0.008
Sunflower oil	0.998	0.195	0.859	-0.003	0.971	4.690	0.956	0.405	8.394	0.953	0.007

Table 3. Kinetic Model Fitting of micronazole Release from Soybean oil and Sunflower oil-Containing NE

In Vivo Skin Irritation: The use of a topical gel has the potential to induce irritation in both the epidermal and dermal layers of the skin. The binding of surfactants and polymers to skin tissue and proteins, such as keratin, can lead to the occurrence of acute irritation or poisoning. Consequently, an investigation was conducted to assess the possible adverse or toxic effects of our formulations on the skin of representative animal models. The animals were regularly monitored for dermal irritation, namely erythema (redness) or edoema (swelling). [20]

Histology of Treated Skin: Skin micrographs of the 20% Soybean-oil−NEG-treated group, the 0.7% formalin-treated group, and the 15% Sunflower-oil−NEG-treated group are shown in Figure 12A−C. Histology of formulation-treated animal skin shows the normal layer of epidermis, the subcutaneous

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layer, the dermis, and blood vessels. Therefore, the developed formulation was deemed to be safe for topical application due to its excellent tolerance to the skin. On the other hand, formalin-treated skin showed irritation produced on the epidermal and dermal layers with an irritation score of 2.5 (moderate erythema). [21]

In Vitro Antifungal Activity: When the antifungal zones of inhibition were examined, it became clear that the formulations that had been developed were more effective in inhibiting fungal growth. Both the Soybean oil and the Sunflower oil had zones of inhibition that were similar in size, measuring 52.9 7 and 48.75 5.8 mm, respectively. The designed product's decreased zone of inhibition, which was 34.9 4 mm in size. Due to the presence of Soybean and Sunflower oil in the placebo formulation, a zone of inhibition of 10 mm x 4 mm was seen. [22]

DISCUSSION

The issue of irregular drug solubility, leading to variable absorption and unclear pharmacokinetics, poses challenges for lipophilic therapeutic candidates. Various strategies have been documented in the scientific literature to improve the solubility of lipophilic medications. These approaches encompass solid dispersion, drug delivery through nanocarriers, complexation, and physicochemical modification. Oral administration of drugs carries the potential for unpredictability and limited bioavailability due to many clinical factors, including significant first-pass metabolism, enzymatic degradation, and systemic toxicity. [23] By employing a topical administration method as a viable alternative to oral delivery, the aforementioned concerns can be mitigated. One of the main challenges that a topical treatment may face is to its ability to traverse a protective, stratified skin barrier, therefore impeding its penetration into the dermis and other interconnected components of the skin. [24] The achievement of cutaneous disruption required for drug release and permeation via the topical administration route can be facilitated by the use of various techniques such as penetration enhancers, ultrasonic mediation, microneedles, and other related methodologies. A nanoemulsion, which is a type of colloidal preparation, consists of a heterogeneous mixture of oil and water. In this mixture, either the oil or water might act as the dispersion medium or the dispersed phase. In this particular formulation, the use of an emulsifier is employed to effectively diminish surface tension and provide stability within the solution. When comparing this system to a suspension or an emulsion, it exhibits greater durability and thermodynamic stability. Nevertheless, the practicality of using nanoemulsions in topical applications was limited due to their reduced viscosity and inadequate spreadability. [25-53] However, this challenge may be addressed by transforming the nanoemulsion into a suitable gelling agent, commonly referred to as nanoemulgel. The use of nanoemulgel has been shown to improve the retention and skin penetration of medicine, while also providing protection against enzymatic degradation and hydrolysis. Nonetheless, it also has notable advantages such as enhanced drug loading capacity, increased drug diffusion properties, biocompatibility, and decreased irritation. The present investigation elucidated the utilisation of Hydroxypropyl methylcellulose (HPMC), a gelling agent derived from carbopol 943, in conjunction with nanoemulsion gels (NEGs) containing micronazole. The NEGs were formulated using Soybean oil (Soybean-oilNEG) and Sunflower oil (Sunflower oil NEG) as the foundation. In order to develop a robust, reliable, and effective pharmaceutical formulation, an extensive preformulation investigation

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was conducted on the active pharmaceutical ingredients (APIs) and their physical-chemical properties. To provide optimal conditions for therapeutically beneficial delivery systems, it is essential to determine the physicochemical properties of the medicine prior to its incorporation into the formulation. This phase entails the characterization of the physical, chemical, and mechanical properties of a pharmaceutical compound, both independently and in combination with excipients. These research provide crucial principles for the development of stable, dependable, and secure pharmaceutical formulations. The solubility of an active pharmaceutical ingredient (API) is a critical determinant in the accurate prediction of its bioavailability, dissolving characteristics, and ultimately, the efficacy of the therapeutic treatment. The process of drug development poses challenges due to the presence of poorly soluble medicines, which hinder the processes of absorption and breakdown. [26] The primary aim of preformulation research is the identification and selection of appropriate excipients based on the solubility characteristics of the pharmaceutical compound. Excipients possessing high solubility facilitate precise dissolution, enhance bioavailability, reduce dosing intervals, and enhance patient adherence. The existing body of literature encompasses several approaches to enhance solubility, such as the formation of salts, utilisation of cosolvents, development of solid dispersions, implementation of size reduction techniques, application of physical and chemical modifications, and incorporation of surfactants. [27] The occlusive impact of the solvent in topical administrations is contingent upon the interplay between the solubility of the excipients and their ability to penetrate the skin. The solvent solubility of the medicine must be adequate to accommodate the dosage of the drug without causing precipitation and ensuring its physical stability. The solubility of micronazole in water is rather low. When immersed in water, the substance has the potential to undergo destabilisation, leading to potential injury or degradation. Hence, the augmentation of solubility has the potential to significantly enhance the therapeutic effectiveness and absorption at the specific site of action. Various combinations of surfactants and cosurfactants were evaluated in the NE formulations. Furthermore, we conducted a series of experiments with various Smix ratios. Among these ratios, the 3:1 ratio proved to be the most appropriate as it effectively targeted the region with the greatest NE (non-equilibrium) area on the pseudoternary phase diagram. [28] The optimal droplet size for percutaneous absorption is the following. The absorption of particles bigger than 200 nm poses a challenge for several layers of the skin. The presence of these tiny values indicates a uniform distribution of globules and a consistent preparation process. The presence of surface charges on globules can create a repulsive force between them, impeding the aggregation of globules to a sufficient extent that stable non-equilibrium (NE) structures are not formed. The negative surface charge of the NE is likely attributed to the presence of hydroxyl ions in the medium. Furthermore, the incorporation of a polymeric gel imposes constraints on the movement of globules, so conferring stability to the gel system. [29] The size distribution of the micronazole PLGA nanoparticles mentioned before was found to be similar. One potential consequence is that bigger dispersed particles have the capacity to cause skin irritation or lead to undesirable abnormalities. Furthermore, there is a potential for the drug's absorption via the skin and subsequent release to be compromised, resulting in a diminished efficacy of the formulation. In contrast, diminutive particles have enhanced solubility and absorption rates. Hence, it is imperative that the active component is evenly distributed throughout the whole vehicle. Particle sizes below 100 nm, which are crucial for facilitating the profound penetration of topical medications into the skin, fall within the range

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deemed acceptable in the existing body of literature. The nanoemulgel was synthesised by the amalgamation of a nano emulsion with a gel matrix. The homogenous dispersion of drugs within the formulation may contribute to the drug content, while the little drug loss observed during processing suggests that the medication exhibits favourable stability in carbopol and HPMC-based gelling agents.[30] Carbopol, a cross-linked polyacrylic polymer that is soluble in water, has been extensively employed as a gelling agent in topical applications for a considerable period of time. Furthermore, it is utilised in several pharmacological and biological contexts as a stabiliser, suspending agent, and emulsifier. Triethanolamine is included into the gel in order to adjust the pH of the produced solution, which is intended to mimic the pH of human skin, either by neutralising or raising it. The preservation of the acid-base balance, reduction of cutaneous irritation, and enhancement of absorption are critical factors in maintaining the stability, safety, and efficacy of the active ingredient in topical dosage forms. Consequently, it is imperative to ensure the appropriate pH levels when formulating topical delivery to the skin. It is recommended that the pH level of skincare products should closely approximate the pH range of the skin, which typically falls between 4 and 6. The gel's viscosity, which has an impact on the dispersion and flow of medication following application and perhaps influences patient adherence, plays a critical role in drug release. Increased viscosity might potentially lead to a decelerated release of drugs, while conversely, it may impede the drainage of drugs when topically administered [31]. Furthermore, the crucial attributes of topically applied medicines encompass spreadability and gel adherence. The viscosity measurements (in Poes) of the gel indicate the presence of thixotropic behaviour within the range of shear rates from 0 to 250 (s1), whereby the viscosity of the gel decreases with an increase in shear rate. The rheological characteristics of gels can be influenced by several variables, including the kind of gelling agents, the synthesis processes employed, the molecular weight of the polymer, and the pattern of cross-linking. The rheological findings indicate that the gels formed exhibit a high degree of dispersibility with the application of light stress. The gels that were produced had a uniform, uninterrupted, and impermeable composition, as seen by the scanning electron microscopy (SEM) images of the gels. The formation exhibited unaltered IR absorption peaks, each of which has individual characteristics. Except for the amorphous condition of the drug in the formulation, it was observed that micronazole exhibited compatibility with the excipients and did not exhibit any interactions with them. This was supported by the observation that the intensity of the peaks reduced in the formulations including Soybean oil and Sunflower oil. The spectroscopic examination of the micronazole-Pluronic F127 system and the infrared spectra of micronazole-loaded nanoemulsion gels (NEGs) exhibit notable similarities. [31] The utilisation of X-ray diffraction (XRD) as a method for investigating polymorphism, which refers to the extent of crystal structure present in both the analyte and excipients within the test sample, is a valuable technique. The stability of the tested sample has been confirmed via the utilisation of X-ray diffraction (XRD) analysis. The alteration in the physical structure of a molecule has adverse effects on its solubility profile, drug dissolution, absorption, and systemic availability. [32] The X-ray diffraction (XRD) analysis revealed a significant reduction in the intensity of the prominent XRD peaks for both the 20% Soybean-oil–NEG and 15% Sunflower–NEG samples, as seen in Figure 9A–C. This observation indicates the transition of the drug from a crystalline form to an amorphous state. The formulations containing 15% Sunflower oil and 20% Soybean oil exhibited an initial abrupt release

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pattern. For example, the formulations exhibited an initial quick release of the medication, which was afterwards followed by a consistent and moderate release for the remaining period, suggesting a controlled release pattern. The initial burst release of a medication confers advantages by facilitating the attainment of a therapeutic concentration in the early stages, followed by the sustained release of the drug to maintain a steady state over an extended duration. [33] The process of nanoprecipitation facilitates the acceleration of drug release from NE (nanoemulsion) by inducing the partitioning of the oil component into the surfactant layer, followed by its subsequent transfer into the aqueous phase. Negative ions (NEGs) have the ability to penetrate the skin layers more effectively and release their therapeutic components upon topical application due to the liberation of oil globules from the gel matrix.. 45. When considering skin compatibility and efficacy as a penetration booster, natural oil emerges as a preferable alternative to synthetic oil. The results obtained from the aforementioned experimental studies reveal the collective impacts of PEG 200, Soybean oil, Sunflower oil, and a permeation enhancer. In addition, the application of nanoemulsion droplets resulted in the modification of the skin's structure through the alteration of the lipid or protein bilayer. This modification led to an increase in the fluidity of the skin and facilitated the diffusion of drugs through the cutaneous layer. The use of micronazole nanoemulsion gels (NEGs) with Sunflower and Soybean oil leads to enhanced spreadability, stability, and skin hydration. Consequently, this promotes improved penetration into the skin. [34] The dual functionality of the formulation serves to both hydrate the skin and enhance the transportation of therapeutic agents to the underlying tissues, such as the dermis, muscles, and capillaries. The natural oils employed in this study are non-toxic, possess moisturising properties, facilitate penetration, and serve to prevent the loss of electrolytes and fluids, hence retaining skin tonicity. The inadequate flux seen in the pure micronazole gel formulation can be attributed to deficiencies in drug solubility, dissolution, and penetration. [35] Shahid et al. developed a cationic nanoemulsion containing micronazole for the purpose of topical application in the treatment of cutaneous fungal infections. According to the researchers, the scientists observed a maximum drug penetration of 95.34 ± 1.22 g cm2. Additionally, they recorded a nanoemulsion size of 239 nm. A zone of inhibition of 44.2 mm by 1.4 mm was seen in the presence of the Candida krusei fungal strain. The investigation on in vivo skin irritation found that the internally developed formulation had a high level of skin tolerance due to its biocompatibility. The results of our investigation on skin irritation align with the findings of Shahid et al. on acute dermal irritation[36]. The previous work on micronazole-loaded polylactic nanoparticles against C. albicans and other species reported an encapsulation efficiency of only 45% for micronazole. Furthermore, the study did not investigate the skin adhesiveness of the nanoparticles. The nanoemulgel containing luliconazole was prepared in advance for the treatment of fungal infections. The size of the dispersed globules of the optimum drug-loaded nanoemulsion was reported to be 17 ± 3.67 nm. The luliconazole-NEGs exhibited a maximum zone of inhibition of 6 mm in diameter against Candida albicans.[37] A transferosomal gel containing Micronazole was discovered, characterised by vesicles with an average size of 126.9 ± 5.45 nm and an entrapment efficiency of 82.6%. Cumulative release of the drug amounted to 97%. The diameter of the zone of inhibition seen in the transferosomal gel was approximately 38 mm. The enhanced antifungal activity seen in our current experiment may be attributed to the incorporation of

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micronazole into natural oils containing NE, followed by its transfer into the nanoemulgel for better retention. [38]

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