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RESEARCH ARTICLE

Development of Ornidazole-Loaded Emulgel: Formulation Optimization and *In Vitro* Characterization

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SUMMARY

Ornidazole (ORN) is a nitroimidazole derivative widely used in the treatment of anaerobic bacterial and protozoal infections. Although it is usually administered orally, topical application can provide a localized therapeutic effect, reduced systemic exposure, and improved patient compliance, especially in skin and mucosal infections. Various dosage forms of ORN have been studied, but the development of emulgel systems has not been extensively researched. Therefore, this study aimed to optimize an emulsion base and to develop and comparatively evaluate ORN-loaded emulgels prepared with different gelling agents. Formulations were prepared using different oil phases (oleic acid, liquid paraffin, and castor oil) and surfactants (Tween 80 and Span 80). The optimal emulsion was determined through short-term physical stability, organoleptic evaluation, centrifugation and thermodynamic tests. Subsequently, emulgels were prepared using carbomer and poloxamer 407. All formulations exhibited pseudoplastic behavior suitable for topical use; the poloxamer-based emulgel showed higher viscosity. In vitro release studies revealed sustained release from both emulgels compared to the ORN solution; this release reached 84.48% at 2 hours and 97.41% at 24 hours. Release from carbomer and poloxamer emulgels increased from 62.60% and 63.15%, respectively, at 2 hours to 92.37% and 96.09% at 24 hours. Kinetic analysis showed first-order release for poloxamer and Korsmeyer-Peppas behavior for carbomer formulations. These findings highlight the effect of polymer type on release behavior and support the potential of emulgels as promising topical delivery systems for ORN.

Keywords: *Ornidazole, emulgel, in vitro release, viscosity.*

Ornidazol Yüklü Emüljel Geliştirilmesi: Formülasyon Optimizasyonu ve İn Vitro Karakterizasyon

ÖZ

Ornidazol (ORN), anaerobik bakteriyel ve protozoal enfeksiyonların tedavisinde yaygın olarak kullanılan bir nitroimidazol türevidir. Genellikle oral yolla uygulanmasına rağmen, topikal uygulama, özellikle deri ve mukoza enfeksiyonlarında lokalize terapötik etki, azaltılmış sistemik maruziyet ve iyileştirilmiş hasta uyumu sağlayabilir. ORN'nin çeşitli dozaj formları incelenmiştir, ancak emüljel sistemlerinin geliştirilmesi kapsamlı bir şekilde araştırılmamıştır. Bu nedenle, bu çalışma, bir emülsiyon bazını optimize etmeyi ve farklı jelleştirici maddelerle hazırlanan ORN yüklü emüljelleri geliştirmeyi ve karşılaştırmalı olarak değerlendirmeyi amaçlamıştır. Formülasyonlar, farklı yağ fazları (oleik asit, sıvı parafin ve hint yağı) ve yüzey aktif maddeler (Tween 80 ve Span 80) kullanılarak hazırlanmıştır. Optimal emülsiyon, kısa süreli fiziksel stabilite, organoleptik değerlendirme, santrifüj ve termodinamik testler yoluyla belirlenmiştir. Daha sonra, karbomer ve poloksamer 407 kullanılarak emüljeller hazırlanmıştır. Tüm formülasyonlar, topikal kullanım için uygun psödoplastik davranış sergilemiştir. Poloksamer bazlı emüljel daha yüksek viskozite göstermiştir. İn vitro salım çalışmaları, her iki emüljelden de ORN çözeltisine kıyasla sürekli salım olduğunu ortaya koymuştur; bu salım 2 saatte %84,48'e ve 24 saatte %97,41'e ulaşmıştır. Karbomer ve poloksamer emüljellerinden salım, 2 saatte sırasıyla %62,60 ve %63,15'ten 24 saatte %92,37 ve %96,09'a yükselmiştir. Kinetik analiz, poloksamer için birinci dereceden salım ve karbomer formülasyonları için Korsmeyer-Peppas davranışı göstermiştir. Bu bulgular, polimer tipinin salım davranışı üzerindeki etkisini vurgulamakta ve emüljellerin ORN için umut vadeden topikal uygulama sistemleri olarak potansiyelini desteklemektedir.

Anahtar Kelimeler: *Ornidazol, emüljel, in vitro salım, viskozite*

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INTRODUCTION

Ornidazole is a nitroimidazole derivative widely used in the treatment of anaerobic bacterial and protozoal infections. Although it is commonly administered orally, systemic use may lead to gastrointestinal disturbances and variable bioavailability (Agrahari, Khatri, & Manigauha, 2025). Topical delivery of ORN represents a promising alternative approach for localized infections, enabling high drug concentration at the site of application while minimizing systemic exposure and adverse effects.

However, the development of an effective topical formulation requires careful consideration of both drug properties and formulation variables. ORN exhibits limited aqueous solubility, which may restrict its uniform distribution in conventional gel systems. Emulsion-based systems represent a suitable approach to enhance drug solubilization within an oil phase while maintaining compatibility with aqueous external environments (Agrawal & Garg, 2020; Mohite et al., 2024).

Emulgels have emerged as advanced semisolid delivery systems that combine the advantages of emulsions and gels. The emulsion phase facilitates solubilization of hydrophobic drugs, while the gel matrix improves physical stability, enhances residence time at the application site, and modulates drug release (Ochoa-Andrade, Parente, Jimenez-Kairuz, Boinbaser, & Torregrosa, 2017; Shen et al., 2015). However, the stability and performance of emulgel systems strongly depend on the physicochemical properties of the oil phase and the selection of appropriate surfactant systems.

One of the critical parameters governing emulsion stability is the hydrophilic–lipophilic balance (HLB) value of the surfactant system. Proper matching of the surfactant HLB with the required HLB of the oil phase is essential for forming stable oil-in-water (O/W) emulsions. Additionally, the type of oil used in the formulation can significantly influence droplet size distribution, interfacial film strength, and long-term stability. Variations in oil polarity, viscosity, and interfacial characteristics may result in different stability profiles even within the same HLB range (Park & Kim, 2021; Schmidts, Dobler, Guldan, Paulus, & Runkel, 2010). Therefore, systematic optimization of both oil type and HLB value is necessary to obtain a physically stable emulsion suitable for incorporation into a gel matrix.

Incorporation of emulsions into gel matrices leads to the formation of emulgels, which combine the solubilization capacity of emulsions with the favorable rheological characteristics of gels. The type of gelling agent used may significantly influence the structural integrity, viscosity, and drug release behavior of the final formulation. Carbomer, a cross-linked poly (acrylic acid) polymer, forms a highly swollen and structured network upon neutralization (Dano et al., 2021), while poloxamer 407 forms thermoreversible micellar gels at higher concentrations through self-assembly mechanisms (Ferreira et al., 2020). Due to these distinct gelation mechanisms, the internal architecture of carbomer- and poloxamer-based emulgels may differently regulate drug diffusion and mechanical properties. Previous studies have reported that formulations containing 1% Carbopol exhibit improved viscosity, mechanical properties, and physical stability compared to lower polymer concentrations (Dano et al., 2021), while Poloxamer 407 concentrations in the range of 20–30% provide suitable gel strength and controlled drug release characteristics (Mazurkeviciute, Matulyte, Ivaskiene, & Zilius, 2024). Therefore, 1% Carbopol and 30% Poloxamer 407 concentrations were selected in the present study to obtain stable emulgel formulations with appropriate rheological behavior and sustained release properties.

In this study, ORN-loaded emulsions were systematically optimized by evaluating different oil types and surfactant HLB values to determine the most physically stable formulation. The optimized emul-

sion was subsequently incorporated into carbomer (1%) and poloxamer (30%) gel bases to prepare two distinct emulgel systems. The influence of oil phase selection, HLB optimization, and gel matrix type on physical properties, rheological behavior, and *in vitro* drug release was comparatively investigated.

MATERIALS AND METHODS

Materials

ORN was donated by Deva Holding A.Ş. (Türkiye). Span 80 and Poloxamer 407 were purchased from Sigma-Aldrich (St. Louis, MO, USA). Tween 80 was obtained from ISOLAB (Germany). Triethanolamine (97%) was purchased from ACROS Organics (Belgium). All chemicals and reagents used in the study were of analytical grade and used as received without further purification.

Analytical method

The analytical method was validated according to ICH guideline Q2 (R1) with parameters of accuracy, sensitivity, Limit of Detection (LOD), Limit of Quantification (LOQ) and linearity (Jha, Shah, Talele, & Amin, 2020). To establish the calibration line of the ORN, a stock solution was prepared in pH 7.4 phosphate buffer at a concentration of 200 µg/mL. This solution was then diluted to concentrations of 25, 20, 15, 12.5, 10 and 6.25 µg/mL to prepare samples. These samples were read at 319 nm using a spectrophotometer (Cary 60 UV-vis), and the line equation was established using the obtained absorbance values. The study was performed in three parallel runs, and the mean values were plotted along with their standard deviations.

Preparation and optimization of emulsions

Initially, the most suitable emulsion formulation for the emulgel system was optimized. Different oil phases, including oleic acid, liquid paraffin, and castor oil, were evaluated due to their varying polarity, viscosity, and potential effects on emulsion stability. Different HLB values (10.5–15) were investigated by varying the ratio of Tween 80 and Span 80 to determine the optimum emulsifier blend capable of producing stable emulsions for the selected oil phases. This approach is commonly used to approximate the required HLB value of the oil phase and to identify the surfactant combination that provides maximum emulsion stability. For this purpose, the emulsions given in Table 1 were prepared and evaluated in terms of physical appearance, homogeneity, and stability to determine the most suitable system for further formulation development. Based on these evaluations, the optimized emulsion formulation was selected for incorporation into the gel bases.

Table 1. Composition of emulsion formulations prepared with different oil phases and HLB values

Formulation Code	Oil Type	HLB Value	Oil (g)	Tween 80 (g)	Span 80 (g)	Water (g)
OA-1	oleic acid	10.5	2.00	0.580	0.420	17.00
OA-2	oleic acid	11.5	2.00	0.670	0.330	17.00
OA-3	oleic acid	11.5	2.00	1.340	0.660	16.00
OA-4	oleic acid	11.5	2.00	2.010	0.990	15.00
OA-5	oleic acid	13.0	2.00	0.810	0.190	17.00
OA-6	oleic acid	15.0	2.00	1.000	0.000	17.00
LP-1	liquid paraffin	10.5	2.00	0.580	0.420	17.00
LP-2	liquid paraffin	11.5	2.00	0.670	0.330	17.00
LP-3	liquid paraffin	11.5	2.00	1.340	0.660	16.00
LP-4	liquid paraffin	11.5	2.00	2.010	0.990	15.00
LP-5	liquid paraffin	13.0	2.00	0.810	0.190	17.00
LP-6	liquid paraffin	15.0	2.00	1.000	0.000	17.00
CO-1	castor oil	10.5	2.00	0.580	0.420	17.00
CO-2	castor oil	11.5	2.00	0.670	0.330	17.00
CO-3	castor oil	11.5	2.00	1.340	0.660	16.00
CO-4	castor oil	11.5	2.00	2.010	0.990	15.00
CO-5	castor oil	13.0	2.00	0.810	0.190	17.00
CO-6	castor oil	15.0	2.00	1.000	0.000	17.00

The emulsion formulations were prepared using the compositions given in Table 1. Briefly, the aqueous phase was prepared by mixing Tween 80 with distilled water, while the oil phase was prepared by mixing Span 80 with the selected oil phase (liquid paraffin, oleic acid, or castor oil). Both the aqueous and oil phases were heated separately in a water bath at 70 °C. Subsequently, the oil phase was added dropwise into the aqueous phase under continuous stirring at 500 rpm for 10 min. The resulting emulsions were then allowed to cool to room temperature to obtain stable formulations.

Physical examination

The emulsion formulations were visually examined at room temperature to assess their homogeneity, color and overall physical appearance.

Centrifuge and thermodynamic test

The emulsion formulations were centrifuged at 15,000 rpm for 15 min using a centrifuge to observe whether phase separation had occurred. For thermodynamic testing, emulsions were kept at −20 °C for 12 h and then kept at room temperature for 12 h (Kral, Hennep, Uslu, & Yücel, 2026). This process was repeated twice. The formulations were examined for homogeneity, phase separation, and turbidity. Thus, the effect of temperature changes on the formulations was determined.

Preparation of ORN-loaded emulsion

The optimized emulsion formulation was selected as OA-4 and loaded with ORN. Briefly, ORN was dissolved in the aqueous phase before emulsification, and Tween 80 was added. The oil phase was prepared by mixing Span 80 and oleic acid. Then, the oil phase was added dropwise to the aqueous phase under continuous stirring at 500 rpm for 10 minutes. The resulting ORN-loaded emulsions were allowed to cool to room temperature to obtain homogeneous formulations, which were then used in emulgel preparation.

Preparation of carbomer-based emulgel

The gel base was prepared by gradually dispersing Carbomer (1%, w/w) in cold distilled water under continuous stirring at medium speed until a homogeneous distribution was obtained. Then, the pH of the gel base was adjusted to 6.0-6.5 using triethanolamine (TEA) to achieve the desired gel consistency. Subsequently, the ORN-loaded emulsion and the carbomer gel were mixed in a 1:1 (w/w) ratio until a homogeneous emulgel was obtained (Ali Khan, Ullah, Khan, Alshahrani, & Braga, 2020; Ermawati, Nugraheni, Zuardina, & Saputri, 2020).

Preparation of poloxamer-based emulgel

Poloxamer-based emulgel was prepared using Poloxamer 407 as the gelling agent. Briefly, Poloxamer 407 (30%, w/w) was gradually added to cold distilled water under continuous stirring until complete dissolution was achieved. The dispersion was then kept at 4 °C to ensure full hydration and formation of a clear gel base. Subsequently, the ORN-loaded emulsion and the poloxamer gel were mixed in a 1:1 (w/w) ratio until a homogeneous emulgel was obtained (de Souza Ferreira & Bruschi, 2021).

Characterization of emulgel formulations

The emulgel formulation's physical characteristics, ORN content, pH, FTIR, viscosity, and *in vitro* release studies were all assessed as part of the characterisation investigations.

Evaluation of physical properties

Emulsion formulations were evaluated in terms of color, homogeneity, and physical appearance properties.

Drug content

Approximately 20 mg of the emulgel formulation was weighed and stirred in a pH 7.4 phosphate buffer until completely dispersed. The sample was filtered, and the ORN concentration was determined by analysis at 319 nm using a UV spectrophotometer (n=3).

Fourier transform- infrared spectroscopy (FT-IR)

The spectra of pure ORN, ORN-loaded emulgels, and blank emulgels were investigated using an FT-IR spectroscopy device (Thermo Scientific, Nicolet IS150). Using the FTR-ATR disk printing technology, the analysis was conducted within the scanning range of 600–4000 cm^{-1} (Kral, Eralmaç, & Aydin, 2025).

pH determination

The pH value of the emulgel formulation was measured using a pH meter at room temperature (n=3). The pH value was intended to be close to the skin pH so that the formulation would not cause any irritation.

Viscosity measurement

The viscosities of the emulgels were measured using a rotational-type viscometer (Lamy B-One Plus, France) equipped with an MK-R3 spindle at room temperature. Shear stress and viscosity were measured corresponding to increasing shear rate values ranging from 5 to 50 s^{-1} (n=3). Viscosity-shear rate graphs were created based on the data.

***In vitro* release study**

Franz diffusion cells were used for the *in vitro* release study. The study was performed using a cellulose membrane (Dialysis Tube, molecular weight cutoff point 12000–14000, Sigma-Aldrich, USA) at 37±0.5 °C in pH 7.4 phosphate buffer. 120 mg of the emulgel formulation was placed in the donor compartment. 2.5 mL of phosphate buffer was added to the recipient compartment. 2.5 mL of sample was taken at the indicated times over 24 hours, and the recipient compartment was refilled with the same volume of phosphate buffer. The samples were filtered and analyzed by UV spectrophotometry (n=3) (Çulcu, Tunçel, Tamer, & Tırnaksız, 2020).

As a result of the *in vitro* study, the ORN release profile was examined using DDSolver software. Zero-order kinetic, first-order kinetic, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models were evaluated (Erawati et al., 2023).

Statistical analysis

The *in vitro* release profile was mathematically analyzed using DDSolver software. GraphPad Prism® 5.0 software was used to conduct ANOVA and the T-test in comparative statistical studies.

RESULTS AND DISCUSSION

Analytical method

The accuracy and sensitivity of the analytical method were evaluated at three concentration levels representing low, medium, and high concentrations (6.25 µg/mL, 12.5 µg/mL, and 25 µg/mL, respectively). The mean percentage recoveries at the tested concentration levels were found to be 99.52±0.18 %, 98.65±0.15 %, and 101.35±0.24 %, respectively. The %RSD values were found to be below 2%, demonstrating good precision and repeatability of the developed method (Arisoy, Yapar, Karakurt, Bakal, & Örgül, 2026). The LOD value was found to be 0.513 µg/mL, and the LOQ value was 1.55 µg/mL. The calibration equation was prepared according to the ICH guideline, and the R2 value was found to be 0.9991 (Figure 1.). All results indicate the validity of the method. Furthermore, the selectivity of the method at 319 nm showed no significant interference from formulation excipients. This also shows that the method is selective for determining the amount of ORN in emulgel formulations.

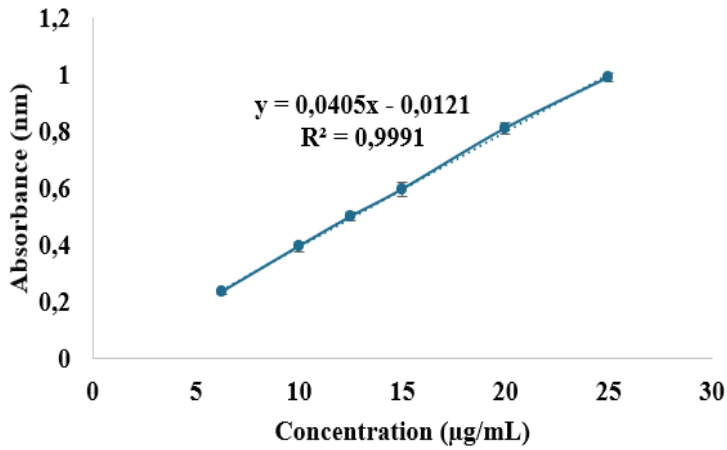

Figure 1. Calibration graph of Ornidazole concentration (µg/mL) vs. absorbance (nm)

Optimization of emulsions

For emulgel systems to be organized and stable, it is crucial to consider the presence, concentration, and kind of hydrophobic, hydrophilic, and emulsifying agents (Said dos Santos et al., 2021). In this study, pre-emulsions were prepared using three different oil phases (oleic acid, liquid paraffin, and castor oil) with different HLB values using a Tween 80/Span 80 combination, and systematically screened for physical stability. The goal of the pre-selection phase was to obtain homogeneous, milky-looking O/W emulsions without phase separation and to maintain structural integrity under stress conditions. This approach was considered critical for verifying the kinetic stability of the emulsions before their conversion to emulgel form. The prepared formulations were assessed in terms of homogeneity, color and appearance, and the findings are presented in Table 2.

Table 2. Evaluation of physical properties of the prepared emulsion formulations

Formulation Code	Homogeneity	Color	Physical appearance (After one hour)
OA-1	4	White	**Creaming (++)**
OA-2	4	White	**Creaming (+)**
OA-3	4	White	**Creaming (+)**
OA-4	5	White	**No creaming**
OA-5	4	White	**Creaming (+)**
OA-6	4	White	**Creaming (++)**
LP-1	4	White	**Creaming (+)**
LP-2	4	White	**Creaming (+)**
LP-3	3	White	**Creaming (+)**
LP-4	4	White	**Creaming**
LP-5	4	White	**Creaming (+)**
LP-6	1	White	**Phase separation**
CO-1	1	Light yellow	**Phase separation**
CO-2	1	Light yellow	**Phase separation**
CO-3	1	Light yellow	**Phase separation**
CO-4	1	Light yellow	**Phase separation**
CO-5	1	Light yellow	**Phase separation**
CO-6	1	Light yellow	**Phase separation**

** Homogeneity:5, excellent:4, very good:3, good:2, bad: 1 nonhomogeneous.*

In CO series formulations containing castor oil (CO-1, CO-2, CO-3, CO-4, CO-5, CO-6), the expected homogeneous milky appearance did not form after preparation, and significant phase separation was observed in a short time. The absence of a milky appearance suggests that sufficient droplet distribution was not achieved in the system and that emulsification was ineffective. Furthermore, phase separation indicates that the CO series could not form a stable interfacial film with the current surfactant combination and the targeted HLB range (Park & Kim, 2021). Therefore, CO series emulsions were eliminated at an early stage without being advanced to further stability tests.

In the OA series containing oleic acid, different HLB targets and surfactant ratios were tested; it was observed that stability depended not only on the HLB value but also on the total surfactant amount of the system and the flow properties of the resulting emulsion. In particular, the OA-4 formulation (HLB 11.5; Tween 80 = 2.010 g, Span 80 = 0.990 g, water = 15 g) had a higher surfactant content compared to other OA formulations and showed higher viscosity as a practical observation. This may have reduced the mobility of the emulsion droplets, decreasing the tendency for creaming/precipitation and limiting coalescence. In contrast, the irreversible phase separation of the OA-1, OA-2, and OA-5 formulations after 1 week at room temperature suggests that the long-term kinetic stability of these systems is insufficient and that the interfacial film may weaken over time. Therefore, OA-1, OA-2, and OA-5 were eliminated in the later stages.

OA-6 and LP-6, formulated using Tween 80 as the sole surfactant, exhibited lower homogeneity and reduced physical stability compared to mixed surfactant systems. The absence of Span 80 likely resulted in weaker interfacial film formation and insufficient stabilization of the oil droplets. Consequently, these formulations were excluded from further consideration. A higher yield stress is known to reduce droplet mobility and prevent phase separation, sedimentation, or

aggregation in emulsion systems (Hong, Kim, & Lee, 2018). The superior stability observed in OA-4 may therefore be attributed to its higher structural resistance, which likely limited droplet movement under stress conditions such as centrifugation and freeze–thaw cycles.

When all results are evaluated together, the OA-4 formulation showed the highest physical stability compared to other formulations due to (i) homogeneous appearance after production, (ii) no phase separation in the centrifuge test, (iii) higher structural stability under freeze-thaw conditions, and (iv) stability after 1 week of storage at room temperature. Therefore, OA-4 was selected as the optimized emulsion to be moved to the emulgel development stage. The selected optimized emulsion (OA-4) was incorporated into two different gel bases (carbomer and poloxamer) in a 1:1 ratio to prepare emulsified gel formulations in order to evaluate the final topical product performance. This approach allowed for the comparison of only the effect of the gelling agent type while maintaining the same emulsion core and enabled the separate investigation of the role of the gel base on rheological properties and stability.

Characterization of emulgel formulations

Evaluation of physical properties

After selecting the optimized emulsion (OA-4), two separate emulgel formulations were prepared by incorporating the emulsion into carbomer (1%) and poloxamer (30%) gel bases in a 1:1 ratio. Both emulgel formulations appeared homogeneous and exhibited a uniform white color, indicating successful incorporation of the emulsion into the gel matrices without apparent phase separation or aggregation (Figure 2.). However, significant differences in texture and consistency were observed between the two systems.

The carbomer-based emulgel exhibited a softer, creamier consistency and a smoother texture. In contrast, the poloxamer-based emulgel showed a harder, more structured, gel-like appearance and a relatively higher apparent viscosity. The increased stiffness of the poloxamer formulation can be attributed to the formation of a dense micelle network at the high polymer concentration (30%), which increases structural stability (Burki et al., 2020). Conversely, carbomer, primarily through pH-dependent swelling, forms a three-dimensional polymeric network, resulting in a softer and more easily spreadable matrix at a 1% concentration.

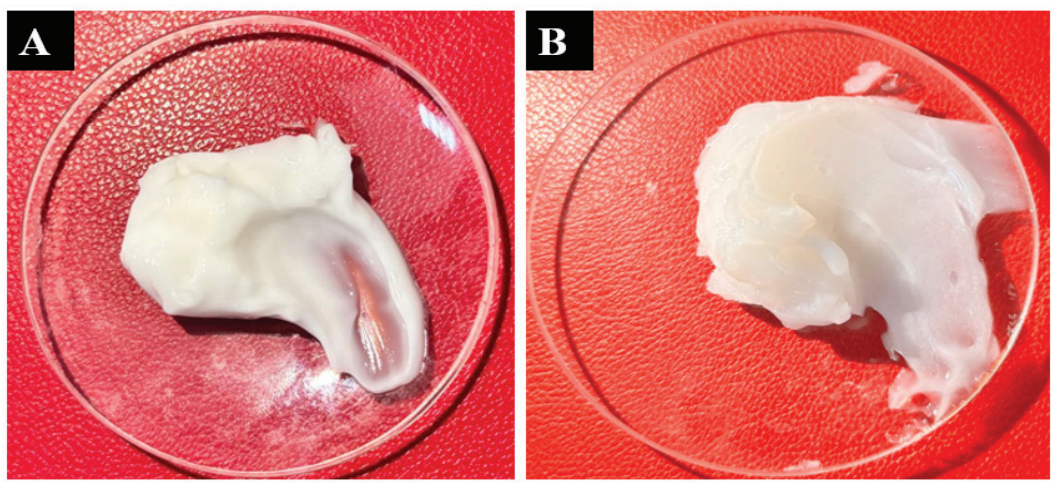

Figure 2. Carbomer emulgel (A), poloxamer emulgel (B)

Drug content

The ORN amount was determined as 98.3±1.56 % for the carbomer emulgel and 96.3±1.95% for the poloxamer emulgel formulation.

Fourier transform- infrared spectroscopy (FT-IR)

The FTIR spectra of ORN, ORN-loaded emulgels, and empty emulgels are shown in Figure 3. Pure ORN shows characteristic peaks at approximately 3112 (stretching CH_2), 1538 (in-plane bending HCH), 1148, and 882 (Rajesh, Gunasekaran, Gnanasambandan, & Seshadri, 2016). Peak intensity may shift or change slightly as a result of potential interactions between ORN and the polymer matrix. The strength of ORN peaks in the FTIR spectra of emulgel formulations decreased with increasing ORN concentration (Jagdale & Chandekar, 2017; Kral et al., 2026).

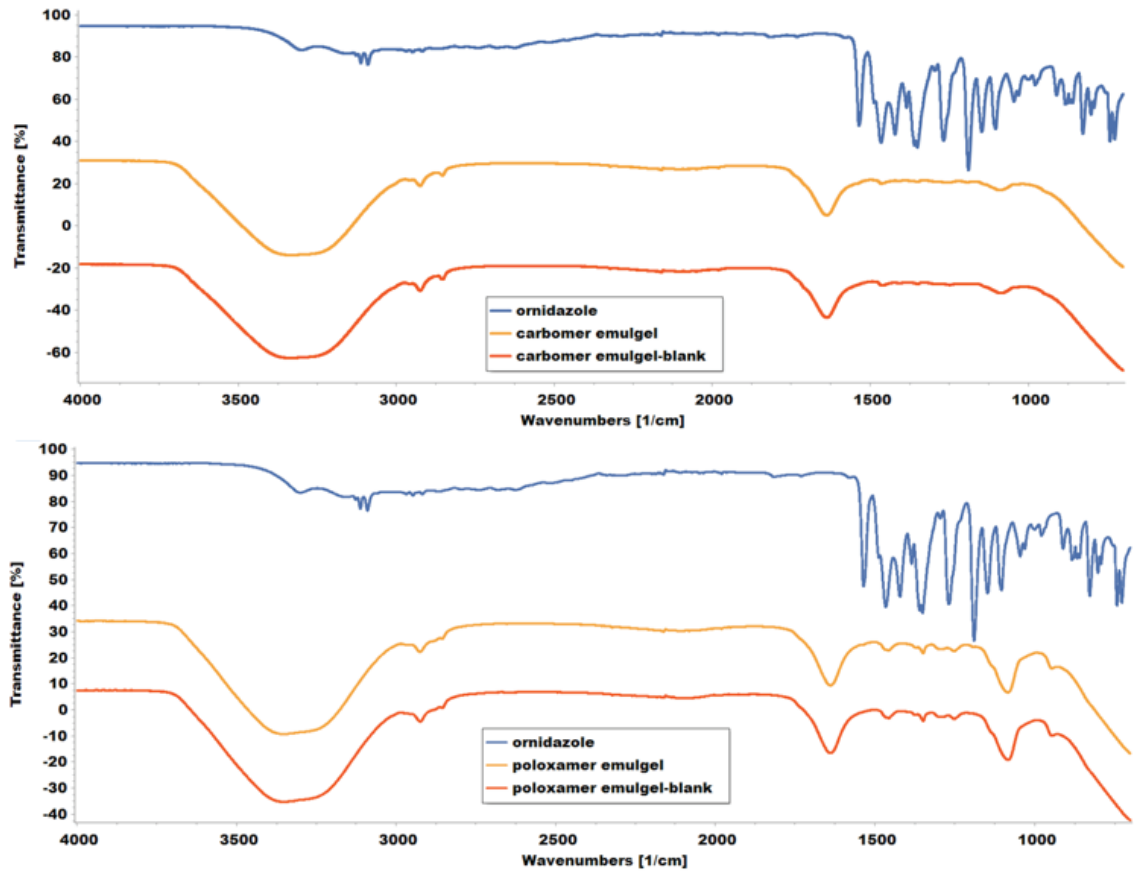

Figure 3. FTIR spectra of pure ORN, ORN-loaded and blank emulgels

pH determination

The appropriateness of a formulation for topical application is determined by its pH. If it is in the range of 4.8 to 6.6, which is the pH of the skin, it seems to be safe for dermal application and non-irritating (Garala, Joshi, Patel, Ramkishan, & Shah, 2013; Masood, Arshad, Khan, Begum, & Khan, 2023). The pH of carbomer emulgel was found to be 6.4±0.46, and that of poloxamer emulgel was found to be 5.5±0.35.

Viscosity measurement

Topical/transdermal formulations' rheological behavior significantly affects the formulation's spreadability, retention, and duration of contact with the skin's surface (Badruddoza et al., 2024). The graph showing the viscosity measurement results of carbomer and poloxamer emulgels is given in Figure 4. The rheological evaluation revealed a decrease in viscosity with increasing shear rate for both emulgel formula-

tions, indicating pseudoplastic (shear-thinning) behavior. Similar pseudoplastic flow behavior has been reported for various emulgel formulations in the literature, confirming that shear-thinning properties are typical for polymer-based semisolid systems (Shen et al., 2015; Yassin, 2014). Such flow characteristics are highly desirable for topical and transdermal preparations. During application, the increased shear stress reduces viscosity, facilitating easy spreading over the skin surface. Once the shear force is removed, viscosity increases again, enhancing retention and prolonging contact time at the site of application (Batheja, Sheihet, Kohn, Singer, & Michniak-Kohn, 2011). Therefore, both formulations exhibit rheological properties suitable for topical use.

The rheological characteristics of formulations are influenced by variables such as co-solvent, oil phase, auxiliary emulsifying agent, surfactant, and gelling agent. Viscosity and gelling agent concentration are correlated; that is, when the concentration of the gelling agent increases, so does viscosity (Burki et al., 2020). The poloxamer-based emulgel in this study had 30% poloxamer, while the carbomer-based formulation had 1% carbomer. The poloxamer formulation had a far higher concentration of polymer, which probably caused the higher viscosity values that were seen. Poloxamer also forms a three-dimensional micellar network structure at greater concentrations, which may make the structure stronger and more resistant to flow than the carbomer system.

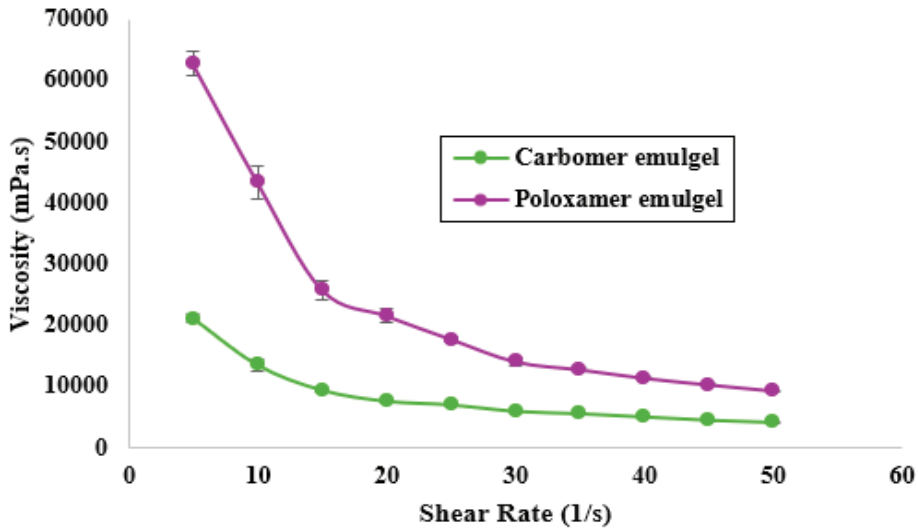

Figure 4. Viscosity versus shear rate profiles of carbomer and poloxamer-based emulgels

***In vitro* release study**

The *in vitro* release study demonstrated that incorporation of the drug into emulgel systems significantly modified its release behavior compared to the drug solution (Figure 5.). The solution exhibited rapid release, reaching 84.48% at 2 hours and 97.41% at 24 hours, which is expected due to the absence of a structural barrier and the immediate availability of the dissolved drug. In contrast, both emulgel formulations showed a reduced initial release rate. At 2 hours, cumulative release was 62.60% for the carbomer-based emulgel and 63.15% for the poloxamer-based emulgel. At 2 hours, the cumulative percentage of ORN released from the solution differed significantly from that of the emulgel formulations (unpaired Student's t-tests, $p < 0.05$). In contrast, no statistically significant difference was observed between the emulgel formulations (unpaired Student's t-tests, $p > 0.05$). This decrease in early drug release can be attributed to the presence of a three-dimensional polymeric matrix that restricts molecular mobility and introduces

diffusional resistance. It is well established that polymer-based semisolid systems act as diffusion-controlling barriers, modulating drug transport from the formulation to the external medium (Khunt, Mishra, & Shah, 2012).

Emulgels are emulsions incorporated into a gel matrix using suitable gelling agents, thereby combining the structural characteristics of both emulsions and gels. In such systems, the drug is primarily entrapped within the internal phase of the emulsion and is gradually released into the external phase, resulting in a controlled release profile. Moreover, the presence of a gel matrix further modulates drug diffusion, allowing emulgels to function as dual-controlled release systems (Raeisi Estabragh, Sajadi Bami, Dehghannoudeh, Noudeh, & Moghimipour, 2023).

At 24 hours, cumulative release values increased to 92.37% for the carbomer emulgel and 96.09% for the poloxamer emulgel, both approaching the release profile of the solution. Although the emulgel systems exhibited a slower initial release, the cumulative release at 24 hours was not statistically different from the solution (unpaired Student's t-tests, $p > 0.05$), indicating comparable overall drug availability over time. The slightly lower release observed with carbomer may be related to its cross-linked poly(acrylic acid) network, which forms a densely swollen gel structure capable of imposing greater resistance to diffusion (Bonacucina, Cespi, Misici-Falzi, & Palmieri, 2006). In contrast, poloxamer 407 forms a thermoreversible micellar gel structure, where drug diffusion may occur through aqueous channels within the micellar network, potentially facilitating slightly higher cumulative release over time (Dumortier, Grossiord, Agnely, & Chaumeil, 2006).

The observed slower release from emulgel formulations compared to the solution is advantageous for topical applications. Controlled release from semisolid systems can enhance drug residence time at the application site and reduce rapid drug depletion, thereby potentially improving therapeutic performance (Raeisi Estabragh et al., 2023). The absence of an excessive burst effect in the gel systems further supports their suitability as modified-release topical delivery platforms.

Overall, conversion of the drug solution into emulgel systems successfully transformed an immediate-release profile into a more controlled diffusion-based release pattern, with minor differences attributable to the distinct structural characteristics of carbomer and poloxamer gel matrices.

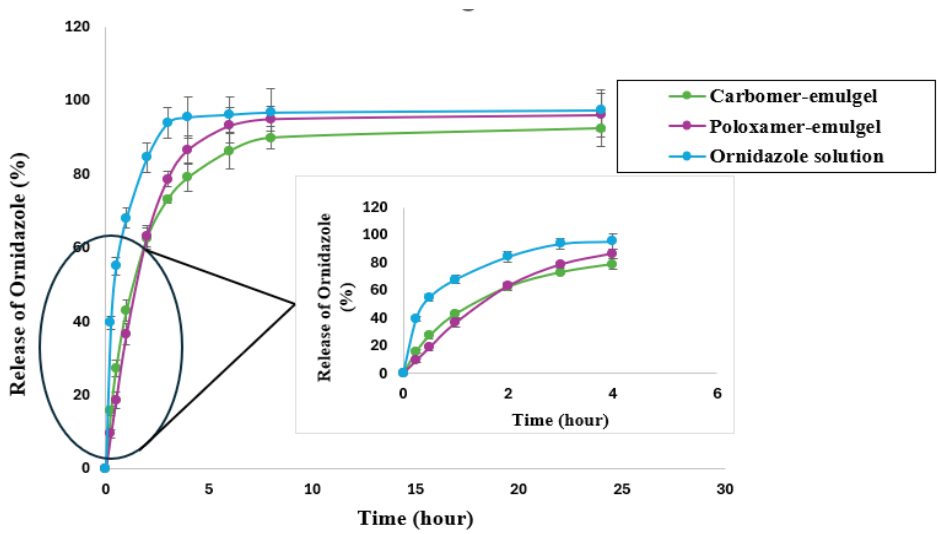

Figure 5. Cumulative percentage release of ORN from carbomer emulgel, poloxamer emulgel and ORN solution

Five popular mathematical models were employed to assess the release kinetics, and it was discovered that the ORN-solution and carbomer emulgel formulations fit the Korsmeyer-Peppas model the best. On the other hand, it was found that the poloxamer emulgel matched the first-order model (Table 3.). According to the Korsmeyer-Peppas model, the release exponent (n) values for the Carbomer emulgel and ORN-solution were 0.252 and 0.133, respectively. For spherical systems: n≤0.43 for purely Fickian diffusion, 0.43<n<0.85 for anomalous (nonFickian transport), n=0.85 for zero-order release systems, and values>0.85 indicate super case-II transport (Siepmann & Siepmann, 2008).

DDSolver offers many statistical criteria for the assessment of the dissolving model. R^2_{adj}, AIC, and MSC are the most prominent and commonly used of these parameters for figuring out how to model dissolving data. This suggests that the mathematical model is better for the release profiles when R^2_{adj} becomes closer to 1, AIC goes down, and MSC goes up (Zhang et al., 2010). The adjusted R^2, AIC, and MSC values used to choose the best model showed that the First-order model best explained how the poloxamer emulgel was released. The Korsmeyer–Peppas model, on the other hand, was the best mathematical fit for the carbomer-based formulation.

Table 3. Model-dependent release parameters and goodness-of-fit criteria obtained by DD Solver for ORN formulations

		Carbomer emulgel	Poloxamer emulgel	Ornidazole solution
Zero order	**R^2_{adj}**	-0.773	-0.472	-2.360
	AIC	99.82	100.64	105.76
	MSC	-1.164	-0.882	-2.220
First order	**R^2_{adj}**	0.712	**0.996**	0.298
	AIC	81.64	**40.99**	90.11
	MSC	0.652	**5.082**	-0.650
Higuchi	**R^2_{adj}**	0.562	0.618	-0.128
	AIC	85.84	87.14	94.86
	MSC	0.233	0.468	-1.120
Hixson-Crowell	**R^2_{adj}**	0.501	0.682	-0.282
	AIC	87.13	85.31	96.140
	MSC	0.104	0.650	-1.250
Korsmeyer -Peppas	**R^2_{adj}**	**0.814**	0.799	**0.880**
	AIC	**78.07**	81.51	**73.067**
	MSC	**1.010**	1.030	**1.054**
	n	**0.252**	0.269	**0.133**

CONCLUSION

The present study successfully developed and optimized ORN-loaded emulgel formulations using carbomer and poloxamer as gelling agents. Both systems demonstrated pseudoplastic flow behavior, which is advantageous for topical administration. The higher viscosity observed in the poloxamer-based formulation reflects differences in polymer concentration and gel network structure. In vitro release studies indicated that both emulgels provided a slower and more controlled drug release profile compared to the ORN solution, particularly during the initial phase. Although cumulative release values at 24 hours approached those of the solution, the emulgel systems effectively moderated the early release rate, suggesting sustained release behavior. Overall, these findings demonstrate that polymer selection plays a decisive role in modulating release behavior and rheological

performance. The developed emulgel systems offer a promising and patient-friendly topical delivery approach for ORN, with potential advantages in localized therapy.

AUTHOR CONTRIBUTION STATEMENT

The conceptualization, methodology, investigation, data curation, formal analysis, visualization, writing – original draft, writing – review & editing, project administration (ÖK), the investigation, literature review, methodology, writing – original draft, data curation, formal analysis (İÖ).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

Agrahari, N., Khatri, S., & Manigauha, A. (2025). Formulation and Evaluation of Ornidazole Loaded Ethasomol Gel for Treatment of Bacterial Infection. *Journal of Molecular Science*, *35*, 606–614. doi:10.004687/1000-9035.2025.083

Agrawal, G. P., & Garg, A. (2020). Polymorphic transformation of ornidazole with nicotinamide in solid dispersion to enhance solubility and dissolution rate. *Acta Pharmaceutica Sciencia*, *58*(3), 259–275. doi:10.23893/1307-2080.APS.05815

Ali Khan, B., Ullah, S., Khan, M. K., Alshahrani, S. M., & Braga, V. A. (2020). Formulation and evaluation of Ocimum basilicum-based emulgel for wound healing using animal model. *Saudi Pharmaceutical Journal*, *28*(12), 1842–1850. doi:10.1016/j.jsps.2020.11.011

Arisoy, S., Yapar, Ö., Karakurt, B., Bakal, R., & Örgül, D. (2026). Intranasal Delivery of Nicotine Via Thermoresponsive Hydrogel Systems: Design, Characterization, and In Vitro Evaluation. *Fabad Journal of Pharmaceutical Sciences*, *51*(1), 53–66. doi:10.55262/fabadeczacilik.1804119

Badruddoza, A. Z. M., Zahid, M. I., Walsh, T., Shah, J., Gates, D., Yeoh, T., & Nurunnabi, M. (2024). Topical drug delivery by Sepineo P600 emulgel: Relationship between rheology, physical stability, and formulation performance. *International Journal of Pharmaceutics*, *658*, 124210. doi:10.1016/j.ijpharm.2024.124210

Batheja, P., Sheihet, L., Kohn, J., Singer, A. J., & Michniak-Kohn, B. (2011). Topical drug delivery by a polymeric nanosphere gel: Formulation optimization and in vitro and in vivo skin distribution studies. *Journal of Controlled Release*, *149*(2), 159–167. doi:10.1016/j.jconrel.2010.10.005

Bonacucina, G., Cespi, M., Misici-Falzi, M., & Palmieri, G. F. (2006). Rheological, adhesive and release characterisation of semisolid Carbopol/tetraglycol systems. *International Journal of Pharmaceutics*, *307*(2), 129–140. doi:10.1016/j.ijpharm.2005.09.034

Burki, I. K., Khan, M. K., Khan, B. A., Uzair, B., Braga, V. A., & Jamil, Q. A. (2020). Formulation Development, Characterization, and Evaluation of a Novel Dexibuprofen-Capsaicin Skin Emulgel with Improved In Vivo Anti-inflammatory and Analgesic Effects. *AAPS PharmSciTech*, *21*(6). doi:10.1208/s12249-020-01760-7

Çulcu, Ö., Tunçel, E., Tamer, S. İ., & Tırnaksız, F. F. (2020). Characterization of thermosensitive gels for the sustained delivery of dexketoprofen trometamol for dermal applications. *Journal of Gazi University Health Sciences Institute*, *2*(2), 1–12.

Dano, M. E. L., Said dos Santos, R., Bassi da Silva, J., Junqueira, M. V., de Souza Ferreira, S. B., & Bruschi, M. L. (2021). Design of emulgel platforms for local propolis delivery: The influence of type and concentration of carbomer. *Journal of Molecular Liquids*, *334*. doi:10.1016/j.molliq.2021.116025

de Souza Ferreira, S. B., & Bruschi, M. L. (2021). Investigation of the physicochemical stability of emulgels composed of poloxamer 407 and different oil phases using the Quality by Design approach. *Journal of Molecular Liquids*, *332*. doi:10.1016/j.molliq.2021.115856

Dumortier, G., Grossiord, J. L., Agnely, F., & Chaumeil, J. C. (2006). A review of poloxamer 407 pharmaceutical and pharmacological characteristics. *Pharmaceutical Research*, *23*(12), 2709–2728. doi:10.1007/s11095-006-9104-4

Erawati, E., Hamid, H., Musthofa, M., Fatoni, R., Nurwaini, S., & Rahmah, A. U. (2023). Drug release kinetics of capsule shells from seaweed carrageenan extract (Eucheuma cottonii) and potato starch as a gelling agent. *Bulletin of the National Research Centre*. doi:10.1186/s42269-023-01045-6

Ermawati, D., Nugraheni, R. W., Zuardina, N., & Saputri, M. H. (2020). *Formulation and Antibacterial Activity Test of Emulgel Containing Citronella Oil (Cymbopogon Nardus L.) with Variaton of Gelling Agent Carbomer* (pp. 223–227). Scitepress. doi:10.5220/0009130302230227

Ferreira, S. B. de S., Slowik, K. M., Castro Hoshino, L. V. de, Baesso, M. L., Murdoch, C., Colley, H. E., & Bruschi, M. L. (2020). Mucoadhesive emulgel systems containing curcumin for oral squamous cell carcinoma treatment: From pre-formulation to cytotoxicity in tissue-engineering oral mucosa. *European Journal of Pharmaceutical Sciences*, *151*(6), 105372. doi:10.1016/j.ejps.2020.105372

Garala, K., Joshi, P., Patel, J., Ramkishan, A., & Shah, M. (2013). Formulation and evaluation of periodontal in situ gel. *International Journal of Pharmaceutical Investigation*, *3*(1), 29. doi:10.4103/2230-973x.108961

Hong, I. K., Kim, S. I., & Lee, S. B. (2018). Effects of HLB value on oil-in-water emulsions: Droplet size, rheological behavior, zeta-potential, and creaming index. *Journal of Industrial and Engineering Chemistry*, *67*(5), 123–131. doi:10.1016/j.jiec.2018.06.022

Jagdale, S., & Chandekar, A. (2017). Optimization of chitosan and cellulose acetate phthalate controlled delivery of methylprednisolone for treatment of inflammatory bowel disease. *Advanced Pharmaceutical Bulletin*, *7*(2), 203–213. doi:10.15171/apb.2017.025

Jha, D. K., Shah, D. S., Talele, S. R., & Amin, P. D. (2020). Correlation of two validated methods for the quantification of naringenin in its solid dispersion: HPLC and UV spectrophotometric methods. *SN Applied Sciences*, *2*(4). doi:10.1007/s42452-020-2536-3

Khunt, D. M., Mishra, A. D., & Shah, D. R. (2012). Formulation design & development of piroxicam emulgel. *Int J PharmTech Res*, *4*(3), 1332–1334.

Kral, Ö., Eralmaç, A., & Aydin, T. (2025). Development and Characterization of a Topical Herniarin Ointment from Tarragon. *ChemistrySelect*, *10*(33). doi:10.1002/slct.202500651

Kral, Ö., Hennep, G., Uslu, E. N., & Yücel, Ç. (2026). Formulation and Cytotoxicity Assessment of Methylprednisolone Aceponate Microemulsions for Topical Delivery. *Journal of Pharmaceutical Innovation*, *21*(1), 38.

Masood, S., Arshad, M. S., Khan, H. M. S., Begum, M. Y., & Khan, K. ur R. (2023). Encapsulation of Leptadenia pyrotechnica (Khip) Extract in Carbomer Based Emulgel for Its Enhanced Antioxidant Effects and Its In Vitro Evaluation. *Gels*, *9*(12). doi:10.3390/gels9120977

Mazurkeviciute, A., Matulyte, I., Ivaskiene, M., & Zilius, M. (2024). Modeling, the Optimization of the Composition of Emulgels with Ciclopirox Olamine, and Quality Assessment. *Polymers*, *16*(13). doi:10.3390/polym16131816

Mohite, P., Sule, S., Pawar, A., Alharbi, H. M., Maitra, S., Subramaniyan, V.,…Okoye, O. N. N. (2024). Development and characterization of a self-nano emulsifying drug delivery system (SNEDDS) for Ornidazole to improve solubility and oral bioavailability of BCS class II drugs. *Scientific Reports*, *14*(1). doi:10.1038/s41598-024-73760-7

Ochoa-Andrade, A., Parente, M. E., Jimenez-Kairuz, Á., Boinbaser, L., & Torregrosa, A. (2017). Study of the Influence of Formulation Variables in Bioadhesive Emulgels Using Response Surface Methodology. *AAPS PharmSciTech*, *18*(6), 2269–2278. doi:10.1208/s12249-016-0707-8

Park, Y. H., & Kim, H. J. (2021). Formulation and stability of horse oil-in-water emulsion by HLB system. *Food Science and Biotechnology*, *30*(7), 931–938. doi:10.1007/s10068-021-00934-8

Raeisi Estabragh, M. A., Sajadi Bami, M., Dehghannoudeh, G., Noudeh, Y. D., & Moghimipour, E. (2023). Cellulose derivatives and natural gums as gelling agents for preparation of emulgel-based dosage forms: A brief review. *International Journal of Biological Macromolecules*, *241*, 124538. doi:10.1016/j.ijbiomac.2023.124538

Rajesh, P., Gunasekaran, S., Gnanasambandan, T., & Seshadri, S. (2016). Experimental and theoretical study of ornidazole. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, *153*, 496–504. doi:10.1016/j.saa.2015.08.032

Said dos Santos, R., Rosseto, H. C., Bassi da Silva, J., Vecchi, C. F., Caetano, W., & Bruschi, M. L. (2021). The effect of carbomer 934P and different vegetable oils on physical stability, mechanical and rheological properties ofemulsion-based systems containing propolis. *Journal of Molecular Liquids*, *332*, 115856. doi:10.1016/j.molliq.2020.112969

Schmidts, T., Dobler, D., Guldan, A. C., Paulus, N., & Runkel, F. (2010). Multiple W/O/W emulsions—Using the required HLB for emulsifier evaluation. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, *372*(1–3), 48–54. doi:10.1016/j.colsurfa.2010.09.025

Shen, Y., Ling, X., Jiang, W., Du, S., Lu, Y., & Tu, J. (2015). Formulation and evaluation of Cyclosporin A emulgel for ocular delivery. *Drug Delivery*, *22*(7), 911–917. doi:10.3109/10717544.2013.861883

Siepmann, J., & Siepmann, F. (2008). Mathematical modeling of drug delivery. *International Journal of Pharmaceutics*, *364*(2), 328–343. doi:10.1016/j.ijpharm.2008.09.004

Yassin, G. E. (2014). Formulation and evaluation of optimized clotrimazole emulgel formulations. *British Journal of Pharmaceutical Research*, *4*(9), 1014–1030.

Zhang, Y., Huo, M., Zhou, J., Zou, A., Li, W., Yao, C., & Xie, S. (2010). DDSolver: An Add-In Program for Modeling and Comparison of Drug Dissolution Profiles. *The AAPS Journal*, *12*(3), 263–271. doi:10.1208/s12248-010-9185-1