Advances in Bioresearch
Adv. Biores., Vol 17 (6) June 2026: 331-340

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL: http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.17.6.331340

Advances in Bioresearch

ORIGINAL ARTICLE

Formulation, Development and Evaluation of Lyotropic Liquid Crystal Gel of Ornidazole

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ABSTRACT
To formulate, develop, and evaluate a liquid crystalline system for the effective delivery of ornidazole, ensuring enhanced its controlled drug release for prolong period of time. Lipid and stabilizer concentrations as well as stabilizer type were among the variables under investigation. The polarized light microscopic approach was used to identify the LC formation. Variables' influence on formulation properties, including drug release, rheological behavior, and particle size, were assessed. The optimized Batch-2 (OZ-LLC gel) was evaluated for various parameters, showing a particle size of 201.3 nm, an entrapment efficiency of 88.70%, and a zeta potential of -46.90 mV. The formulation exhibited a polydispersity index (PDI) of 0.318, indicating uniform particle distribution. Additionally, the drug release profile demonstrated 99.408% release over a period of 12 hours. According to the drug release characteristics, OZ showed a most consistent release among all formulations, and the formulation made with 1.5 percent of glyceryl monostearate and 0.5 percent of Pluronic F127 a had overall best dissolving efficiency. The developed formulations had particle sizes ranging from 201.3 to 290.7 nm, according to the results. According to the drug release characteristics, OZ had a consistent release throughout all formulations, and the formulation made with 1.5 percent glyceryl monostearate and 0.5 percent Pluronic F127 had overall maximum efficiency.
Keywords: *Controlled release, Glyceryl Monostearate, OZ-LLC, Ornidazole, OZ-LLC , Pluronic F-127*

Received 18.04.2026 Revised 21.05.2026 Accepted 26.06.2026

How to cite this article:
Rohan B. S, Mayuri P, Laxmikant B. Formulation, Development and Evaluation of Lyotropic Liquid Crystal Gel of Ornidazole. Adv. Biores. Vol 17 [6] June 2026. 331-340.

INTRODUCTION

When amphiphilic molecules like lipids or surfactants mix with a polar solvent (usually water), a self-assembling structure known as a lyotropic liquid crystal system is created. These systems provide special benefits for uses such as drug administration because they combine the characteristics of liquids and crystalline solids (1). Lyotropic liquid crystals (LLCs) form when Self-assembling amphiphilic molecules in water, creating structured nanostructures to reduce free energy. Their organization depends on factors like amphiphile concentration, water content, temperature, and ionic strength. The lamellar phase (Lα), with alternating lipid and water layers, is low in viscosity and commonly used in topical and oral drug formulations (2). The hexagonal phase consists of hexagonally packed cylindrical micelles, offering two-dimensional periodicity and moderate viscosity, ideal for sustained release of hydrophobic drugs (3). BI continuous cubic phases possess three-dimensional periodicity with interlinked lipid and water channels, forming highly viscous, isotropic gels suitable for controlled drug release (4–6) The reverse hexagonal phase, composed of water-filled cylinders encased in hydrophobic lipid tails, forms with minimal water and is used for long-acting drug depot formulations (7).

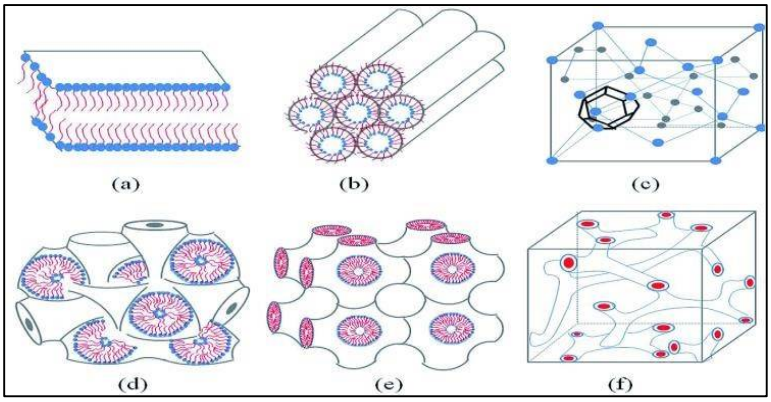


Fig1: Lyotropic liquid crystalline phases, which are frequent in neutral lipid/water networks, are depicted schematically (a) Lamellar phase (b) Reverse hexagonal phase (c) Reversed micellar cubic (Fd3m) (d) Reversed BI continuous cubic (Im3m) (e) Reversed BI continuous cubic (Pn3m) (f) Reversed BI continuous cubic (Ia3d).

Advantages and Preparation of LLC Systems:

Lyotropic liquid crystals provide efficient drug loading and prolonged release due to their unique internal structures such as lamellar, cubic, and hexagonal phases. Composed of safe, biodegradable GRAS lipids like glyceryl monostearate, these systems are both effective and biocompatible for drug delivery (5,7).

Preparation Methods and applications:

LC systems are created using either top-down or bottom-up methodologies. The top-down approach produces a viscous bulk phase of lipids and stabilizers, which is subsequently dispersed into water via high-energy procedures such as homogenization or sonication. It keeps structure while requiring a large amount of time and work (8,9). The bottom-up technique creates cubosomes through controlled self-assembly of components under exact temperature and water control, utilizing less energy and producing little fragmentation (10,11) It is faster and avoids the use of organic solvents but may result in milky white (12,13). LLC systems are commonly employed in formulations because to their various features and adaptability. Oral medication administration improves the solubility and bioavailability of numerous weakly water-soluble drugs (14). Lipid-based formulations enhance drugs oral bioavailability by integrating it into lipid suspensions, emulsions, and gels. This improves the regulated and sustained release qualities of the medication (15,16). Topical and transdermal medication administration improves drug absorption via the skin. Topical products are easy to apply to the skin and have non-invasive, painless qualities. Certain properties of the reversed cubic and hexagonal phases allow them to be appropriate for topical medication administration (17,18). LLC systems are primarily employed in parenteral medication delivery to provide prolonged drug release. Bicontinuous cubic phases cause sustained release by forming injectable depots. These phases also have small particle sizes, biocompatibility, thermodynamic stability, along with a low viscosity. Cubosomes and hexosomes are appropriate for intravenous injections (19).

Drug Profile

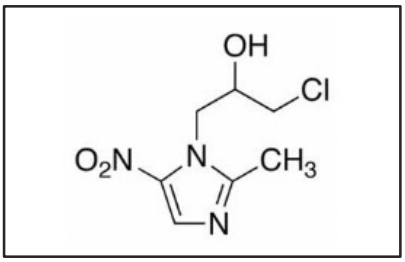


Fig 2: Structure of Ornidazole

Ornidazole is a nitroimidazole derivative with the chemical name 1-chloro-3-(2-methyl-5-nitro1H-imidazol-1-yl)propan-2-ol. It possesses antiprotozoal, antibacterial, antiamoebic, and anti-infective effects. Ornidazole acts by interacting with microbial DNA, which inhibits protein synthesis and finally causes cell death. It is used to treat conditions such as hepatic and intestinal amoebiasis, giardiasis, trichomoniasis, and bacterial vaginosis. Additionally, it is utilized to cure and prevent anaerobic infections, especially in dental and gastrointestinal treatments (20,21).

MATERIAL AND METHODS

The OZ-LLC gel was formulated using quality ingredients from reliable sources. Ornidazole, the active drug, was provided by ENDOC Pharma, while Glyceryl Monostearate (GMS) from Gattefossé acted as the amphiphilic lipid for LLC formation. Ethanol from Abitec Corporation served as a solvent, aiding in the uniform mixing of components (22). Pluronic F-127 (BASF) acted as a thermoresponsive polymer, promoting gelation, sustained drug release, and improved mucosal retention. Characterization was performed using Shimadzu DSC (DSC 60 Plus), Perkin Elmer FTIR (Spectrum Two), and Lab India UV-Vis spectrophotometer (UV 3200). Key instruments for formulation and analysis included the Orchid probe sonicator, REMI microcentrifuge, Horiba particle size and zeta potential analyzers, Franz diffusion cells, and a Brookfield viscometer.

Liquid crystal formulation by magnetic Stirring method

OZ-loaded lyotropic liquid crystal (LLC) formulations were prepared by dissolving OZ in ethanol with Glyceryl Monostearate (GMS) as the lipid phase, followed by adding a water-based solution of Pluronic F-127 (PF-127) as a stabilizer. The mixture was heated to 50 °C and sonicated (POWER-SONIC 505, 500 W). The study evaluated the effects of varying concentrations of GMS, PF-127, and water. Sixteen formulations (T1–T16) were prepared with increasing amounts of GMS (50–2000 mg) and PF-127 (50–1000 mg), with water added q.s. to each batch.

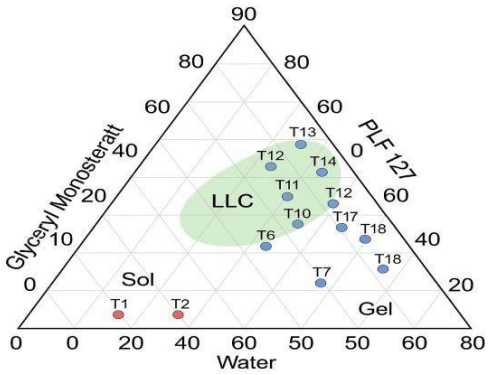


Fig 3: Ternary Phase Diagram

The moderate-to-high GMS and PLF-127 seen in T4 to T12 batches allow amphiphilic molecules to self-assemble into lyotropic liquid crystalline (LLC) structures such lamellar or cubic phases.

There is still enough water present for mobility and phase organization.

Preformulation study:

To help with the creation of dosage forms, preformulation experiments evaluated the physicochemical characteristics of ornidazole. The medicine and excipients were heated progressively using the capillary tube method to determine the melting point, and the average value was calculated from three trials (23). To assess the solubility of ornidazole, excess medication was mixed with phosphate buffer (pH 6.8), methanol, and ethanol, and then vortexed for ten minutes. Calibration curves were used to determine the results. To detect thermal changes and possible medication interactions, 5 mg samples were heated from 25°C to 300°C at a rate of 10°C per minute for DSC analysis (24). To assess for physical changes, ornidazole was combined in different ratios with Glyceryl Monostearate and Pluronic F-127 and stored for 14 days at room temperature and under accelerated environments. (25,26).

Fourier transfer infrared Spectroscopy:

To evaluate possible interactions between Ornidazole and excipients, AT-IR spectroscopy was employed. Using a Perkin Elmer device, IR spectra of the formulation, physical combination, and pure drug were captured by scanning 1–2 mg samples throughout 550–4000 cm^{-1}. Analysis of spectral alterations was done with an emphasis on distinctive functional group peaks(27).

Drug Content analysis

The drug content of each manufactured batch of Liquid Crystal Gel was examined. Dissolve the 0.1 gm Ornidazole Liquid Crystal Gel in a sufficient amount of phosphate buffer with a pH of 6.8. The final volume was then obtained by pipetting out 1 g of the gel and diluting it with 10 ml of pH 6.8 methanol. The mixture was then filtered. A UV spectrophotometer was used to measure the filtrate's UV absorbance at 311 nm.(28).

Entrapment Efficiency:
To extract the unentrapped drug, an LC gel loaded with ornidazole was ultracentrifuged for 20 minutes at 8000 rpm. After filtering and diluting with methanol, the supernatant was subjected to UV analysis. Using the conventional formula, entrapment efficiency was determined (29);

$$\text{Entrapment efficiency\%} = \frac{\text{Total amount of drug added - Amount of drug in supernatant} \times 100\%}{\text{Total amount of drug added}}$$

Determination of particle size and Zeta potential Determination:
The particle size, PDI, and zeta potential of the Ornidazole LC formulation were evaluated using a Zetasizer Nano ZS (Malvern, UK). Readings were made at 25 °C and a 90° angle after 1 mL of the formulation was diluted with 10 mL of distilled water and stirred for 1 minute (30). Zeta potential was determined using the same apparatus and laser diffraction following the agitation and similar dilution of 1 mg of the formulation (31).

Viscosity Study
To evaluate OZ-LLC gel's thermoresponsive behavior, its viscosity was evaluated at 4°C and 37°C. The gel altered to a higher viscosity suitable for prolonged release at 37°C, while it retained its low-viscosity liquid condition for easy administration at 4°C. The results confirmed that every batch operated reliably(32).

In Vitro Release Studies:
40 mL of phosphate buffer (pH 6.8) was used as the medium in a Franz diffusion cell to assess the liquid crystal gel's in vitro release. For two hours, the setup was kept at 37 ± 0.5°C while being stirred at 250 rpm. Five milliliters of samples were taken out at predetermined intervals, filtered using a 0.45 µm Whatman filter, and then examined using UV spectrophotometry at 314 nm**.** (33).

Antibiotic activity
The agar plate method was used to determine antibiotic activity against Candida albicans, Staphylococcus, and Streptococcus species. Microorganisms were injected onto sterilized agar in petri dishes and incubated at 20-37 °C for 24-48 hours. The zones of inhibition around the samples were evaluated to determine antibacterial efficacy (34).

RESULTS AND DISCUSSION

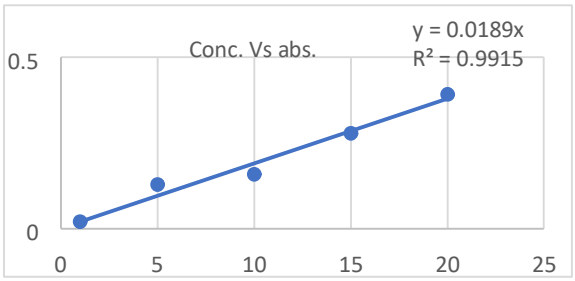


Fig4: Calibration Curve of Ornidazole in Phosphate Buffer Ph 6.8

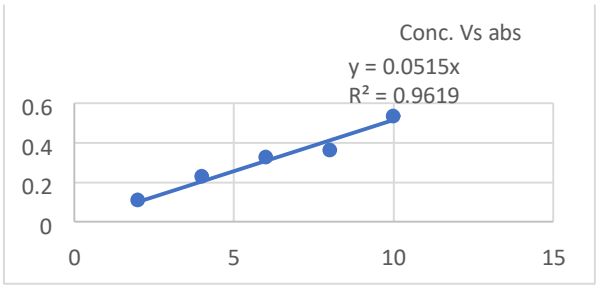


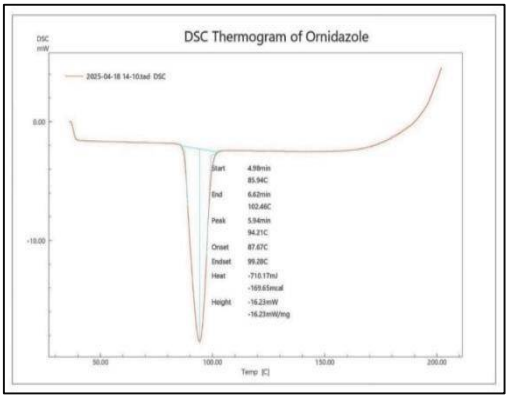
Fig5: Calibration Curve of Ornidazole in Ethanol

Solubility study

Table 1: Solubility study of Solvent

Solvent	**Solubility**
Phosphate Buffer PH 6.8	1.05 mg/ml
Ethanol	49.75 mg/ml

Differential scanning calorimetry Analysis:



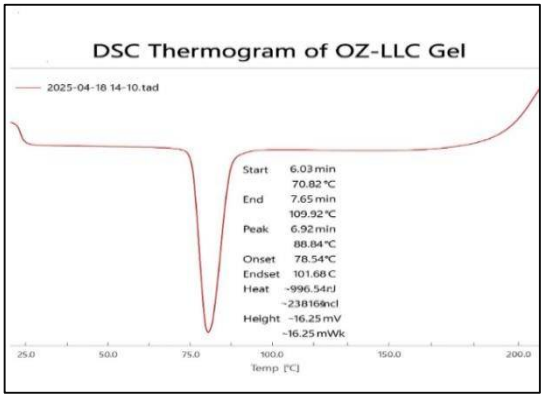
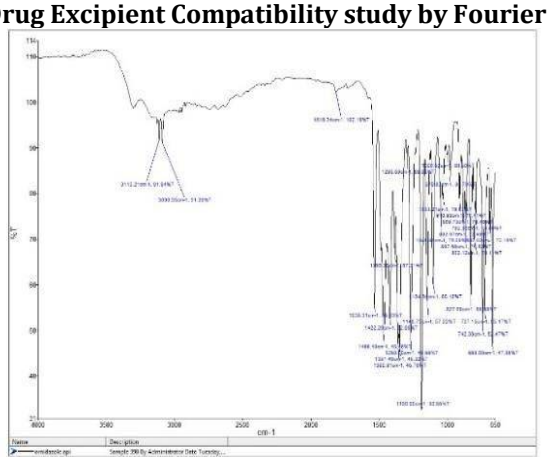


Fig 6: DSC Thermogram of ornidazole Fig 7: DSC Thermogram of OZ-LLC Gel

Interpretation: The DSC thermogram of the OZ-LLC gel formulation shows a significant reduction in Ornidazole crystallinity, indicating that the drug was successfully incorporated in a partially or completely amorphous state. This transition is likely owing to interactions with GMS, PF127, and ethanol, and it may improve the thermodynamic solubility and dissolution rate of Ornidazole in the final formulation (35).

Drug Excipient Compatibility study by Fourier transfer infrared Spectroscopy:



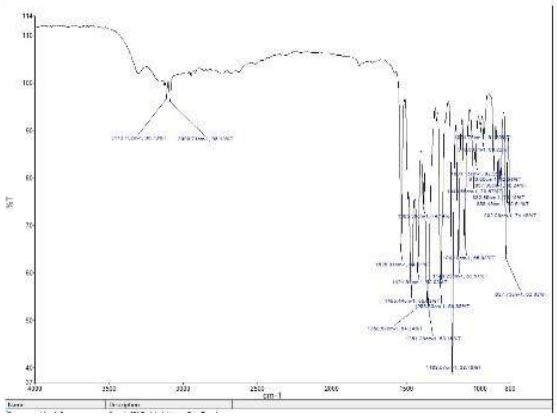


Fig 8: IR Spectra of ornidazole Fig9 : IR spectra of Drug Excipient mixture

Table no.2: Drug- excipient ratio for compatibility test:

DNP+ Excipient	Ratio	Temperature	Duration
OZ+ GMS (mg)	1:1	40 ± 2°C and 75 ± 5% RH	14 days
OZ+ Pluronic F-127	1:1	40 ± 2°C and 75± 5% RH	14 days
OZ + ethanol	1:1	40± 2°C and 75 ± 5% RH	14 days

Table no.3 : FTIR data of IR spectra

Functional groups	Pure Ornidazole		Drug Excipient Mixture	
	Frequency Obtained (cm-1)	Frequency Reported (cm-1)	Frequency Obtained (cm-1)	Frequency Reported (cm-1)
-OH stretch (Alcohol)	3090.55	3300-2500	3090.55	3300-2500
-CH stretch	3113.21	3100-3000	3113.21	3100-3000
NO2 asymmetric stretching	1535.91	1550	1535.91	1550
NO_2 symmetric stretching	1360.57&1258	1365	1360.57&1258	1365 [1]
C-Cl stretching	740.48	785-540	740.48	785-540

Table No 4: Optimized batches

Chemical name	Ornidazole (mg)	Glyceryl Monostearate (mg)	PluronicF127 (mg)	Ethanol (ml)	Water (ml)
F1	100	150	200	2	q.s
F2	100	150	50	2	q.s
F3	100	150	500	2	q.s
F4	100	600	50	2	q.s
F5	100	600	200	2	q.s
F6	100	600	500	2	q.s
F7	100	1000	50	2	q.s
F8	100	1000	200	2	q.s
F9	100	1000	500	2	q.s

Optimization and Screening of Ornidazole loaded Liquid crystal gel

Table no 5: Evaluation of Physicochemical Parameters of optimized Batches

Formulation Batches	Drug content (%)	Particle Size (nm)	Entrapment Efficiency (%)	Zeta Potential (mV)	PDI	Viscosity (cp)
F1	95.65	255.6	88.78	-17.2	0.372	1242
F2	95.85	201.3	90.70	-46.90	0.318	1250
F3	95.18	238.2	83.55	-25.2	0.344	1236
F4	94.04	245.3	80.88	22.4	0.368	1314
F5	94.85	244.3	83..65	-22.50	0.348	1368
F6	94.06	268.2	79.98	-12.15	0.365	1374
F7	90.68	279.1	89.97	-13.18	0.369	1284
F8	90.44	286.7	85.65	-14.04	0.358	1350
F9	88.40	290.7	82.67	-15.06	0.386	1332

Fig. 10: Particle size (F2 Batch)

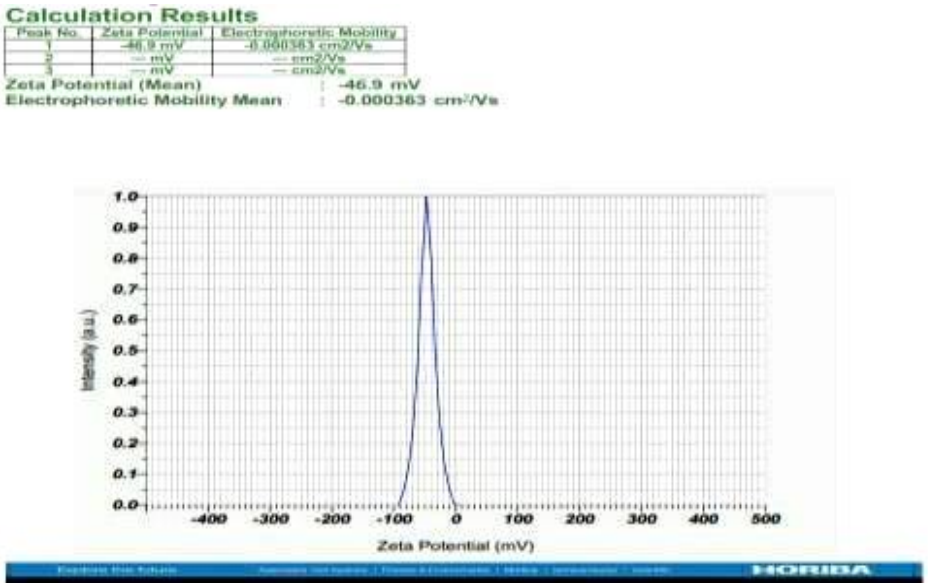


Fig. 11: Zeta graph (F2-Batch)

Polarized Light Microscopy:

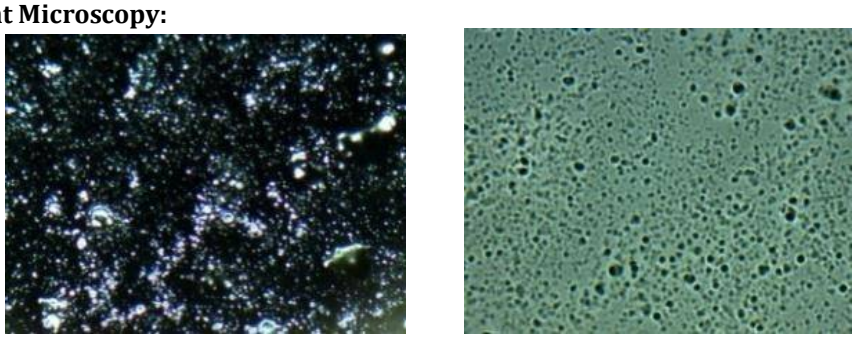


Fig.12: Images Generated by Polarized Light Microscope

Ornidazolelyotropic liquid crystal formulation (10 x) (1) and Ornidazole lyotropic liquid crystal (40 x)

Interpretation: This micrograph shows a multiphase system identical to that seen with GMS (Glyceryl Monostearate), Pluronic F127, water, ethanol, as well as the drug ornidazole. The discovered phases include cubic phases, which are compatible with a lyotropic liquid crystal formulation. Micellar or cubic phase PLM alone shows Cubic phases; it appear quietly birefringent or black having scattered brilliant patches. Some spots with consistent brightness and circular shapes represent micellar or cubic formations (36).

***In Vitro* Release Studies**

Analysis of the diffusion profiles of formulations F1 to F9 revealed that formulation batch F2 exhibited a superior drug release profile compared to the other formulations as shown in table.

Table No.6: Drug release kinetic model Release

Time (min)	%CDR	% Drug Remaining	Log % Drug Remaining	Cube root % Drug Remaining	log MT/M∞	Log Time
0	0	0	0	0	0	0
15	3.87027027	96.12972973	1.982857721	4.58091859	-1.38344175	1.176091259
30	5.28535135	94.71464865	1.976417153	4.558329526	-1.24810918	1.477121255
45	7.89313514	92.10686486	1.964292	4.51610468	-1.0739335	1.653212514
60	10.6155135	89.38448649	1.951262149	4.471165201	-0.94524203	1.77815125
90	15.9392432	84.06075676	1.924593295	4.38057478	-0.76871534	1.954242509
120	21.1681081	78.83189189	1.896701949	4.2877947	-0.645501	2.079181246
150	23.3829189	76.61708108	1.884325602	4.247256935	-0.60228432	2.176091259
180	36.4139459	63.58605405	1.803361875	3.991357466	-0.4099153	2.255272505

210	46.9909189	53.00908108	1.724350276	3.756500277	-0.2991691	2.322219295
240	61.486789	38.5145344	1.585618626	3.37706595	-0.1824068	2.380211242
270	84.1251351	15.87486486	1.200710037	2.513255716	-0.04625727	2.431363764
300	92.8745405	7.125459459	0.852812873	1.924291927	-0.00328636	2.477121255
360	95.9155676	4.084432432	0.611131716	1.598492386	0.01070606	2.556302501
420	96.4771351	3.522864865	0.546895984	1.52159356	0.013241358	2.62324929
480	97.0395135	2.960486486	0.471363083	1.435889526	0.01576557	2.681241237
540	97.6027027	2.397297297	0.379721896	1.338363134	0.018278803	2.73239376
600	98.9234595	1.076540541	0.032030389	1.024888916	0.024116255	2.77815125
660	99.1658378	0.834162162	-0.078749514	0.941347909	0.025179045	2.819543936
720	99.4082162	0.591783784	-0.22783694	0.839565054	0.02623924	2.857332496

Kinetics Analysis of OZ-LLC gel:

The OZ-LLC formulation's drug release best describes the zero-order kinetic model (R^2 =0.996), showing a constant release rate irrespective of drug concentration. This is useful for maintaining therapeutic levels. The Hixson-Crowell model reveals a strong fit (R^2 = 0.9944), indicating that surface area and particle size affect release. The Higuchi model (R^2 = 0.9605) suggests diffusion-controlled release, and the Korsmeyer-Peppas model (R^2 = 0.9752) has a strong correlation with experimental results. The first-order model (R^2 = 0.0429) does not well represent the release behavior, suggesting that it is not concentration dependent (37,38).

Table No7:Recession Coefficient analysis

Zero order	First order	Higuchi model	Korsmeyers Peppas model	Hixon Crowell
0.996	0.9934	0.9605	0.9752	0.9944

The elevated R^2 values in these models suggest that the formulation's release behavior is accurately represented by these established kinetics, likely integrating the distinctive characteristics of liquid crystals, including temperature sensitivity and structural alterations, of liquid crystals, to achieve controlled, prolonged release (39).

Antibiotic activity

The agar plate technique was used to evaluate antibiotic activity against pathogens such as Candida albicans, Staphylococcus, and Streptococcus. Microorganisms were added to sterilized agar on petri dishes and cultured at 20-37 °C for 24-48 hours. The zones of inhibition around the samples were evaluated to estimate the antibacterial efficacy (40)**.**

Table No. 8: zone of inhibition study

Medium	**Zone of Inhibition (cm)**
Candida albicans sp.	2.5
Staphylococcus.	2.4
Streptococci sp.	2.35
Marketed formulation	2.2

CONCLUSION

The research focuses on creating and obtaining Lyotropic liquid crystal (LLC) using Ornidazole (ORNIDAZOLE) mixed into an OZ-LLC formulation. The primary goal was to increase medication delivery efficacy and manage drug release. Formulation Success: The researchers successfully created LLCs containing ORNIDAZOLE, demonstrating appropriate particle size, zeta potential, and encapsulation efficiency. These LLCs demonstrated durability and favorable physical and chemical properties for drug delivery. OZ-LLC formulation properties: Incorporating LLC into an OZ-LLC gel matrix provided a twofold advantage. The gel remained liquid at normal temperature, making it simple to give, and transformed into a gel at body temperature, assuring retention over time at the administration site. In Vitro Release Studies involves Conclusions from the in vitro release studies showed that the formulation adhered to the zero-order model, meaning that the drug's release was mostly determined by diffusion. The release profile showed a sustained release, which is useful for maintaining therapeutic medication concentrations over a long time. Drug release kinetics include an examination of the drug release dynamics found that the formulation adhered strongly to the Zero-order model, indicating a controlled release mechanism. This means that medication release is controlled and sustained, reducing the need for frequent doses.

Conflict of Interest: No any conflicts of interest are there

Financial Support: No financial support or funding

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