

Formulation and Evaluation of Metronidazole Liposomal Gel for Topical and Mucosal Delivery

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ABSTRACT

Background: Metronidazole is a commonly prescribed nitroimidazole antibiotic for Bacterial Vaginosis (BV), rosacea, periodontal infections, and other anaerobic or protozoal infections. However, conventional topical dosage forms suffer from low skin penetration, short duration of action, and reduced therapeutic efficiency, negatively impacting treatment efficacy and patient adherence. Liposomal encapsulation incorporated into a gel base offers a promising strategy to overcome these limitations. **Materials and Methods:** Metronidazole-loaded liposomes were prepared by the thin-film hydration method using phosphatidylcholine and cholesterol in a 2:1 (w/w) ratio and subsequently incorporated into a Carbopol® 940 gel base. The optimized liposomal gel was characterized for vesicle size, Polydispersity Index (PDI), zeta potential, Entrapment Efficiency (EE), pH, viscosity, spreadability, and drug content. *In vitro* drug release was evaluated using the Franz diffusion cell method, and stability was assessed under refrigerated, room temperature, and accelerated storage conditions for 90 days. **Results:** The optimized liposomes exhibited a mean vesicle size of 285.4 ± 12.3 nm, PDI of 0.32 ± 0.05 , zeta potential of -32.6 ± 2.8 mV, and EE of $68.4 \pm 3.2\%$. The liposomal gel demonstrated satisfactory physicochemical properties: pH 6.2 ± 0.2 , viscosity $4,850 \pm 245$ cps, spreadability 11.4 ± 0.6 g-cm/sec, and drug content uniformity of $98.6 \pm 1.4\%$. *In vitro* release showed 93.6% cumulative drug release over 24 hr, following anomalous (non-Fickian) transport behavior per the Korsmeyer-Peppas model ($n=0.512$). The formulation remained stable under refrigerated and room temperature conditions, with notable degradation observed only under accelerated storage. **Conclusion:** The metronidazole liposomal gel demonstrated favorable physicochemical characteristics, sustained drug release, and adequate stability, supporting its potential as a once-daily topical and mucosal drug delivery system for conditions such as BV, rosacea, and periodontal infections.

Keywords: Metronidazole, Liposomal gel, Thin-film hydration; Carbopol® 940, Sustained release, Topical delivery.

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INTRODUCTION

Metronidazole [1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole] is a synthetic nitroimidazole that has strong activity against anaerobic bacteria and protozoa. It belongs to the Biopharmaceutics Classification System (BCS) Class I of drugs which are highly soluble and highly permeable. The antimicrobial activity is due to the reduction of the nitro group in anaerobic microorganisms, which produces toxic radicals that cause microbial DNA damage. For this reason, it is extensively used to treat bacterial vaginosis, rosacea, periodontal infections, anaerobic bacterial infections, trichomoniasis, and amebiasis

(Bradshaw and Sobel, 2020; Thiboutot and Del Rosso, 2020; Imran *et al.*, 2024).

Although clinically useful, conventional topical metronidazole preparations like creams, gels and ointments have significant drawbacks. The stratum corneum creates a barrier to permeation of drugs, reducing the local delivery and therapeutic effect (Shah and Patel, 2023). Furthermore, numerous formulations have short half-life, high frequency of dosage, and high systemic bioavailability, which could be a source of adverse reactions such as nausea, metallic taste, and neurotoxicity (Abutaleb and Seleem, 2021). These constraints can impact patients' adherence and poorer clinical outcomes.

In this regard liposomes are an attractive option to solve these issues. These are vesicular systems that can be used to enclose drugs in the phospholipid bilayers and improve penetration through skin and mucosal barriers (Bozzuto and Molinari, 2015; Sercombe *et al.*, 2015). They are also controlled-release, biocompatible, and give less systemic exposure (Antimisariis *et*



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al., 2021). Handling of the formulation and formulation viscosity is improved by incorporation of liposomes into gel base and the time of residence at the site of application is improved (Sguizzato and Cortesi, 2023).

Liposomal and related vesicular systems have been previously shown to enable efficient delivery of metronidazole topically, vaginally and to the periodontal tissues (Shah *et al.*, 2021; Sharif *et al.*, 2021; Mahmoud *et al.*, 2023). The aim of this study was to prepare metronidazole liposomes by thin-film hydration technique, formulate the prepared liposomes in Carbopol® 940 gel, characterize the formulation, *in vitro* release study and stability of this formulation under various storage conditions.

MATERIALS AND METHODS

Materials

Metronidazole pharmaceutical grade, phosphatidylcholine (lecithin), cholesterol, Carbopol® 940, chloroform, methanol, potassium dihydrogen phosphate, sodium hydroxide, triethanolamine, methyl paraben, propyl paraben, and other routine reagents were used as received from standard suppliers. Distilled water was freshly prepared in the laboratory

Preparation of Phosphate buffer

Phosphate buffer (pH 6.8) was prepared as per the Pharmacopoeial guidelines using potassium dihydrogen phosphate in distilled water and adjusting the pH with 0.1 N NaOH. Liposomes were hydrated, diluted and subjected to *in vitro* release studies in the buffer.

Preparation of Metronidazole Liposomes

Metronidazole liposomes were prepared by the thin-film hydration method. The dispersion components (100 mL) were dissolved in chloroform: methanol (2:1) in a round-bottom flask using the following amounts: metronidazole (1.0 g), phosphatidylcholine (3.0 g) and cholesterol (1.5 g). The solvent was evaporated in a rotary vacuum evaporator at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ under reduced pressure to get a thin lipid film. The film was further dried and then hydrated with preheated phosphate buffer, pH 6.8, at 50°C and rotated for the preparation of multilamellar vesicles. The vesicles were then sonicated to break the vesicles down in size and stored in amber glass vials at $4^{\circ}\text{C} \pm 2^{\circ}\text{C}$.

Preparation of liposomal gel

The swelling time for Carbopol® 940 was set as the time required for their complete hydration in distilled water. Preservatives (methyl paraben and propyl paraben) and pH adjusted with triethanolamine were added. The liposomal dispersion of metronidazole was added to the gel base without applying any shaking force to break the vesicles and distilled water was used to prepare the final formulation. The homogenized gel was left to settle out to remove air bubbles from it.

Characterization of liposomes

Dynamic light scattering and laser Doppler velocimetry were used to determine vesicle size, polydispersity index and zeta potential. The entrapment efficiency was calculated by ultracentrifugation and further analyzed by UV spectrophotometric analysis at 320 nm. The equations used were standard equations for calculating the drug loading.

Characterization of Liposomal Gel

The gel was assessed in terms of appearance, pH, viscosity, spreadability, extrudability, uniformity of drug content and phase stability. The spreadability was determined by the standard slide method and viscosity was calculated by a Brookfield viscometer. A weighed portion of gel was dissolved in phosphate buffer and its absorbance at 320 nm was measured to determine the drug content.

Morphological analysis

Shape, surface features and integrity of the vesicles were investigated by transmission electron microscopy and scanning electron microscopy.

In vitro Drug Release

Drug release was determined by Franz diffusion cell, using phosphate buffer pH 6.8 as receptor and cellulose acetate as membrane. Samples were taken at fixed times and the concentration of the solution measured spectrophotometrically at 320 nm.

Release kinetics

The release data were modeled using four kinetic models, which were zero-order, first-order, Higuchi and Korsmeyer-Peppas. The highest correlation coefficient was chosen as the best fit model.

Vesicle count

Using a light microscope, the number of vesicles in the field was counted in a Neubauer hemocytometer.

Stability studies

The drugs were subjected to stability testing under the ICH Q1A(R2) conditions for 90 days at refrigerated, room temperature and accelerated conditions. Various samples were tested for vesicle size, PDI, zeta potential, pH, viscosity, drug leakage, drug content, and appearance.

Statistical analysis

All experiments were done in triplicate and the results are presented as Mean $\pm$ SD. Data were analyzed by using standard statistical software, using ANOVA-based methods, and taking significance at $p < 0.05$.

RESULTS AND DISCUSSION

Liposome characterization

The nanoscale properties of the liposomes containing metronidazole were desirable by the thin-film hydration technique. The average vesicle size of 285.4 ± 12.3 nm is within a beneficial range for topical application, where vesicles facilitate prolonged local drug release without easy aggregation (Has and Sunthar, 2020). The PDI value of 0.32 ± 0.05 suggests a moderately uniform size distribution, suitable for topical or mucosal vesicular formulations. The zeta potential of -32.6 ± 2.8 mV indicates good electrostatic repulsion between particles, leading to colloidal stability (Figure 1) (Nsairat *et al.*, 2022). An Entrapment Efficiency of $68.4 \pm 3.2\%$ was obtained, reflecting adequate incorporation of metronidazole within the vesicular system, likely due to the amphiphilic properties of the drug and the membrane-stabilizing effect of cholesterol on the phospholipid bilayer (Lombardo and Kiselev, 2022). The drug loading was $15.2 \pm 1.1\%$, which is acceptable for achieving a balance between drug loading and vesicle stability (Nair *et al.*, 2021). All physicochemical parameters of the optimized liposomes are summarized in Table 1.

Liposomal gel properties

The liposomal gel exhibited a pale yellow, translucent, and homogeneous appearance with no visible aggregation. The pH of 6.2 ± 0.2 is near-neutral and compatible with mucosal and skin surfaces, which will minimize irritation at the site of application. The viscosity of $4,850 \pm 245$ cps facilitates easy application and reduces run-off from the application site (Anwer *et al.*, 2020). Spreadability of 11.4 ± 0.6 g-cm/sec and extrudability of $92.5 \pm 2.1\%$ confirmed patient-friendly application characteristics. The uniformity of drug content was $98.6 \pm 1.4\%$, which is indicative of uniform distribution of the drug throughout the gel matrix, meeting the pharmacopoeial requirement of 85-115%

(Hassan *et al.*, 2022). The centrifugation test showed no phase separation, confirming the physical stability of the gel system. All physicochemical properties of the liposomal gel are summarized in Table 2.

Morphology

TEM images indicated that there were no apparent structural defects and spherical vesicles with clear bilayer boundaries (Figure 2). SEM images also revealed smooth, spherical vesicles with well-separated structures, corroborating the TEM findings (Figure 3). These results together demonstrate that the formulation process resulted in maintenance of liposome integrity, confirming the suitability of the formulation for topical and mucosal delivery (Mirchandani *et al.*, 2021).

In vitro release

The formulation delivered controlled and sustained release of metronidazole over 24 hr. An initial moderate release of $12.4 \pm 1.2\%$ was observed at 0.5 hr, indicating minimal burst effect, which is desirable to avoid dose dumping at the site of application. Cumulative release progressively increased to $52.3 \pm 2.5\%$ at 4 hr and reached $93.6 \pm 1.9\%$ at 24 hr. The time-dependent cumulative drug release data are presented in Table 3 and illustrated graphically in Figure 4. The sustained release effect is attributed to the synergistic diffusion barrier provided by the liposomal phospholipid bilayers and the polymeric gel network of Carbopol® 940, which together retard drug diffusion and prolong residence time at the application site (Sguizzato and Cortesi, 2023).

Release kinetics

To understand the mechanism governing the sustained release profile observed in Table 3 and Figure 4, the cumulative release data were fitted to four mathematical kinetic models: zero-order, first-order, Higuchi, and Korsmeyer-Peppas (Table 4). The

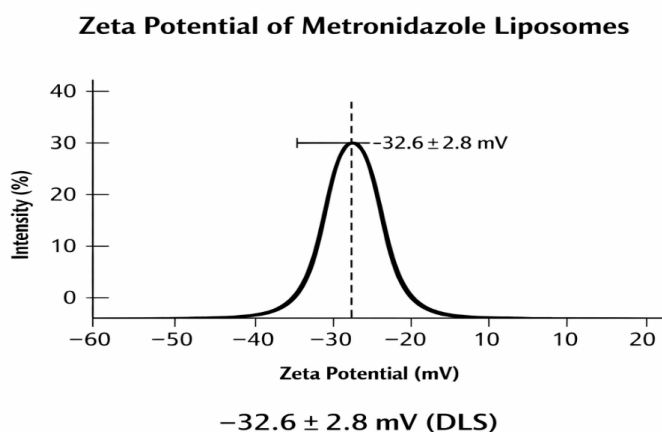


Figure 1: Zeta potential distribution of metronidazole-loaded liposomes measured by Dynamic Light Scattering (DLS), showing a mean zeta potential of -32.6 ± 2.8 mV, indicative of good colloidal stability.

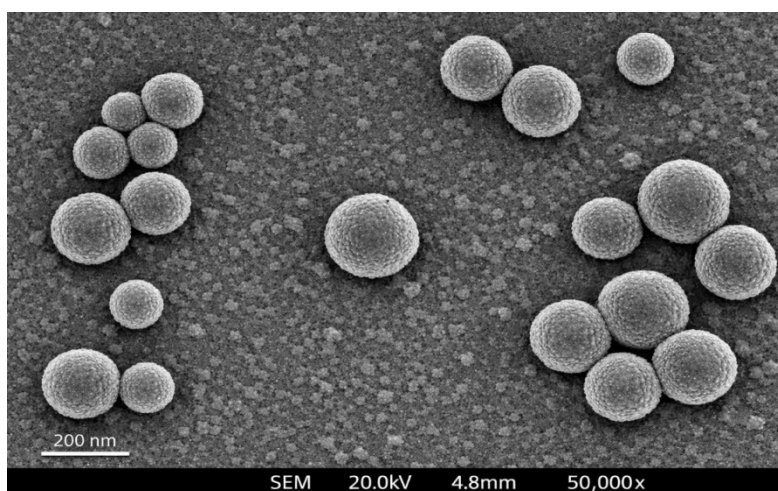


Figure 2: Transmission Electron Micrograph (TEM) of metronidazole liposomal gel showing spherical, well-defined vesicles embedded within the gel matrix. Vesicles display intact bilayer boundaries with no apparent structural defects, confirming formulation integrity.

Table 1: Liposome characterization.

Parameter	Result
Vesicle size	285.4±12.3 nm
Polydispersity index	0.32±0.05
Zeta potential	-32.6±2.8 mV
Entrapment efficiency	68.4±3.2%
Drug loading	15.2±1.1%

Table 2: Liposomal gel properties.

Parameter	Result
Appearance	Pale yellow, translucent, homogeneous
pH	6.2±0.2
Viscosity	4,850±245 cps
Spreadability	11.4±0.6 g·cm/sec
Extrudability	92.5±2.1%
Drug content	98.6±1.4%
Centrifugation test	No phase separation

Table 3: *In vitro* release profile.

Time (hr)	Cumulative drug release (%)
0.5	12.4±1.2
1	22.6±1.8
2	35.8±2.1
4	52.3±2.5
6	64.7±2.8
8	74.2±2.6
12	84.5±2.3
24	93.6±1.9

Table 4: Kinetic modeling.

Model	R ²	Constant
Zero-order	0.8952	k ₀ =3.82%/hr
First-order	0.9764	k ₁ =0.128 hr ⁻¹
Higuchi	0.9918	k _H =19.26%/√hr
Korsmeyer-Peppas	0.9941	n=0.512

zero-order model gave the poorest fit ($R^2=0.8952$), indicating that drug release was not concentration-independent. The first-order model showed a moderate fit ($R^2=0.9764$), suggesting partial concentration-dependent release. The Higuchi model gave a good fit ($R^2=0.9918$), indicating that diffusion through the gel matrix played a significant role in drug release (Costa and Lobo, 2001). The Korsmeyer-Peppas model gave the best fit with $R^2=0.9941$, and the release exponent $n=0.512$ indicates anomalous (non-Fickian) transport, implying that both diffusion and matrix relaxation/erosion contributed to the overall release mechanism (Bruschi, 2020). This combined mechanism is desirable for topical products as it ensures prolonged drug activity at the application site. The release profile shown in Figure 4 was fitted to four mathematical

models to determine the drug release mechanism. The kinetic modeling results are summarized in Table 4.

Vesicle count

The vesicle count was $4.82 \times 10^{11} \pm 0.34 \times 10^{11}$ vesicles per mL. This high vesicle population is due to sonication which increases the number of vesicles and makes them smaller in size from the initial multilamellar system (Ramezani *et al.*, 2020). Increased vesicles may help with the delivery and distribution of drugs and a more consistent delivery.

Stability

The stability of the metronidazole liposomal gel was evaluated over 90 days under three storage conditions as per ICH Q1A(R2)

Table 5: Stability results.

Parameter	Day 0	4°C, 90 days	25°C/60% RH, 90 days	40°C/75% RH, 90 days
Vesicle size (nm)	285.4±12.3	297.8±14.1	301.3±15.6	333.6±18.2
PDI	0.32±0.05	0.35±0.06	0.38±0.07	0.48±0.09
Zeta potential (mV)	-32.6±2.8	-31.2±3.1	-29.4±3.4	-24.8±4.2
Drug leakage (%)	0	2.8±0.6	4.2±0.8	12.8±1.6
pH	6.2±0.2	6.1±0.2	6.0±0.2	5.6±0.3
Viscosity (cps)	4,850±245	4,780±268	4,740±282	4,320±310
Drug content (%)	98.6±1.4	97.3±1.6	95.8±1.9	86.2±2.4

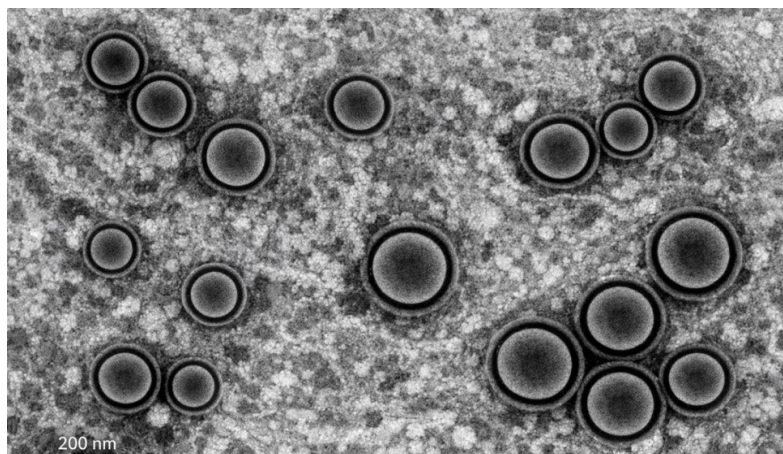


Figure 3: Scanning Electron Micrograph (SEM) of metronidazole liposomes showing smooth, spherical morphology with uniform size distribution and well-separated vesicular structures, consistent with the dynamic light scattering size data (285.4±12.3 nm).

In Vitro Drug Release Profile of Metronidazole Liposomal Gel

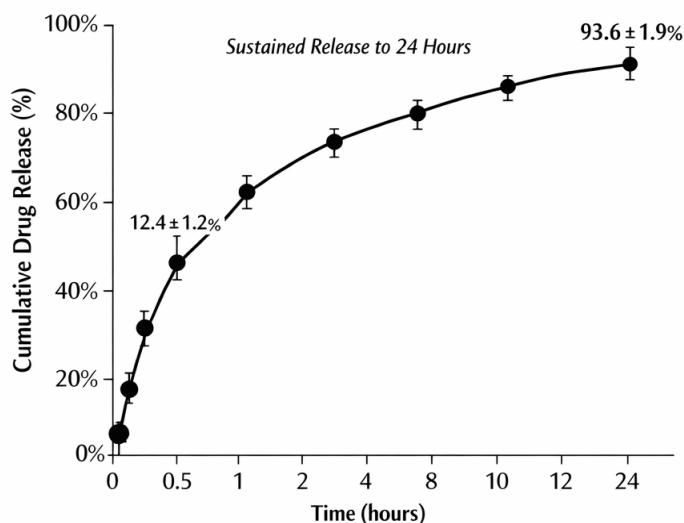


Figure 4: *In vitro* cumulative drug release profile of metronidazole liposomal gel through cellulose acetate membrane using Franz diffusion cell in phosphate buffer (pH 6.8) at 37±0.5°C over 24 hr. Data represented as mean±SD (n=3).

guidelines: refrigerated (4°C), room temperature (25°C/60% RH), and accelerated (40°C/75% RH). The formulation did not show any significant change in vesicle size, PDI, zeta potential, pH, viscosity, drug leakage, or drug content under refrigerated and room temperature conditions throughout the study period (Yusuf *et al.*, 2022). The complete stability data across all storage conditions and time points are summarized in Table 5. However, under accelerated storage conditions (40°C/75% RH), a notable increase in vesicle size from 285.4±12.3 nm to 333.6±18.2 nm, increase in PDI from 0.32±0.05 to 0.48±0.09, reduction in zeta potential from -32.6±2.8 mV to -24.8±4.2 mV, and drug leakage of 12.8±1.6% were observed, indicating vesicle aggregation, reduced colloidal stability, and membrane disruption at elevated temperature and humidity (Patel *et al.*, 2020). The drug content decreased significantly to 86.2±2.4% under accelerated conditions, likely due to drug degradation and leakage from the liposomal membrane at elevated temperatures. The viscosity reduction from 4,850±245 cps to 4,320±310 cps under accelerated conditions suggests partial gel network disruption. These findings collectively indicate that refrigerated storage at 4°C is the preferred storage condition, while room temperature storage is acceptable for short-term use (Kaur *et al.*, 2020).

CONCLUSION

The study successfully developed a metronidazole liposomal gel with favorable physicochemical properties, effective drug entrapment, and sustained *in vitro* release. The formulation remained physically stable under refrigerated and room temperature conditions over 90 days, although accelerated storage caused measurable degradation. The results support the potential of this liposomal gel as a promising once-daily delivery system for topical and mucosal use in conditions such as bacterial vaginosis, rosacea, and periodontal infections.

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ABBREVIATIONS

BV: Bacterial Vaginosis; **PDI:** Polydispersity Index; **EE:** Entrapment Efficiency; **TEM:** Transmission Electron Microscopy; **SEM:** Scanning Electron Microscopy; **ICH:** International Council for Harmonisation; **DLS:** Dynamic Light Scattering; **RH:** Relative Humidity; **SD:** Standard Deviation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Ladi Alik Kumar: Conceptualization, methodology, experimental work, data collection, writing - original draft. **Gurudutta Pattnaik:** Supervision, project administration, writing - review and editing. **Himanshu Bhusan Samal:** Methodology, characterization studies, data analysis. **Naga Jogayya K:** *In vitro* release studies, release kinetics analysis, data interpretation. **Chandra Sekhar Patro:** Stability studies design and execution, writing - review and editing. **Gopal Krishna Padhy:** Liposomal gel preparation, physicochemical characterization, validation.

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