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RESEARCH ARTICLE

Development of Innovative Microemulsion-based Gelatine Capsules of Ondansetron Hydrochloride

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SUMMARY

This research investigates the formulation and assessment of gelatine capsules containing a microemulsion of Ondansetron Hydrochloride (ODN) aimed at improving its bioavailability and therapeutic effectiveness. ODN, a commonly utilized antiemetic, is characterized by low oral bioavailability primarily due to significant first-pass metabolism. To mitigate this challenge, a microemulsion system was developed using a blend of oil, surfactant, and co-surfactant, which was subsequently encapsulated within gelatine capsules. The resulting capsules were analyzed for their drug - excipient interactions, drug release profile, etc., ensuring that the formulation possessed optimal characteristics for enhanced drug delivery. Findings indicated that the microemulsion-based gelatine capsules markedly enhanced the dissolution rate of ODN, indicating a viable strategy for addressing its bioavailability challenges. This study presents an innovative formulation approach that holds the potential to improve the therapeutic efficacy of ODN in clinical applications.

Key Words: *Microemulsion, ondansetron hydrochloride, gelatine capsule*

Ondansetron Hidroklorürün Yenilikçi Mikroemülsiyon Bazlı Jelatin Kapsüllerinin Geliştirilmesi

ÖZ

Bu araştırma, biyoyararlanımı ve terapötik etkinliği iyileştirmeyi amaçlayan Ondansetron Hidroklorürün (ODN) mikroemülsiyonu içeren jelatin kapsüllerin formülasyonu ve değerlendirilmesini incelemektedir. Yaygın olarak kullanılan bir antiemetik olan ODN, oral biyoyararlanımı düşük bir ilaçtır ve bu durum, büyük ölçüde belirgin ilk geçiş metabolizmasından kaynaklanmaktadır. Bu sorunu hafifletmek amacıyla, yağ, yüzey aktif madde ve yardımcı yüzey aktif madde karışımı kullanılarak bir mikroemülsiyon sistemi geliştirilmiş ve ardından bu sistem jelatin kapsüller içine yerleştirilmiştir. Elde edilen kapsüller, ilaç - yardımcı madde etkileşimleri, ilaç salım profili gibi özellikler açısından analiz edilerek, formülasyonun geliştirilmiş ilaç salınımı için optimum özelliklere sahip olması sağlanmıştır. Bulgular, mikroemülsiyon bazlı jelatin kapsüllerin ODN'nin çözünme hızını önemli ölçüde artırdığını ve bu durumun biyoyararlanım sorunlarını çözmeye yönelik uygulanabilir bir strateji olduğunu göstermiştir. Bu çalışma, ODN'nin klinik uygulamalardaki terapötik etkinliğini artırma potansiyeline sahip yenilikçi bir formülasyon yaklaşımı sunmaktadır.

Anahtar Kelimeler: *Mikroemülsiyon, ondansetron hidroklorür, jelatin kapsül*

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INTRODUCTION

Ondansetron hydrochloride (ODN) is a potent and selective antagonist of the serotonin 5-HT_3 receptor, renowned for its efficacy in preventing nausea and vomiting. The compound is characterized by the molecular formula $C_{18}H_{19}N_3O.HCl$ possesses a carbazole structure that contributes to its strong receptor binding affinity. ODN is predominantly employed in the prophylaxis and treatment of nausea and vomiting associated with chemotherapy, radiation therapy, and surgical anesthesia. Its mechanism of action involves the inhibition of serotonin at the 5-HT_3 receptors located in both the central nervous system and the gastrointestinal tract, thereby mitigating the emetic reflex. While generally well-tolerated, it may produce side effects such as headache, constipation, and dizziness. Given its critical role in clinical practice, ODN is an essential element of supportive care, particularly in oncology and perioperative settings, providing substantial relief from the debilitating effects of nausea and vomiting (Charyulu et al., 2010; Dhanashree et al., 2022; Gullapalli et al. 2010; Gundu et al., 2020).

The administration of ODN, despite its efficacy, faces several challenges that may limit its therapeutic effectiveness. A primary issue is its relatively low oral bioavailability, which is approximately 60 %. This limitation is largely due to significant first-pass metabolism occurring in the liver, involving cytochrome P450 enzymes such as CYP3A4 and CYP2D6. This metabolic pathway not only reduces the quantity of active drug that reaches systemic circulation but also contributes to variability in patient responses to the treatment. Additionally, the poor solubility of ODN poses a challenge for formulation scientists, potentially impacting the drug's absorption and overall bioavailability (Chitneni et al. 2011; Gosai et al. 2008; Jena et al. 2010; Manavalan et al. 2009).

The oral route of drug administration is widely accepted, accounting for approximately 50-60 % of the total available dosage forms for a given medication. The popularity of solid oral dosage forms can be attributed to several factors, including precise dosing, the potential for self-medication, the avoidance of pain, and, most significantly, the convenience they offer to patients (Breatnach et al., 2000; Fox et al.,1994).

The integration of ODN into a microemulsion system, followed by encapsulation in gelatine capsules, presents numerous advantages compared to traditional marketed formulations. The commonly available dosage forms include tablets, orally disintegrating tablets (ODTs), syrups, and films. Tablets, ODT, and syrups of ODN are well-established in the market, offering convenience and ease of administration for patients suffering from emesis. Films, on the other hand, provide a rapidly dissolving alternative that can be particularly beneficial for patients who experience difficulty swallowing tablets (Abruzzo et al., 2016; Ahmadi et al., 2015; Bansal et al., 2013; Canet al., 2013).

Microemulsions are noted for their thermodynamic stability, reduced droplet size, and superior solubilization capabilities, which can significantly enhance the bioavailability of poorly water-soluble compounds such as ODN. Encapsulation within gelatine capsules creates a protective matrix that mitigates drug degradation and facilitates a controlled, sustained release of the active ingredient. This innovative combination effectively overcomes the challenges associated with conventional oral formulations, which frequently experience variable absorption rates and significant first-pass metabolism, resulting in unpredictable therapeutic outcomes. By enhancing the solubility and dissolution kinetics of ODN, microemulsion-encapsulated gelatine capsules improve the drug's absorption and bioavailability, potentially leading to more effective and consistent antiemetic treatment (Anwar et al., 2020; Anwar et al., 2023).

During the formulation process, a microemulsion containing 4 mg of the drug was optimized to achieve a volume of approximately 0.15 mL (Dhanashree et al., 2024). This specific volume was essential for ensuring its accurate dosing, while also preserving the

stability and efficacy of the microemulsion. Consequently, a size 4 gelatine capsule was chosen, as it accommodates the microemulsion effectively, preventing leakage and maintaining the capsule's structural integrity. Size 4 capsules typically have a fill volume capacity of up to 0.21 mL, making them ideally suited for this formulation. This selection guarantees that each capsule delivers the precise 4 mg dose of ODN, thereby ensuring consistency in dosing and therapeutic outcomes, while also enhancing patient convenience and adherence.

MATERIALS AND METHODS

Materials

ODN was received as a gift sample from M/s ZIM Laboratories in Kalmeshwar, Nagpur, India. Lauroglycol-90, Acconon MC 82, and Transcutol-P were also provided as gift samples by ABITEC Corporation based in Columbus, USA. Size 4 capsules were sourced from Prasadh Pharma in Chennai, India. Additionally, various other compounds and analytical grade solvents were employed in the study.

Preparation of ODN-microemulsion-loaded gelatine capsules

The formulation of the ODN microemulsion was achieved through the water titration method. The water titration method is a simple and effective technique for preparing microemulsions, particularly for drugs with low aqueous solubility like ODN. This method involves gradual addition of water to a pre-mixed combination of oil, surfactant, and co-surfactant, leading to the spontaneous formation of a thermodynamically stable microemulsion. Here, lauroglycol-90, acconon MC 82, and transcutol-P were selected as oil, surfactant and co-surfactant. Subsequently, a specified amount of drug was incorporated into the microemulsion, which was then subjected to sonication for 30 minutes. After this process, acesulfame potassium, titanium dioxide, and levomenthol were introduced, followed by an additional sonication period of 10 minutes to finalize the microemulsion. It was found that 0.15mL of this microemulsion contains 4mg of ODN. Hence size 4 gelatine capsules were selected to encapsulate the prepared ODN-microemulsion and were filled manually (Basu et al., 2012; Dhanashree et al., 2024).

Physicochemical Characterization

Weight variation test

The prepared microemulsion formulation was loaded into gelatine shells, and 20 of them were selected for examination. Each capsule was individually weighed and recorded. The average weight of the capsules was calculated, ensuring that no more than two individual weights deviated from the average (Farmer et al., 2002).

Disintegration test

The disintegration test for capsules was performed using a tablet disintegration test apparatus. Six capsules were randomly selected and placed in a disintegration apparatus containing distilled water maintained at 37 ± 2 °C. A capsule was deemed to have successfully passed the test if no drug residue remained on the No. 10 mesh screen of the tubes (United States Pharmacopeial Convention, 2010).

Drug content test

The assessment of drug content was performed through UV spectroscopy at a wavelength of 247 nm. Initially, a capsule sample was selected and weighed. The contents were then dissolved in methanol to ensure complete extraction of the active pharmaceutical ingredient (API). The solution was subsequently filtered to remove any undissolved substances and diluted to a predetermined concentration. The absorbance was measured at 247 nm, and the concentration of ODN was determined using a calibration curve. The calibration curve exhibited excellent linearity, with an R^2 value of 0.999, confirming a strong correlation between absorbance and drug concentration. The drug content analysis was conducted in triplicates to ensure accuracy and reproducibility (Dhanashree et al., 2024).

Content uniformity test

The content uniformity test for capsules involved random selection of 10 individual capsules from a given batch. Each capsule underwent a separate assay to quantify the API present. The extraction of the API was carried out using methanol, followed by analysis of the resultant solution through UV spectroscopy. The ODN content in each capsule was then determined and compared against the claimed amount. The test was deemed successful if the API concentration in each capsule was within the range of 85-115% of the claimed amount, allowing for a maximum of one capsule to fall outside this range, with none showing a deviation beyond 75-125% (Bedford et al., 1980).

Differential scanning calorimetry (DSC)

The weighed portion of the capsule was sealed into a DSC pan. The sample was then heated at a controlled rate under a nitrogen atmosphere. The DSC system recorded thermal events such as melting and crystallization, which provided critical insights into the thermal stability and phase behavior of the components within the capsule (Chatham et al., 1992).

Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR)

After the capsule was opened, the microemulsion was poured directly onto the ATR crystal. The sample was then firmly pressed against the crystal to ensure adequate contact. The ATR-FTIR instrument subsequently acquired the infrared spectrum, which illustrated the characteristic molecular vibrations associated with the components. This approach provided valuable information regarding the chemical composition and possible interactions occurring within the formulation (Heussen et al., 2012).

***In vitro* dissolution test**

The *in vitro* dissolution studies of ODN microemulsion-loaded gelatine capsules were conducted using USP apparatus II (paddle). A dissolution medium of 500 mL 0.1 N HCl was employed. The capsules were positioned in the vessel and rotated at a speed of 50 rpm, with the temperature maintained at 37 °C ± 0.5 °C. To assess the in vitro drug release, 10 mL aliquots were extracted from each vessel at intervals of 5 min, 10 min, 20 min, and 30 min, which were subsequently filtered. The filtered samples were then analysed using a Shimadzu UV Spectrophotometer at a wavelength of 249 nm (United States Pharmacopeial Convention, 2010; U.S. Department of Health and Human Services, 2018; Newton et al., 1997).

RESULTS

Preparation of ODN-microemulsion-loaded gelatine capsules

The ODN microemulsion was successfully formulated using the water titration method, employing lauroglycol-90 as the oil phase, Acconon MC 82 as the surfactant, and Transcutol-P as the co-surfactant (Table 1). The optimized formulation was subjected to sonication to ensure homogeneity, followed by encapsulation in size 4 gelatine capsules, which were chosen based on their capacity to hold 0.15 mL of the microemulsion, equivalent to 4 mg of ODN.

Table 1. Composition of ODN Microemulsion-Loaded Gelatine Capsules

Components	Function
Ondansetron Hydrochloride	Active Pharmaceutical Ingredient
Lauroglycol-90	Oil Phase
Acconon MC82	Surfactant
Transcutol-P	Co-Surfactant
Acesulfame Potassium	Sweetener
Titanium Dioxide	Opacifier
Levomenthol	Cooling Agent

Physicochemical characterization

Weight variation test

The average weight of the capsule was found to be 216.4 mg ± 0.61mg. According to the pharmacopeial specifications, the acceptable limit for weight variation for capsules with specified weight range of 80 to 250 mg ± 7.5% from the mean. All the tested capsules were within this limit, confirming that the formulation complied with the required weight uniformity standards.

Disintegration test

The average disintegration time was approximately 3 min. All capsules disintegrated within the IP specified limit of 30 min for capsules, confirming that the formulation met the required standards. No residue was observed on the mesh, indicating complete disintegration.

Drug content test

The optimized formulation exhibited a drug content of 99.04%, which falls within the acceptable limits of ± 10% of the labeled claim for each capsule, which is established by the IP.

Content uniformity test

The average drug content was found to be 95.45% ± 1.82% with individual contents ranging from 92.75% to 98.5%. According to the IP specifications for content uniformity, not more than two capsules may deviate from the labeled claim by more than ± 10%, and none may deviate by more than ± 15%. In this analysis, all capsules met these criteria, confirming the uniformity and quality of the formulation.

Differential scanning calorimetry (DSC)

DSC was employed to evaluate the thermal properties of Ondansetron HCl and the microemulsion formulation. The thermogram of pure Ondansetron HCl exhibited an endothermic peak at 187.9°C, corresponding to its melting point. In the optimized microemulsion formulation, a broadening and slight shift in the peaks were observed. These changes are attributed to the encapsulation of the drug within the microemulsion system, which may alter the drug's physical state due to the formation of the microemulsion matrix. However, the absence of significant thermal events in the DSC thermogram indicates that the microemulsion system successfully maintained the stability of the drug during formulation. This confirms that the selected excipients did not induce any undesirable interactions that would compromise the integrity or stability of the drug (Ammar et al., 2018; Changizi et al., 2017).

Attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR)

ATR-FTIR was utilized to assess the compatibility of ODN with various excipients in the microemulsion formulation as shown in Figure 1. The analysis indicated that no new peaks were observed, and the disappearance of certain existing peaks suggested that there were no significant chemical interactions between the drug and the excipients. Furthermore, the characteristic peaks of ODN were still present in the infrared spectra of the formulation, confirming the stability of the drug within the microemulsion system. This stability indicates that ODN remains compatible with the selected excipients, which is crucial for ensuring the efficacy of the drug delivery system. The FTIR spectra were recorded using a SHIMADZU FTIR 8400 S spectrometer, with a scanning range from 4000 cm^{-1} to 400 cm^{-1} at a resolution of 4 cm^{-1}, providing a comprehensive understanding of the molecular interactions within the formulation.

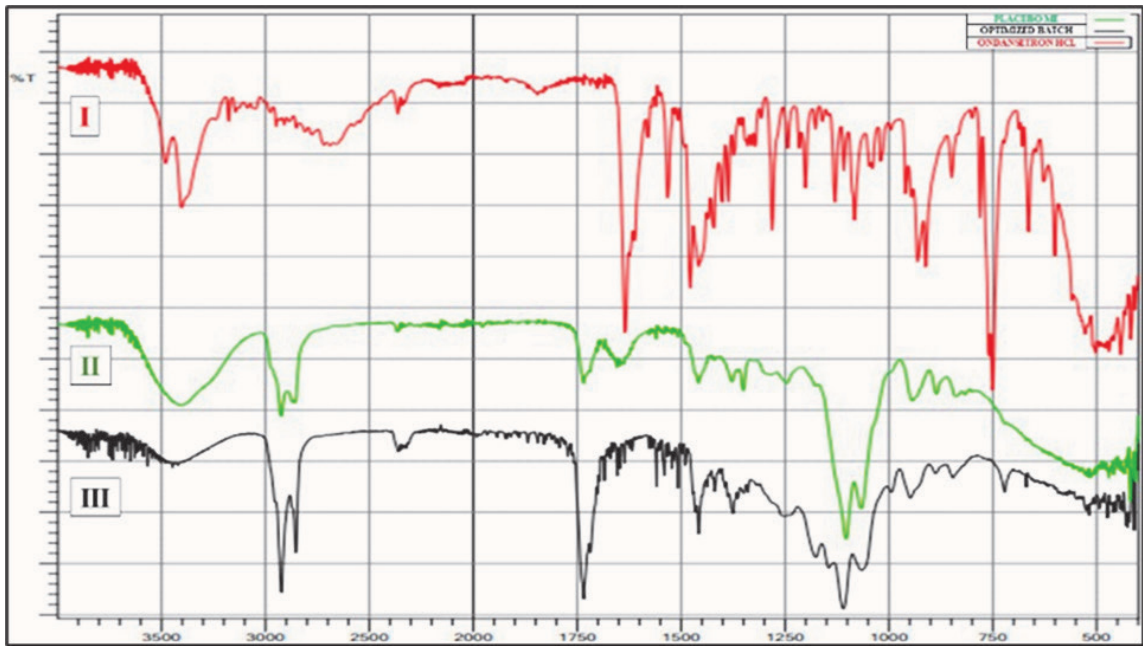

Figure 1. (I) Pure Ondansetron HCL is shown by the red peak (II) Placebo is represented by the green peak (III) Optimized batch of Microemulsion is shown by the black peak.

***In vitro* dissolution test**

The in vitro dissolution of the ODN microemulsion-loaded gelatine capsules (Optimized Batch B2) was significantly faster than the marketed tablets (Emeset-4 and Ondem-4). As shown in Figure 2, the capsules released approximately 110% of the drug within 5 min, while the marketed tablets released around 80-90%. By 30 min, the capsules reached nearly 120% release, compared to about 98-100% release for both marketed formulations. These results indicate that the microemulsion-loaded capsules offer superior dissolution and a faster release profile, suggesting better bioavailability and quicker therapeutic action compared to conventional tablets. To enhance the reproducibility and clarity of the results, Table 2 presents the numerical dissolution data along with the corresponding standard error (SE) values for each formulation across all time points.

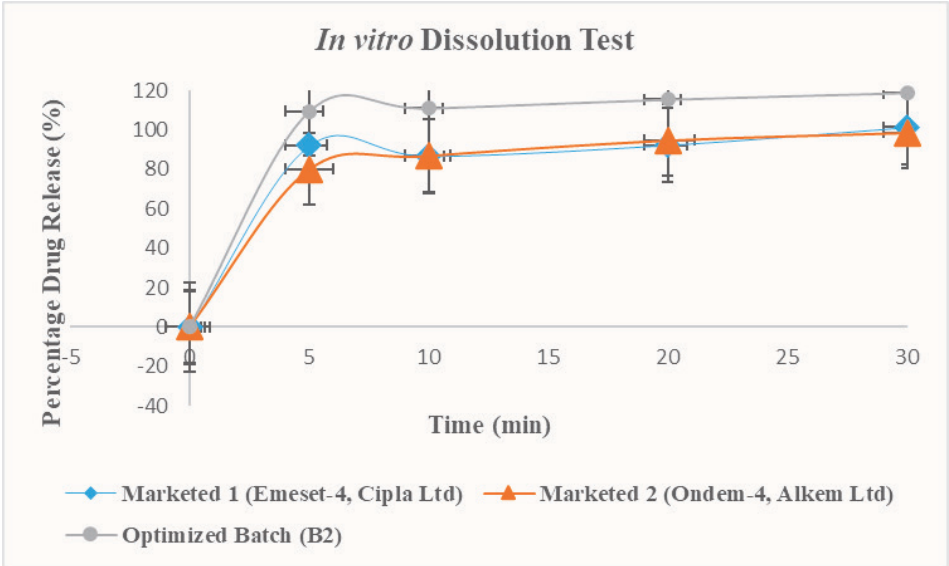

Figure 2. *In vitro* dissolution profile of ODN microemulsion-loaded gelatin capsules compared to marketed formulations.

Table 2. The dissolution data for the mentioned formulations includes the mean and standard error (SE) values.

Time (min)	Marketed 1 (Emeset-4, Cipla Ltd)	Marketed 2 (Ondem-4, Alkem Ltd)	Optimized Batch (B2)
0	0 ± 0	0 ± 0	0 ± 0
5	92.2 ± 0.61	80.18 ± 0.86	109.5 ± 0.49
10	86.8 ± 0.73	87 ± 1.02	111 ± 0.57
20	92.36 ± 0.65	94.84 ± 0.90	115.5 ± 0.61
30	101.41 ± 0.82	98.72 ± 1.14	118.9 ± 0.53

CONCLUSION

The study successfully demonstrated that the innovative formulation not only improved the dissolution rate of ODN but also ensured compatibility between the drug and the excipients used in the microemulsion system, as evidenced by the ATR-FTIR analysis which indicated no significant chemical interactions. The disintegration tests confirmed that the capsules met the required standards, with an average disintegration time of approximately 3 min, well within the specified limit of 30 min. Furthermore, the drug content analysis showed a high percentage of 99.04%, indicating that the formulation maintained its integrity and efficacy. The findings of this research highlight the potential of microemulsion systems in overcoming the challenges associated with the low oral bioavailability of ODN, primarily due to first-pass metabolism. By utilizing a blend of oil, surfactant, and cosurfactant, the study provides a viable strategy for improving the therapeutic effectiveness of ODN in clinical settings. Overall, this innovative approach not only enhances the delivery of ODN but also opens avenues for further research into similar formulations for other poorly soluble drugs, thereby contributing to the advancement of pharmaceutical sciences and improving patient outcomes.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION STATEMENT

Performed experiments (Nair S.), mentor, hypothesis, design, manuscript preparation, framed discussion of the manuscript (Sanap D.; Jadhav K.), writing manuscript, literature research preparing figures, writing manuscript (Nair S.).

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