

FORMULATION AND EVALUATION OF CLOTRIMAZOLE-LOADED INVASOMAL GEL FOR ENHANCED TOPICAL DRUG DELIVERY

Parthiban S.¹, Nikhilgowda Y. V.^{2*}

Department of Pharmaceutics, Bharathi College of Pharmacy, Bharathinagara, Mandya,
Karnataka, India-571422.

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*Corresponding Author

Nikhilgowda Y. V.

Department of Pharmaceutics,
Bharathi College of Pharmacy,
Bharathinagara, Mandya, Karnataka,
India-571422.



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ABSTRACT

Clotrimazole is a widely used broad-spectrum antifungal drug; however, its poor aqueous solubility and limited skin permeation may restrict its effective topical delivery. The present study aimed to formulate and optimize Clotrimazole-loaded invasomes for enhanced topical drug delivery using the mechanical dispersion technique. Invasomes were prepared using soya lecithin, menthol, thymol and ethanol as vesicle-forming and penetration-enhancing components. Preformulation studies, including melting point determination, solubility analysis, UV spectroscopy and FTIR compatibility studies, were performed to confirm the suitability of the drug and excipients. Twenty formulations (F1–F20) were prepared and evaluated for drug content, entrapment efficiency, vesicle size, in-vitro drug release and release kinetics. Among the formulations, F7 was selected as the best formulation based on

its satisfactory overall physicochemical characteristics, drug content of 94.61%, entrapment efficiency of 81.65%, favourable vesicle-size distribution and sustained drug release. The release kinetics of F7 best fitted the Korsmeyer–Peppas model ($R^2 = 0.9781$) with an n value of 0.3695, indicating a predominantly Fickian diffusion-controlled release mechanism. F7 was further incorporated into Carbopol 934 gel. The optimized invasomal gel exhibited satisfactory appearance, pH, viscosity, spreadability, extrudability and drug content, indicating its suitability for topical application. Thus, Clotrimazole-loaded invasomes, particularly F7, demonstrated promising potential as a vesicular carrier for sustained and enhanced topical drug delivery.

KEYWORDS: Clotrimazole, Invasomes, Topical Drug Delivery, Mechanical Dispersion Technique.

INTRODUCTION

Vesicular drug delivery systems are structured assemblies composed of one or more concentric bilayer membranes formed through the self-assembly of amphiphilic molecules in an aqueous environment. Lipid-based vesicles of biological origin were first identified by Bingham in 1965 and were therefore termed *Bingham bodies*.^[1] These systems play a significant role in targeted drug delivery, as they can concentrate the drug at the desired site or organ of action, thereby minimizing drug distribution and associated side effects in other parts of the body.^[2]

Invasomes are modified liposomal vesicles composed of phospholipids, ethanol, and one or more terpenes, designed to combine the drug-carrying capability of liposomes with the penetration-enhancing properties of ethanol and terpenes.^[3] The concept of invasomes was introduced to address the shortcomings of conventional liposomes and ethosomes by providing a vesicular system with superior elasticity, deformability, and skin penetration capability.^[4]

Unlike conventional liposomes, which possess rigid bilayers and limited ability to traverse the stratum corneum, invasomes exhibit a highly flexible membrane structure that allows them to deform and squeeze through narrow intercellular spaces without undergoing vesicle rupture. The incorporation of terpenes further enhances the interaction between invasomes and stratum corneum lipids, resulting in increased lipid fluidization and drug partitioning into deeper skin layers. Numerous comparative studies have demonstrated that invasomes achieve significantly higher skin permeation, drug retention, and therapeutic efficacy than liposomes and ethosomes, establishing them as promising carriers for transdermal and dermal drug delivery.^[5]

Clotrimazole is a broad-spectrum antifungal drug widely used to treat superficial fungal infections. However, its poor aqueous solubility and limited skin penetration reduce its therapeutic effectiveness. Being highly lipophilic, clotrimazole is an ideal candidate for encapsulation in invasomal vesicles. Invasomes enhance drug permeation through the skin and provide controlled drug release. Therefore, clotrimazole-loaded invasomes can improve topical antifungal efficacy and patient outcomes.^[6]

Materials Used

Clotrimazole was purchased from Balaji drug store Mumbai, Menthol and Thymol collected from SD Fine Chem., Mumbai, Soya lecithin collected from Sonic Biochem Extraction Ltd., Indore and Ethanol collected from Thermo Fisher Scientific India Pvt. Ltd. Mumbai.

Preformulation studies^[7-14]**Determination of melting point of the drug**

Melting point of Clotrimazole was determined by using capillary tube method using melting point apparatus.

Fourier transforms infrared spectroscopy (FTIR) studies

Drug-excipients compatibility studies were carried out using FTIR. Infrared spectrum of pure drug (Clotrimazole) and physical mixture of Clotrimazole and Menthol, Thymol, Soya Lecithin was recorded from the ranges to 400 – 4000 cm^{-1} . FTIR analysis was carried out using a Shimadzu FTIR spectrophotometer.

Determination of absorption maximum (λ max) of the drug

Clotrimazole 100 mg/ml concentration was prepared in methanol and buffer pH 6.8 (1:1) the solution was scanned from 200-400 nm by UV Spectrophotometer and a spectrum was observed for absorption maxima.

METHOD OF PREPARATION**Preparation of invasomes by mechanical dispersion technique**

Invasomes were prepared by the mechanical dispersion technique. Accurately weighed phospholipid was dissolved in ethanol to form the organic phase. To this mixture, terpene and the drug sample were added and mixed thoroughly. The resulting mixture was stirred using a magnetic stirrer until all the components were completely dissolved. The organic phase was then added slowly in a dropwise manner to the aqueous phase under continuous stirring to obtain a uniform dispersion. Finally, the dispersion was sonicated using a probe sonicator for 5–10 minutes to obtain uniform Invasomes.^[15]

Preparation of clotrimazole loaded invasomal gel

Carbopol 934 was hydrated in purified water, followed by slow addition of clotrimazole-loaded invasomal suspension containing 100 mg drug with gentle stirring. Triethanolamine

was added dropwise for neutralization, and the mixture was gently stirred to obtain a homogeneous, lump-free gel.

Table 1: Formulation table for the preparation of Invasomes (F1-F20).

F. Code	Drug (mg)	Soya lecithin	Menthol	Thymol
F1	100	150 mg	0 mg	0 mg
F2	100	250 mg	0 mg	0 mg
F3	100	150 mg	300 mg	0 mg
F4	100	250 mg	300 mg	0 mg
F5	100	150 mg	0 mg	300 mg
F6	100	250 mg	0 mg	300 mg
F7	100	150 mg	300 mg	300 mg
F8	100	250 mg	300 mg	300 mg
F9	100	150 mg	150 mg	150 mg
F10	100	250 mg	150 mg	150 mg
F11	100	200 mg	0 mg	150 mg
F12	100	200 mg	300 mg	150 mg
F13	100	200 mg	150 mg	0 mg
F14	100	200 mg	150 mg	300 mg
F15-F20	100	200 mg	150 mg	150 mg

Evaluation of Invasomes^[16-20]

Drug content, Entrapment efficiency, Vesicle size analysis, In-vitro diffusion study and Release Kinetics.

Drug content determination

An invasomal formulation equivalent to 10 mg of Clotrimazole was accurately transferred into a volumetric flask and dissolved in 10 mL of methanol. The resulting dispersion was centrifuged at an appropriate speed for 10–15 minutes to separate the vesicles and obtain a clear supernatant containing the drug. The supernatant was collected and suitably diluted with phosphate buffer (pH 6.8). The absorbance of the diluted solution was measured using a UV–Visible spectrophotometer at 260 nm.

Entrapment efficiency determination

The entrapment efficiency of Clotrimazole Invasomes was determined after hydration with distilled water. 2 ml of distilled water was added to the Invasomes equivalent to 2 mg of drug then the mixture was shaken manually for 2min. For the separation of untrapped Clotrimazole, the Invasomal suspension was subjected to centrifugation on a cooling centrifuge at 25000 rpm for The For the separation of un entrapped drug. The clear supernatant (0.1 ml) was taken and diluted to 10ml with methanol and water solution and

absorbance was recorded at 260 nm using UV visible spectrophotometer then calculates the percentage drug in each formulation.

Vesicle size analysis

A drop of Invasomes with distilled water formulation is added on glass slide without cover slip to observe the formation of Invasomes. Vesicle size analysis was carried out using an optical microscope with a calibrated eye piece micrometer. About 200 Invasomes were measured individually, average was taken and their size distribution range and mean diameter were calculated.

In-vitro drug release

The drug release was evaluated using a treated cellophane membrane attached to one end of a tube containing the formulation. The tube was suspended in 200 mL of pH 6.8 buffer and maintained at $37 \pm 0.5^{\circ}\text{C}$ with continuous stirring at 100 rpm. Samples (1 mL) were withdrawn at predetermined intervals (1, 2, 4, 6, and 8 hours) and replaced with an equal volume of fresh buffer to maintain sink conditions. The withdrawn samples were diluted to 10 mL with pH 6.8 buffer and analyzed using a UV spectrophotometer at 260 nm. The cumulative percentage of drug released was calculated and plotted against time. Release kinetics and the mechanism of Clotrimazole release were determined by fitting the data to various kinetic models.

Release kinetic analysis

The drug release kinetic studies were done by various mathematical models. The model that gives high 'R' value is considered as the best fit of the release data. The release constant was calculated from the slope of the appropriate plots, and the regression coefficient (R^2) was determined.

Evaluation of Invasomal Gel

Appearance

The prepared gels were examined for clarity, Color, homogeneity, presence of foreign particles and fiber.

pH

1gm of gel was dispersed in 100 ml distilled water and the pH was examined using digital pH meter.

Spreadability study

The spreadability of the Invasomal gel was studied by measuring the change in diameter when 500 mg of gel was placed between 2 horizontal plates of 6cm with a standardized weight of 20g placed over it. Calculate the time required for 6cm replacement while applying 20gm of weight (El-Tokhy *et al.*, 2021). Calculate the spreadability using formula:

$$\text{Spreadability} = \frac{\text{weight tied to upper slide (g)} \times \text{length of glass slide (cm)}}{\text{Time taken in sec}}$$

Extrudability study

The prepared Invasomal gel was filled in collapsible tubes and its extrudability was estimated in terms of weight in grams required to produce a 0.5 cm ribbon of gel in 10 seconds.

Viscosity

For determining the viscosity of the invasomal gel Brookfield viscometer (DV-E Brookfield Engineering Laboratories, MA, USA) at 37°C with spindle No.64 was used. An appropriate amount of gel was placed onto the centre of the viscometer plate directly below the spindle using the spatula and viscosities were measured.

Drug content determination (%)

Clotrimazole loaded Invasomal gel was assayed by an UV spectrophotometric method. Invasomal gel containing equivalent to 10 mg of drug were dissolved in a 10 ml of methanol. After suitable dilution absorbance was measured by UV spectrophotometer against blank at λ_{max} 260 nm and drug content was calculated.

$$\% \text{Drug content} = \frac{\text{Actual Drug}}{\text{Theoretical Drug}} \times 100$$

In-vitro diffusion study

The diffusion medium used was phosphate buffer pH 6.8. Assembly of diffusion cell for in-vitro diffusion studies the diffusion cell was designed as per the dimension given. Diffusion cell with an effective diffusion area of 3.14 cm² was used for in-vitro permeation studies. One gm of Invasomal gel containing Clotrimazole was placed in the donor compartment and the receptor compartment was filled with receptor fluid. The egg membrane was mounted carefully and ensured intimate contact with the receptor fluid. The speed of stirring was kept constant throughout the experiment. At 0.5, 1, 2, 4, 6 and 8 h, 1 ml sample was withdrawn and replaced with an equal volume of receptor fluid to maintain sink conditions. The samples

were suitably diluted and absorbance was measured at 260 nm using a UV spectrophotometer.

RESULT

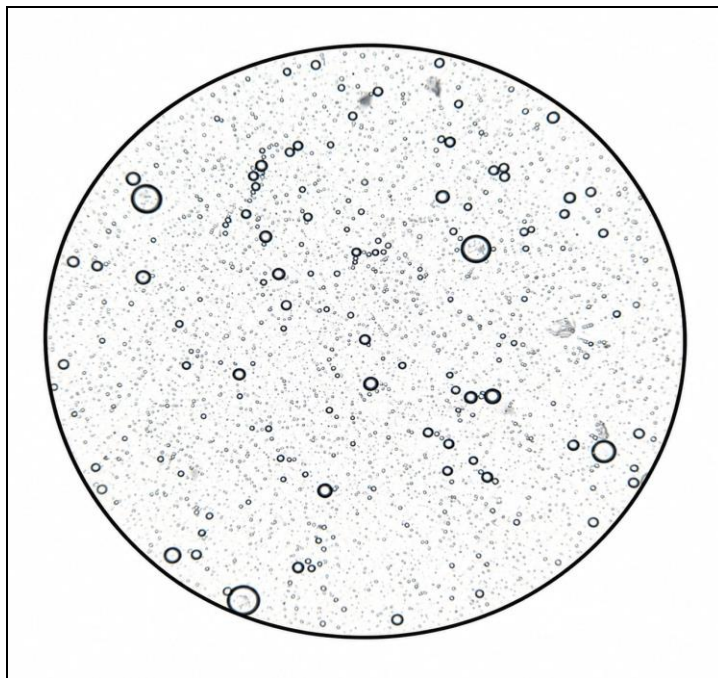


Figure 1: Microphotograph of F7 invasome formulation.

Table 2: Melting point report of Clotrimazole by Theile's tube method.

Trials	Melting Point	Average
1	148°C	147.66°C
2	147°C	
3	148°C	

Table 3: Solubility analysis report.

Solvents	Solubility determined (mg/ml)	Volume of solvent in ml/1gm (ml)	Solubility Criteria
Water	0.05037	19853	Practically insoluble
pH 6.8	0.3851	2596	Very slightly soluble
pH 7.4	0.4296	2327	Very slightly soluble
pH 1.2	0.06259	15976	Practically insoluble
pH 4.6	0.07666	13044	Practically insoluble

Determination of Absorption Maxima ($\lambda_{\max}$)

Absorption Maxima ($\lambda_{\max}$) of the Clotrimazole was found to be 260nm in Methanol and buffer pH 6.8 (1:1) by using UV spectrophotometry.

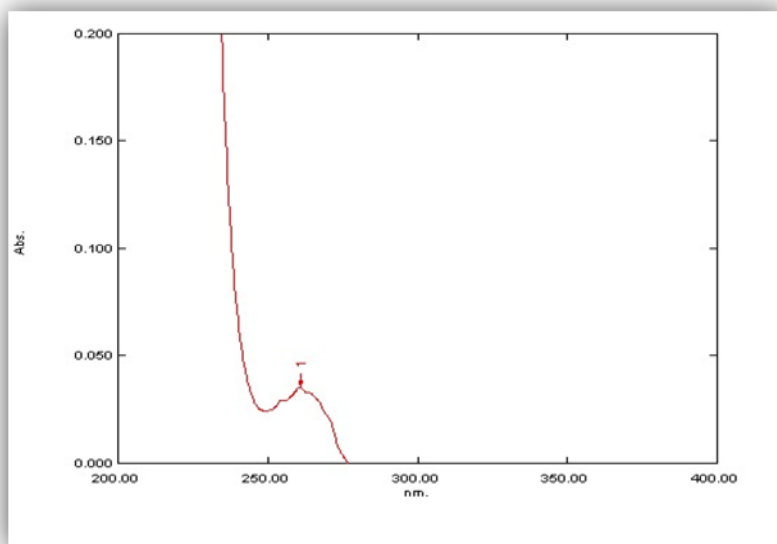


Figure 2: UV spectrum of Clotrimazole at 10 µg/ml concentration.

Table 4: Standard calibration curve of Clotrimazole.

Absorbance at λ_{max} 260 nm				
Conc (µg/ml)	T-1	T-2	T-3	AVG $\pm$ SD
0	0	0	0	0
50µg/ml	0.151	0.153	0.152	0.152 $\pm$ 0.001
100µg/ml	0.283	0.285	0.281	0.283 $\pm$ 0.002
150µg/ml	0.42	0.423	0.422	0.422 $\pm$ 0.002
200µg/ml	0.542	0.543	0.543	0.543 $\pm$ 0.001
250µg/ml	0.675	0.677	0.675	0.676 $\pm$ 0.001
300µg/ml	0.816	0.817	0.816	0.816 $\pm$ 0.001

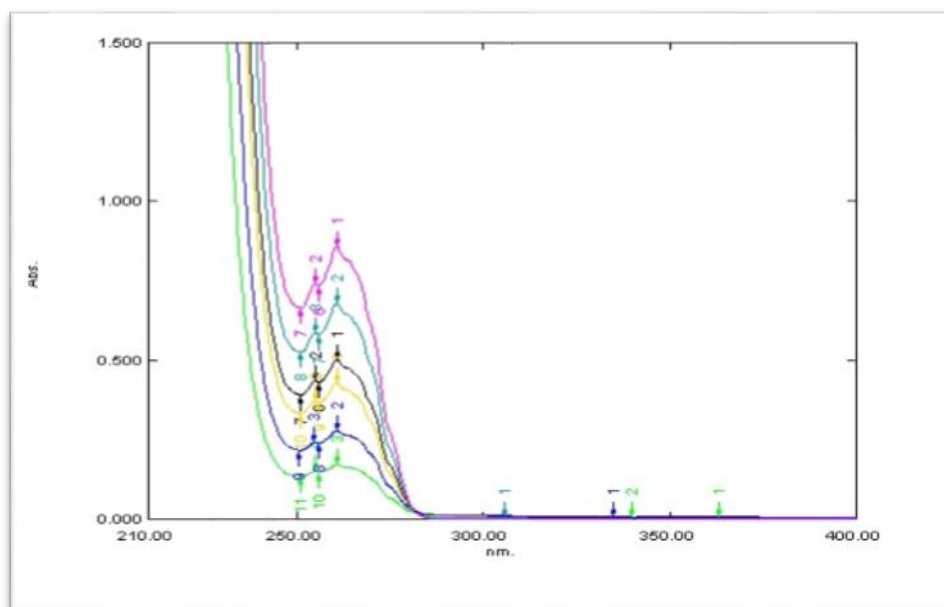


Figure 3: UV spectrum of Clotrimazole at different concentration of 0-300 µg/ml.

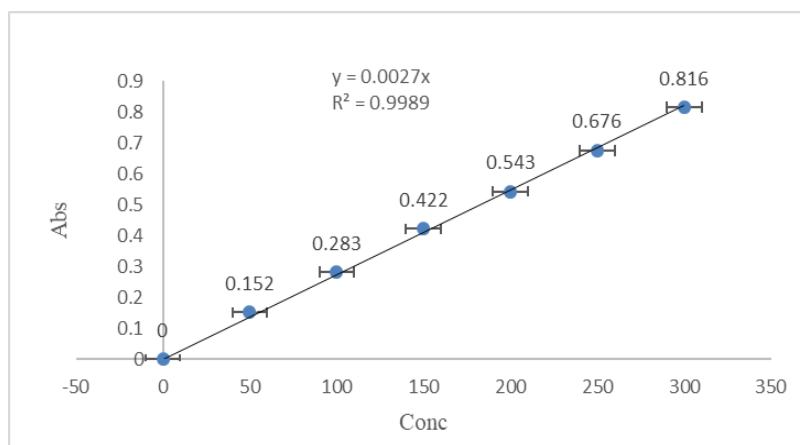


Figure 4: Plot of standard calibration curve of Clotrimazole.

Compatibility studies by FTIR spectrophotometer

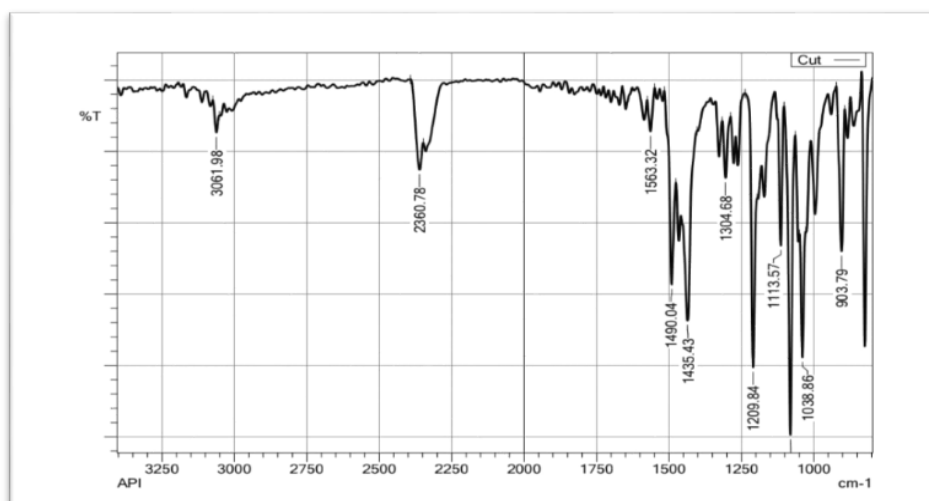


Figure 5: FT-IR Spectrum of Pure Clotrimazole drug.

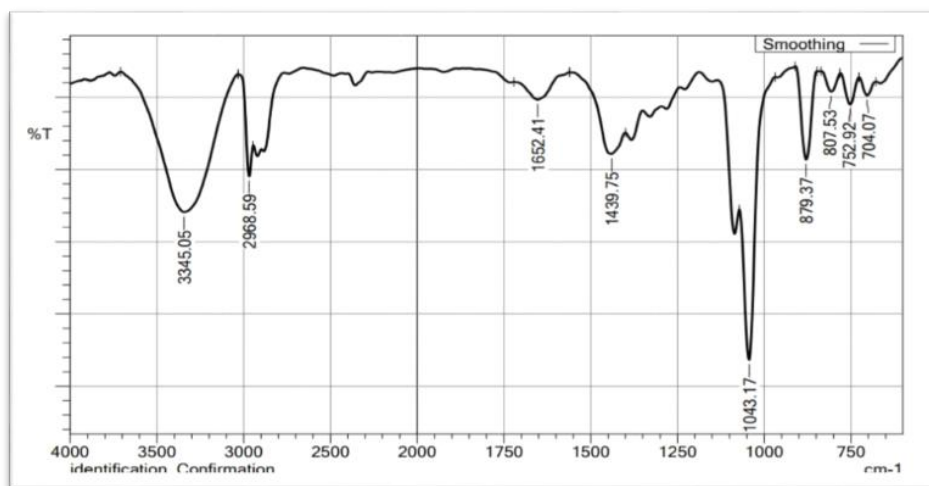


Figure 6: FTIR spectrum of Drug and Physical mixture (Menthol+Thymol+Soya Lecithin).

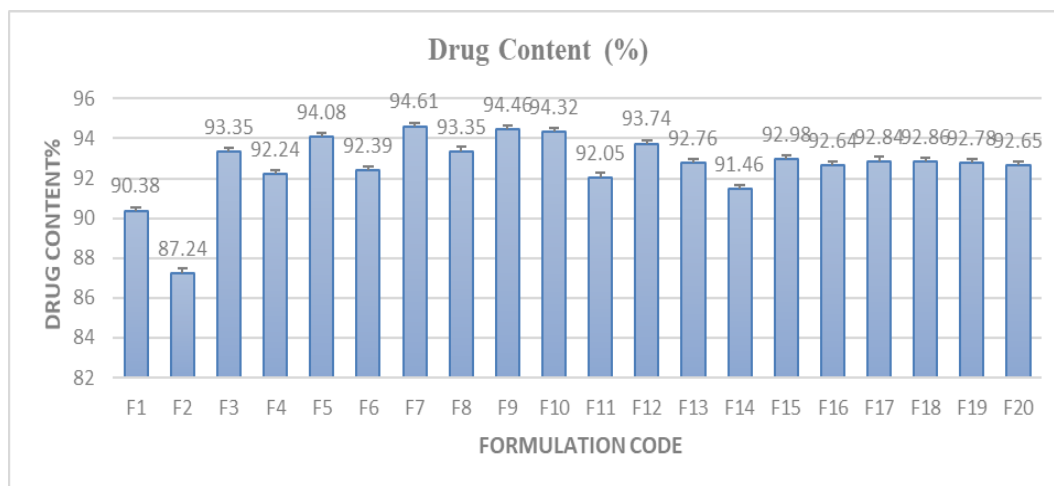


Figure 7: Drug content for formulated invasomes F1-F20.

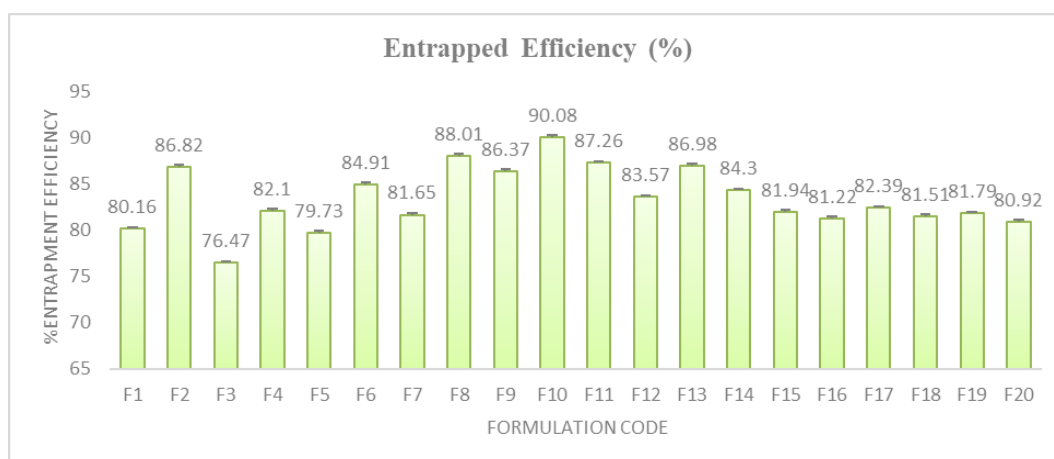


Figure 8: Entrapment efficiency for formulated invasomes F1-F20.

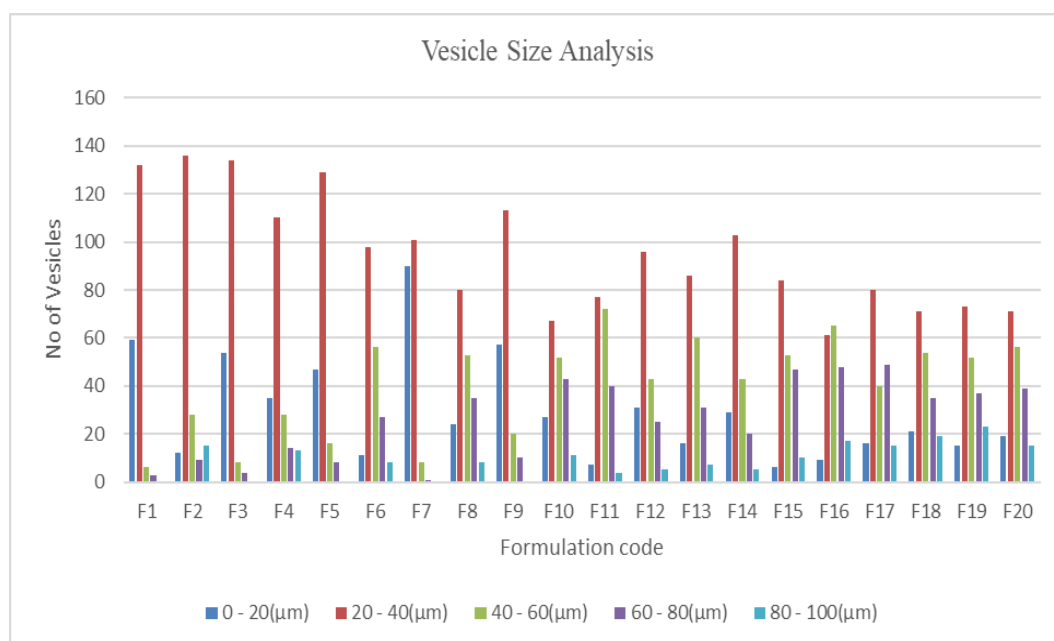


Figure 9: Vesicle size analysis for formulated invasomes F1-F20.

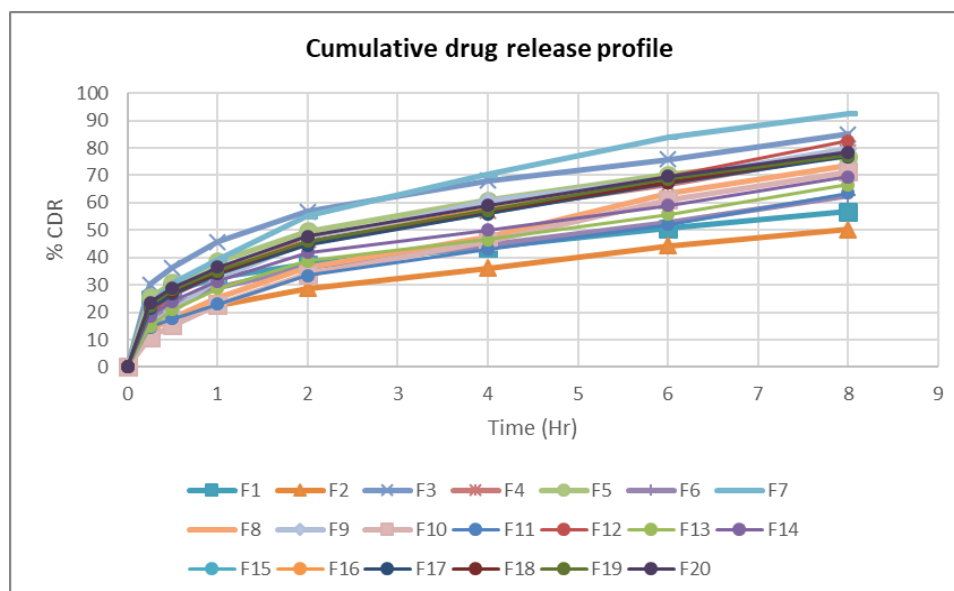


Figure 10: In-vitro diffusion study of formulation F1-F20.

Table 5: Release kinetic analysis.

Formulation code	Zero order	First order	Higuchi	Peppas model	
				R ²	n value
F1	0.7273	0.9458	0.9140	0.9850	0.2467
F2	0.8585	0.9338	0.9181	0.9830	0.2632
F3	0.7629	0.8435	0.9195	0.9255	0.2909
F4	0.8519	0.8364	0.8956	0.8975	0.2614
F5	0.7966	0.8936	0.9219	0.9835	0.3358
F6	0.8452	0.9306	0.9314	0.9277	0.2810
F7	0.8601	0.9225	0.9650	0.9781	0.3695
F8	0.9336	0.8907	0.9114	0.9662	0.2584
F9	0.8778	0.7633	0.9068	0.9639	0.2392
F10	0.9460	0.9023	0.8880	0.9378	0.2140
F11	0.9106	0.8679	0.9228	0.9424	0.2893
F12	0.8864	0.8845	0.9218	0.9567	0.2839
F13	0.8664	0.8459	0.9428	0.9629	0.3271
F14	0.8443	0.8378	0.8703	0.8997	0.2323
F15	0.8531	0.8699	0.9170	0.9695	0.2718
F16	0.8455	0.9639	0.9782	0.9985	0.3575
F17	0.8598	0.9628	0.9656	0.9534	0.3598
F18	0.8543	0.9928	0.9756	0.9463	0.3434
F19	0.8479	0.9246	0.9559	0.9484	0.3512
F20	0.8696	0.9284	0.9666	0.9669	0.3612

Table 6: Physical appearance of invasomal gel.

Formulation code	Appearance
F7IG	Transparent Color, odorless with smooth and uniform appearance

Table 7: pH, Viscosity (cps), Spreadability, Extrudability and Drug content of invasomal gel.

Formulation code	pH	Viscosity(cps)	Spreadability (g.cm/sec)	Extrudability (g)	Drug Content (%)
F7IG	6.71±0.02	3673.33±2.08	12.63±0.63	128.33±5.77	91.88± 0.09

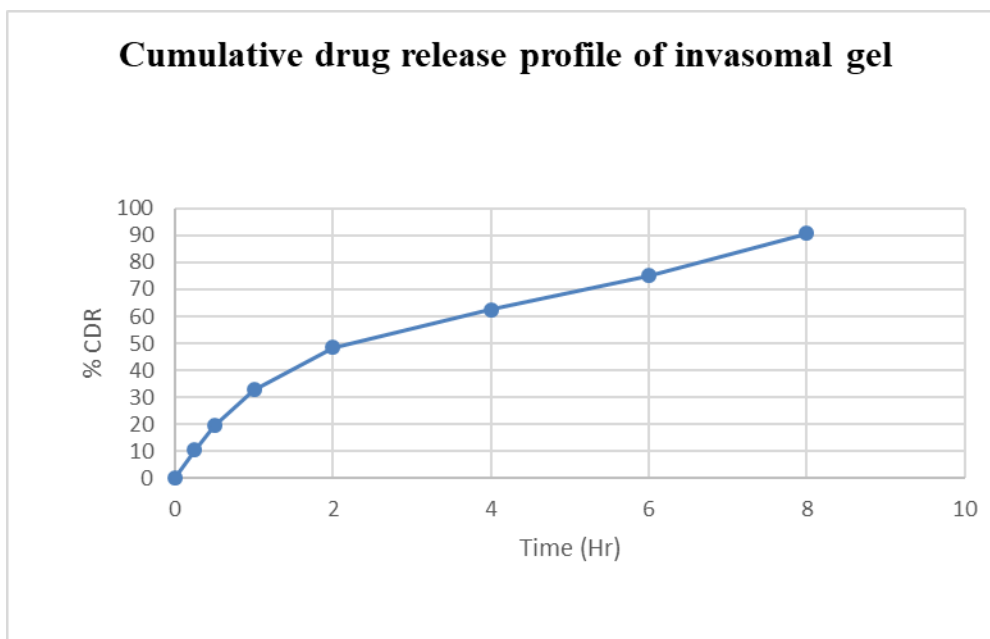


Figure 11: In-vitro diffusion study of invasomal gel.

Table 8: Release Kinetic Analysis.

Formulation code	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Peppas model	
				r^2	n value
F7IG	0.9141	0.9654	0.9949	0.9853	0.529

DISCUSSION

The present study successfully developed Clotrimazole-loaded invasomes using the mechanical dispersion technique for improved topical drug delivery. Clotrimazole has poor aqueous solubility, which may limit its effective topical delivery. Therefore, the invasomal system containing phospholipid, ethanol and terpenes was developed to improve drug incorporation, vesicle formation and sustained drug release.

Preformulation studies supported the suitability of Clotrimazole for formulation development. The observed melting point was 147.66°C, indicating satisfactory purity of the drug. The λ_{max} of Clotrimazole was found to be 260 nm, and the calibration curve showed excellent linearity with an R^2 value of 0.9997. FTIR studies indicated that the characteristic functional

groups of the drug were retained in the physical mixture, suggesting the absence of significant drug–excipient incompatibility.

Twenty invasomal formulations (F1–F20) were prepared by varying the concentrations of soya lecithin, menthol and thymol. The formulations showed variation in drug content, entrapment efficiency, vesicle size and drug-release behaviour, demonstrating the influence of formulation composition on the characteristics of the invasomes.

Among the prepared formulations, F7 showed a high drug content of 94.61% and an entrapment efficiency of 81.65%, indicating efficient incorporation of Clotrimazole into the invasomal vesicles. The composition of F7, containing 150 mg soya lecithin along with 300 mg each of menthol and thymol, appears to provide a suitable vesicular environment for drug incorporation. The phospholipid contributes to bilayer formation, while menthol and thymol can increase membrane fluidity and flexibility, thereby supporting the formation of deformable invasomal vesicles.

Vesicle size analysis showed that the formulations possessed a broad but controlled size distribution. Notably, F7 exhibited the highest number of smaller vesicles in the 0–20 μm range, which may be advantageous for topical application and interaction with the skin. The presence of terpenes such as menthol and thymol may enhance membrane fluidity and facilitate the formation of smaller and more flexible vesicles.

The in-vitro diffusion study demonstrated drug release from the invasomal formulations over 8 hours. F7 showed a satisfactory and sustained drug-release profile, indicating controlled diffusion of Clotrimazole from the vesicular system. The sustained release may be attributed to the entrapment of drug within the phospholipid bilayer and the controlled diffusion of the drug through the vesicular membrane. The presence of menthol and thymol may additionally facilitate drug partitioning and membrane fluidity, contributing to the observed release behaviour.

The release-kinetic analysis of F7 showed R^2 values of 0.8601 for zero-order, 0.9225 for first-order, 0.9650 for Higuchi and 0.9781 for the Korsmeyer–Peppas model, with a Peppas n value of 0.3695. The higher correlation coefficient for the Korsmeyer–Peppas model indicates that this model best described the release behaviour of F7, while the n value suggests a predominantly Fickian diffusion-controlled release mechanism.

Based on the combined evaluation of drug content, entrapment efficiency, vesicle-size distribution and in-vitro drug-release characteristics, F7 was selected as the best formulation. Its favourable vesicle characteristics and sustained release behaviour indicate that the selected concentrations of soya lecithin, menthol and thymol provided an appropriate balance between vesicle formation, drug incorporation and controlled drug release. Therefore, F7 was further incorporated into Carbopol 934-based gel for the development of the invasomal gel.

The prepared F7 invasomal gel (F7IG) showed a transparent, odorless, smooth and uniform appearance. It exhibited a pH of 6.71 ± 0.02 , viscosity of 3673.33 ± 2.08 cps, spreadability of 12.63 ± 0.63 g·cm/sec, extrudability of 128.33 ± 5.77 g, and drug content of $91.88 \pm 0.09\%$, indicating satisfactory physicochemical properties for topical application.

The release-kinetic analysis of F7IG showed the highest correlation coefficient for the Higuchi model ($R^2 = 0.9949$), followed by the Korsmeyer–Peppas model ($R^2 = 0.9853$), with an n value of 0.529. This indicates that drug release from the invasomal gel was predominantly controlled by diffusion through the gel matrix.

Overall, F7 demonstrated satisfactory physicochemical characteristics, efficient drug incorporation, favourable vesicle-size distribution and sustained drug release, supporting its selection as the best formulation for further incorporation into an invasomal gel.

CONCLUSION

The present study successfully formulated Clotrimazole-loaded invasomes using the mechanical dispersion technique for enhanced topical drug delivery. Preformulation studies confirmed the suitability and compatibility of Clotrimazole with the selected excipients. Among the twenty formulations, F7 was selected as the best formulation based on its satisfactory drug content, entrapment efficiency, vesicle-size characteristics and sustained drug-release profile. F7 showed 94.61% drug content and 81.65% entrapment efficiency, with a favourable vesicle-size distribution. The release profile of F7 was best fitted to the Korsmeyer–Peppas model, indicating predominantly Fickian diffusion-controlled drug release.

The selected F7 invasomes were successfully incorporated into Carbopol 934 gel. The resulting F7IG showed satisfactory physical appearance, pH, viscosity, spreadability, extrudability and drug content, demonstrating its suitability for topical application. The

optimized invasomal gel exhibited diffusion-controlled drug release, with the Higuchi model providing the best fit ($R^2 = 0.9949$).

Overall, the findings indicate that F7 Clotrimazole-loaded invasomes incorporated into Carbopol 934 gel provide a promising approach for sustained and effective topical delivery of Clotrimazole.

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