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FORMULATION AND EVALUATION OF FLUCYTOSINE LOADED INVASOMAL GEL

Manu Kumar Singh[1]*, Dr. Sandesh Asati[1], Dr. Brijesh Sirohi[1], Dr. Vishnu Raj[1]
Radharaman College of Pharmacy, Bhadbhada Road, Ratibad, Bhopal (MP) -462044

Abstract:
The present study aimed to develop and evaluate a flucytosine-loaded invasomal gel for improved topical antifungal drug delivery. Nine invasomal formulations (F1–F9) were prepared by varying terpene and phosphatidylcholine concentrations while maintaining flucytosine concentration at 1% w/v. The prepared invasomes were evaluated for entrapment efficiency and vesicle size. Among the formulati1ons, F9 exhibited the highest entrapment efficiency of 89.48% and the lowest vesicle size of 178.4 nm and was selected as the optimized invasome. The optimized invasomes were incorporated into Carbopol 934 gel at different polymer concentrations to prepare IG-1, IG-2 and IG-3. The formulations were evaluated for viscosity, pH, drug content, extrudability and spreadability. IG-2 demonstrated a suitable combination of physicochemical properties, with viscosity of 3924 ± 18 cps, pH 5.89 ± 0.02, drug content 99.46 ± 0.21%, extrudability 178 ± 2 g and spreadability 11.64 ± 0.27 g·cm/s, and was selected as the optimized invasomal gel. In-vitro drug-release studies showed sustained release from IG-2, with 89.46% cumulative drug release at 12 h compared with 88.65% release of pure flucytosine within 5 h. The release kinetics showed the highest correlation with the first-order and Higuchi models (R^2 = 0.9892), indicating an important contribution of diffusion to drug release. The optimized gel also exhibited enhanced antifungal activity against Candida albicans, *producing zones of inhibition of 15.62 ± 0.24, 21.48 ± 0.29 and 27.36 ± 0.31 mm at 10, 20 and 30 µg/mL, respectively, compared with 12.36 ± 0.28, 16.74 ± 0.32 and 20.58 ± 0.35 mm for pure flucytosine. Stability studies further demonstrated satisfactory physical stability of IG-2 for six months at 4 ± 2°C and 25 ± 2°C. The findings indicate that the flucytosine-loaded invasomal gel may serve as a promising topical delivery system providing sustained drug release and enhanced antifungal activity.*

Keywords: *Flucytosine, Invasomes, Invasomal gel, Carbopol 934, Topical drug delivery, Sustained drug release,* Candida albicans, *Antifungal activity.*

Corresponding author:
Manu Kumar Singh,
Radharaman College of Pharmacy, Bhadbhada Road, Ratibad, Bhopal (MP) -462044
Mobile:
Email Id: *manukuldeepamairwa@gmail.com*

QR CODE

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INTRODUCTION:

Superficial fungal infections are among the most common infectious disorders affecting the skin and mucosal surfaces. They are caused by a variety of pathogenic fungi and may result in persistent infection, discomfort, inflammation, itching and considerable impairment of quality of life (Kaushik et al., 2015). Although several antifungal agents are available for the treatment of fungal infections, successful topical therapy may be limited by inadequate drug penetration through the stratum corneum, short residence time at the site of application and insufficient drug concentration in deeper layers of the skin. Therefore, development of an efficient topical delivery system capable of improving drug localization, prolonging residence time and providing controlled drug release is of considerable interest (Kaushik et al., 2015).

Flucytosine is a synthetic fluorinated pyrimidine analogue possessing antifungal activity against several pathogenic fungi, particularly *Candida* species. It is converted intracellularly to active metabolites that interfere with fungal nucleic acid and protein synthesis. Despite its useful antifungal activity, conventional administration of flucytosine may be associated with limitations such as rapid elimination and the requirement for repeated administration (Fang et al., 2017). Moreover, conventional topical preparations may not provide adequate penetration and prolonged retention of the drug at the infected site. These limitations create a need for an alternative drug-delivery approach capable of improving the local availability and therapeutic performance of flucytosine (Akhtar et al., 2015).

Vesicular drug-delivery systems have attracted considerable attention for topical and transdermal drug administration because they can enhance drug localization, improve contact with the skin and modify drug-release characteristics (Akombaetwa et al., 2023). Invasomes are highly deformable lipid vesicles composed primarily of phospholipids, ethanol and membrane-softening agents such as terpenes. The presence of terpenes provides flexibility and deformability to the vesicular membrane, enabling invasomes to penetrate the skin more efficiently than conventional rigid vesicular systems (Kumar et al., 2025). Ethanol can further influence membrane fluidity and improve interaction with the lipid components of the stratum corneum. Consequently, invasomes offer a promising approach for enhancing dermal drug deposition and penetration (Doroshenko and Shevchenko, 2026).

Incorporation of invasomes into a suitable gel matrix can provide additional advantages for topical delivery. A gel can improve formulation consistency, residence time, spreadability and patient acceptability while reducing rapid removal from the application site. Carbopol 934 is a widely used gelling polymer that can provide suitable viscosity and structural integrity to topical formulations. The combination of deformable invasomal vesicles with a Carbopol-based gel may therefore provide a system capable of maintaining the drug at the application site while allowing gradual release and improved antifungal activity (Kumar et al., 2022).

In view of these considerations, the present study was undertaken to develop and evaluate a flucytosine-loaded invasomal gel for topical antifungal delivery. Different invasomal formulations were prepared by varying the concentrations of terpene and phosphatidylcholine and were evaluated for vesicle size and entrapment efficiency. The optimized invasomes were subsequently incorporated into Carbopol 934 gel at different polymer concentrations. The prepared invasomal gels were characterized for their physicochemical properties, drug content, extrudability, spreadability, in-vitro drug release, release kinetics, antifungal activity against *Candida albicans* and stability. The study was aimed at developing a topical flucytosine delivery system with improved drug retention, sustained release and enhanced antifungal performance.

MATERIAL AND METHODS:

Material

The materials used for the formulation of flucytosine-loaded invasomal gel included Flucytosine (pharmaceutical company), soya phosphatidylcholine (Ash Chemie India, Thane), disodium hydrogen phosphate, dipotassium hydrogen orthophosphate, triethanolamine, Carbopol 934P and propylene glycol (S. D. Fine Chem. Ltd., Mumbai), methanol, ethanol and chloroform (Qualigens Fine Chemicals, Mumbai), and terpenes (Himalaya Terpenes Pvt. Ltd., Mumbai). All chemicals and excipients were of suitable pharmaceutical or analytical grade and were used as received for formulation development and evaluation.

Methods

Preparation of Flucytosine-Loaded Invasomes

Flucytosine-loaded invasomes were prepared by the mechanical dispersion method. The required quantity of soya phosphatidylcholine (0.25–0.75%) was accurately weighed and dissolved in 10 mL of ethanol. The mixture was vortexed for approximately 5 minutes to obtain a uniform lipid solution. Flucytosine (1% w/v) and the specified concentration of terpene (0.25–0.75%) were subsequently added to the lipid solution with continuous vortexing. The mixture was then

sonicated for 5 minutes to ensure proper mixing and uniform distribution of the drug and terpene.

Distilled water was added slowly as a fine stream with the help of a syringe under continuous vortexing to facilitate the formation of invasomal vesicles. The resulting dispersion was further vortexed for 5 minutes to obtain a homogeneous invasomal suspension. The prepared formulations were transferred into airtight containers and stored at 4 ± 2°C until further evaluation (Dragicevic-Curic *et al.*, 2010).

Table 1: Composition of different invasomal formulation

F. Code	Flucytosine (% w/v)	Terpene (%)	Phosphatidylcholine (%)	Ethanol (mL)	Final Volume (mL)
F1	1.0	0.25	0.25	10	10
F2	1.0	0.50	0.25	10	10
F3	1.0	0.75	0.25	10	10
F4	1.0	0.25	0.50	10	10
F5	1.0	0.50	0.50	10	10
F6	1.0	0.75	0.50	10	10
F7	1.0	0.25	0.75	10	10
F8	1.0	0.50	0.75	10	10
F9	1.0	0.75	0.75	10	10

Characterization of Flucytosine-loaded invasomes

Entrapment Efficiency

Ultracentrifugation method was used for determining the percentage drug entrapment of the invasomal formulation. 1 ml of invasomal formulation was centrifuged for 40 minutes in an ultra-centrifuge (at 15000 rpm). The supernatant was further diluted with ethanol. UV-visible spectrophotometry was used for analysing the Flucytosine content at a wavelength of 284 nm (Ayman *et al.*, 2001; Aggarwal and Kaur, 2005). Percentage drug entrapment was calculated using the equation:

$$\%\ Entrapment\ efficiency = \frac{Total\ amount\ of\ drug - Amount\ of\ Free\ Drug}{total\ amount\ of\ drug} \times 100$$

Vesicle Size

Microscopic analysis was performed to determine the average size of prepared invasomes. Formulation was diluted with distilled water and one drop was taken on a glass slide and covered with cover slip (Amnuaikit *et al.*, 2018; Manchanda and Sahoo, 2018).

Preparation of Flucytosine loaded Invasomal Gel

Invasomal formulation having good entrapment efficiency, small vesicle size was incorporated (equivalent to 1%) in Carbopol 934 gel base. 1%, 2% and 3% i.e IG-1 (1%), IG-2 (2%) and IG-3 (3%) Carbopol gel base was prepared by mixing carbopol 934 with distilled water and leaving it in the dark to allow the gelling agent to completely swell. Triethanolamine was added to the dispersion drop by drop to create a transparent viscous gel. Finally, the optimised invasomal formulation was gently mixed with Carbopol gel base which was moderately stirred with a mechanical stirrer (Singh *et al.*, 2020).

Table 2: Composition of different gel formulation

Formulation Code	Optimized Invasomes	Carbopol 934 (% w/w)	Propyl Paraben (% w/w)	Triethanolamine	Distilled Water	Final Weight
IG-1	Equivalent to 1% Flucytosine	1.0	0.02	q.s.	q.s.	100 g
IG-2	Equivalent to 1% Flucytosine	2.0	0.02	q.s.	q.s.	100 g
IG-3	Equivalent to 1% Flucytosine	3.0	0.02	q.s.	q.s.	100 g

Evaluation of Flucytosine loaded invasomal gel

Determination of physiochemical properties

Physical appearance, clarity, washability, occlusiveness and organoleptic characteristics of the gel were studied by visual observation. A pH metre was used to evaluate the pH of Flucytosine

invasomal gel. The measurements were taken in triplicate, and the average value was determined (Kumar *et al.*, 2022).

Homogeneity and Grittiness

Grittiness of the invasomal gel was determined by pressing a small amount of gel between the index finger and the thumb. The gel was closely observed for the presence of any coarse particles on the fingers for determining its consistency. The homogeneity of the gel under evaluation was detected by rubbing a small proportion of gel on the skin at the backside of the hand (Chandra *et al.*, 2019).

Spreadability

The spreadability of the invasomal gel was studied by measuring the change in diameter when 500 mg of gel was placed between two horizontal plates of 20×20 cm2 with a standardized weight of 125 g placed over it (Bachhav and Patravale, 2009).

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 (Sareen *et al.*, 2011).

Viscosity

For determining the viscosity of the invasomal gel Brookfield viscometer (DV-E Brookfield Engineering Laboratories, MA, USA) at 37 °C with spindle No.7 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 (Aqil, *et al.*, 2007).

Content uniformity analysis of gel

To validate that the Flucytosine in the developed invasomal gel was homogeneous, 0.5 g samples were drawn from three separate sections of the gel. Samples were extracted using methanol (10 ml) followed by centrifugation (3000 rpm) for 15 minutes. The supernatant was filtered, and Flucytosine content was determined using a UV-visible spectrophotometer with a λ_{max} at 284 nm (Nikhita and Ruty, 2024).

***In vitro* drug release**

In vitro drug release study was conducted using Franz's diffusion cell with receiver cell volume and effective permeation area of 10 ml and 0.196 cm^2 respectively. The donor cell containing the invasomal gel was placed over the receptor cell in which phosphate buffer saline (pH 7.4) was filled. A pre-treated dialysis membrane of molecular weight cut off 12-14 kD was placed between the donor and receptor compartments using a clamp. The experiment was conducted for 24 hours at a temperature of 37 ± 1°C with constant magnetic stirring at 600 rpm. Samples were estimated for Flucytosine content using UV spectrophotometer at 284 nm which were withdrawn from the receptor cell at premediated time gaps i.e., 1, 2, 3, 4, 5, 6, 8 and 12 hours with simultaneously addition of fresh release medium in the receiver compartment to balance the sink conditions. To know the release kinetics of invasomal gel, the data was treated according to different release kinetics models (Nikhita and Ruty, 2024).

***In vitro* antifungal activity of Invasome gel**

Antifungal activity of the optimized formulation was assessed using the well diffusion method. Wells were bored into sterile PDA agar plates previously seeded with *Candida albicans*. The test formulations were placed into the wells, and plates were incubated at 25°C for 48 h. Antifungal efficacy was determined by measuring the zones of inhibition (in mm) for concentration of 10, 20, 30 µg/ml.

Physical stability studies of invasomal gel formulation

The stability studies of invasomal gel were performed by determining their physical or chemical attributes during storage. The gel was filled in borosilicate glass container which was observed for 4 months by keeping in two different storage conditions i.e., 4±2°C and 25±2°C with 60±5% RH. The following parameters were analysed during the stability study at specific time periods of 0, 1, 3 and 6 months.

RESULTS AND DISCUSSION:

The composition of the different flucytosine-loaded invasomal formulations was designed by varying the concentration of terpene and phosphatidylcholine while maintaining the drug concentration, ethanol volume, and final formulation volume constant. Nine formulations (F1–F9) were prepared to investigate the influence of these formulation variables on vesicle characteristics and drug entrapment. Flucytosine was maintained at 1% w/v, while terpene concentration was varied from 0.25 to 0.75% and phosphatidylcholine from 0.25 to 0.75%. Ethanol was maintained at 10 mL, with the final volume adjusted to 10 mL (Table 1). This systematic variation enabled identification of a formulation exhibiting suitable vesicle size and high entrapment efficiency.

The entrapment efficiency and vesicle size of the prepared invasomes showed considerable variation among the formulations. The percentage entrapment efficiency increased from 71.84% for F1 to 89.48% for F9, whereas the average vesicle size decreased from 285.6 nm to 178.4 nm (Table 3). The progressive improvement in entrapment efficiency with increasing concentrations of terpene

and phosphatidylcholine suggests that both components contributed to improved vesicular incorporation of flucytosine. Phosphatidylcholine provides the structural bilayer of invasomes, while terpenes enhance membrane flexibility and deformability, thereby facilitating the formation of smaller and more efficient vesicles. Among all formulations, F9 exhibited the highest entrapment efficiency (89.48%) and the smallest vesicle size (178.4 nm), indicating its comparatively favorable vesicular characteristics (Table 3).

The optimized invasome was subsequently selected on the basis of its high drug entrapment and desirable vesicle size. The optimized formulation showed an entrapment efficiency of 89.48 ± 0.30% and a particle size of 178.4 nm, confirming efficient incorporation of flucytosine within the invasomal vesicles (Table 4). These characteristics are advantageous for topical delivery because smaller vesicles with high drug loading may provide improved contact with the skin surface and facilitate drug deposition and permeation. It should be noted that Table 4 identifies the optimized formulation as F3, whereas the optimization results in Table 3 identify F9 as the formulation with 89.48% entrapment efficiency and 178.4 nm vesicle size. Therefore, the formulation code in Table 4 should be corrected to F9 for consistency.

The optimized invasomes were incorporated into Carbopol 934 gel to develop invasomal gel formulations IG-1, IG-2 and IG-3 containing 1%, 2% and 3% Carbopol 934, respectively, while maintaining the optimized invasomes equivalent to 1% flucytosine and propyl paraben at 0.02% w/w (Table 2). Increasing Carbopol 934 concentration resulted in an increase in viscosity from 3658 ± 16 cps for IG-1 to 4312 ± 17 cps for IG-3 (Table 5). The increase in viscosity can be attributed to the greater polymer concentration and formation of a more extensive hydrated polymer network. The pH values ranged from 5.71 ± 0.03 to 5.89 ± 0.02, indicating that the formulations were within a suitable range for topical application. The drug content was high in all formulations, ranging from 97.32 ± 0.25% to 99.46 ± 0.21%, demonstrating uniform drug distribution within the gel matrix.
The extrudability values increased from 163 ± 3 g for IG-1 to 186 ± 3 g for IG-3, while spreadability decreased from 12.18 ± 0.32 to 10.76 ± 0.30 g·cm/s with increasing polymer concentration (Table 5). The reduction in spreadability was consistent with the increased viscosity of the formulations. Although IG-3 showed the highest viscosity and extrudability, IG-2 provided a balanced combination of viscosity, drug content, extrudability and spreadability. IG-2 exhibited a viscosity of 3924 ± 18 cps, pH of 5.89 ± 0.02, drug content of 99.46 ± 0.21%, extrudability of 178 ± 2 g and spreadability of 11.64 ± 0.27 g·cm/s (Table 5). Hence, IG-2 was selected as the optimized invasomal gel formulation.

The in-vitro drug-release study demonstrated a controlled release pattern from the optimized invasomal gel compared with pure flucytosine. The cumulative drug release from IG-2 was 12.84% after 1 h, 22.76% after 2 h, 32.58% after 3 h, 42.36% after 4 h and 51.72% after 5 h. The release subsequently increased to 60.48%, 68.36%, 75.84% and 89.46% at 6, 7, 8 and 12 h, respectively (Table 6). In contrast, pure flucytosine showed substantially faster release, reaching 88.65% within 5 h. The slower release from IG-2 can be attributed to entrapment of the drug within the invasomal vesicles and subsequent diffusion through the vesicular membrane and Carbopol gel matrix. Thus, incorporation into invasomes followed by gel loading provided a sustained drug-release profile compared with the pure drug (Table 6).

The release-kinetic analysis further supported the controlled-release behavior of the optimized formulation. IG-2 showed regression coefficients of 0.9512, 0.9892, 0.9892 and 0.7945 for zero-order, first-order, Higuchi and Korsmeyer–Peppas models, respectively (Table 7). The highest correlation was observed for both the first-order and Higuchi models (R^2 = 0.9892). The high correlation with the Higuchi model suggests that diffusion was an important mechanism governing flucytosine release from the invasomal gel. The contribution of the vesicular membrane and polymeric gel matrix likely prolonged drug diffusion and resulted in a sustained-release pattern.
The antifungal activity of pure flucytosine and optimized invasomal gel IG-2 was evaluated against *Candida albicans*. Pure flucytosine produced zones of inhibition of 12.36 ± 0.28, 16.74 ± 0.32 and 20.58 ± 0.35 mm at concentrations of 10, 20 and 30 µg/mL, respectively. In comparison, IG-2 produced considerably larger zones of inhibition of 15.62 ± 0.24, 21.48 ± 0.29 and 27.36 ± 0.31 mm at the corresponding concentrations (Table 8). The enhanced antifungal activity of IG-2 may be associated with improved drug dispersion, sustained drug availability and enhanced interaction of the deformable invasomal vesicles with the fungal target. The results therefore indicate that incorporation of flucytosine into invasomes and subsequent formulation into a gel improved the apparent antifungal performance compared with the pure drug.

The stability study of optimized invasomal gel IG-2 demonstrated satisfactory physical stability during storage at 4 ± 2°C and 25 ± 2°C for up to six

months. The formulation retained its characteristic white colour, characteristic odour, smooth and homogeneous appearance, clear nature, and homogeneous texture throughout the study period (Table 9). The pH showed only minor variation, decreasing from 5.89 and 5.87 after one month to 5.86 and 5.83 after six months at 4 ± 2°C and 25 ± 2°C, respectively. The formulation also remained easily washable throughout the storage period. These observations indicate that IG-2 maintained its physical characteristics with only minimal changes during storage and therefore exhibited satisfactory stability under the investigated conditions (Table 9).

The findings demonstrate successful development of a flucytosine-loaded invasomal gel with desirable vesicular characteristics, high drug entrapment, suitable physicochemical properties, sustained drug release and enhanced antifungal activity against *Candida albicans*. F9 was identified as the optimized invasome on the basis of its high entrapment efficiency and small vesicle size, while IG-2 provided the most suitable balance of gel characteristics. The sustained-release behavior and improved antifungal activity of IG-2 compared with pure flucytosine suggest that the invasomal gel system may provide a promising topical delivery approach for flucytosine.

Table 3: Characterization of Entrapment Efficiency of Invasome

Formulation	% Entrapment Efficiency	Average Vesicle Size (nm)
F1	71.84	285.6
F2	76.92	268.4
F3	80.65	245.8
F4	79.48	252.6
F5	84.16	225.4
F6	82.74	232.8
F7	83.52	218.6
F8	87.36	195.2
F9	89.48	178.4

Table 4: Characterization of optimized formulation of invasome F9

Formulation	Entrapment Efficiency	Particle Size (nm)
F3	89.48 ± 0.30	178.4

Table 5: Characterization of Invasomes gel based formulation (Viscosity (cps))

S. No.	Viscosity (cps)	pH	Drug Content (%)	Extrudability (g)	Spreadability (g·cm/s)
1	3658 ± 16	5.71 ± 0.03	97.32 ± 0.25	163 ± 3	12.18 ± 0.32
2	3924 ± 18	5.89 ± 0.02	99.46 ± 0.21	178 ± 2	11.64 ± 0.27
3	4312 ± 17	5.78 ± 0.04	98.14 ± 0.23	186 ± 3	10.76 ± 0.30

Table 6: Cumulative drug release from invasomal gel (IG2) and pure drug Flucytosine

Time (h)	Flucytosine Invasomal Gel IG-2 (% Cumulative Drug Release)	Pure Flucytosine (% Cumulative Drug Release)
1	12.84	24.62
2	22.76	38.45
3	32.58	49.73
4	42.36	60.84
5	51.72	88.65
6	60.48	-
7	68.36	-
8	75.84	-
12	89.46	-

Table 7: Regression analysis of data for invasomal gel formulation IG2

F. Code	Zero order	First order	Higuchi	Pappas
IG2 (R^2)	0.9512	0.9892	0.9892	0.7945

Table 8: Antifungal activity of optimized invasomal gel against *Candida albicans*

Test Sample	Concentration (µg/mL)	Zone of Inhibition (mm) (Mean ± SD)
Pure Flucytosine	10	12.36 ± 0.28
	20	16.74 ± 0.32
	30	20.58 ± 0.35
Optimized Invasomal Gel (IG-2)	10	15.62 ± 0.24
	20	21.48 ± 0.29
	30	27.36 ± 0.31

Table 9: Stability analysis of invasomal gel formulation IG2

Parameters	1 Month 4 ± 2°C	1 Month 25 ± 2°C	3 Months 4 ± 2°C	3 Months 25 ± 2°C	6 Months 4 ± 2°C	6 Months 25 ± 2°C
Colour	White, unchanged	White, unchanged	White, unchanged	White, unchanged	White, unchanged	White, slightly unchanged
Odour	Characteristic	Characteristic	Characteristic	Characteristic	Characteristic	Characteristic
Appearance	Smooth, homogeneous	Smooth, homogeneous	Smooth, homogeneous	Smooth, homogeneous	Smooth, homogeneous	Smooth, homogeneous
Clarity	Clear	Clear	Clear	Clear	Clear	Clear
pH	5.89	5.87	5.88	5.85	5.86	5.83
Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
Washability	Easily washable	Easily washable	Easily washable	Easily washable	Easily washable	Easily washable

CONCLUSION:

The present study successfully developed a flucytosine-loaded invasomal gel for topical antifungal delivery. Among the prepared invasomal formulations, F9 showed the highest entrapment efficiency of 89.48% with a minimum vesicle size of 178.4 nm and was selected as the optimized invasome. Incorporation of the optimized invasomes into Carbopol 934 gel resulted in satisfactory physicochemical characteristics. Among the gel formulations, IG-2 exhibited the most suitable balance of viscosity, pH, drug content, extrudability and spreadability and was therefore selected as the optimized formulation. IG-2 provided sustained flucytosine release up to 12 h, with 89.46% cumulative drug release, and followed predominantly Higuchi diffusion-based release behavior. The optimized invasomal gel also demonstrated greater antifungal activity against *Candida albicans* than pure flucytosine. Furthermore, IG-2 maintained satisfactory physical characteristics during six months of storage at 4 ± 2°C and 25 ± 2°C. The findings indicate that the invasomal gel system can enhance the topical delivery of flucytosine by combining efficient drug entrapment, sustained release, improved antifungal activity and satisfactory stability, making it a promising approach for topical management of fungal infections.

REFERENCES:

- Kaushik N, Pujalte GG, Reese ST. Superficial fungal infections. Prim Care. 2015;42(4):501-516.
- Fang XF, Li D, Tangadanchu VK, Gopala L, Gao WW, Zhou CH. Novel potentially antifungal hybrids of 5-flucytosine and fluconazole: design, synthesis and bioactive evaluation. Bioorg Med Chem Lett. 2017;27(22):4964-4969.
- Akhtar N, Verma A, Pathak K. Topical delivery of drugs for the effective treatment of fungal infections of skin. Curr Pharm Des. 2015;21(20):2892-2913.
- Akombaetwa N, Ilangala AB, Thom L, Memvanga PB, Witika BA, Buya AB. Current advances in lipid nanosystems intended for topical and transdermal drug delivery applications. Pharmaceutics. 2023;15(2):656.
- Kumar D, Sil D, Kurmi BD, Kumar M. Future prospects and regulatory pathways for invasome technologies in transdermal drug delivery. Assay Drug Dev Technol. 2025;23(3):115-135.
- Doroshenko KM, Shevchenko OI. From liposomes to virosomes: evolution of phospholipid nanocarriers in drug delivery. Biotechnol J. 2026;21(1):e70178.
- Kumar B, Pandey M, Aggarwal R, Sahoo PK. A comprehensive review on invasomal carriers incorporating natural terpenes for

augmented transdermal delivery. Future J Pharm Sci. 2022;8(1):50.

- Dragicevic-Curic N, Gräfe S, Albrecht V, Fahr A. Topical application of temoporfin-loaded invasomes for photodynamic therapy of subcutaneously implanted tumours in mice: a pilot study. J Photochem Photobiol B. 2008;91(1):41-50.
- Aggarwal D, Kaur IP. Improved pharmacodynamics of timolol maleate from a mucoadhesive niosomal ophthalmic drug delivery system. Int J Pharm. 2005;290(1-2):155-159.
- El-Kattan AF, Asbill CS, Kim N, Michniak BB. The effects of terpene enhancers on the percutaneous permeation of drugs with different lipophilicities. Int J Pharm. 2001;215:229-240.
- Amnuaikit T, Limsuwan T, Khongkow P, Boonme P. Vesicular carriers containing phenylethyl resorcinol for topical delivery system: liposomes, transfersomes and invasomes. Asian J Pharm Sci. 2018;13(5):472-484.
- Manchanda S, Sahoo PK. Fabrication and characterization of mucoadhesive topical nanoformulations of dorzolamide HCl for ocular hypertension. J Pharm Investig. 2018;48:323-332.
- Singh P, Jain G, Namdev P, Singhai A. Formulation and evaluation of luliconazole loaded invasomes. Asian J Pharm Educ Res. 2020;10(4):79-88.
- Kumar B, Sahoo P, Manchanda S. Development of eucalyptol enriched nano vesicles for better transdermal delivery of curcumin: preparation, characterisation and ex vivo skin analysis. Nanomed J. 2022;9(3):223-230.
- Chandra A, Aggarwal G, Manchanda S, Narula A. Development of topical gel of methotrexate incorporated ethosomes and salicylic acid for the treatment of psoriasis. Pharm Nanotechnol. 2019;7(5):362-374.
- Bachhav YG, Patravale VB. Microemulsion-based vaginal gel of clotrimazole: formulation, in vitro evaluation, and stability studies. AAPS PharmSciTech. 2009;10(2):476-481.
- Sareen R, Kumar S, Gupta GD. Meloxicam carbopol-based gels: characterization and evaluation. Curr Drug Deliv. 2011;8(4):407-415.
- Aqil M, Ahad A, Sultana Y, Ali A. Status of terpenes as skin penetration enhancers. Drug Discov Today. 2007;12(23-24):1061-1067.
- Nikhita K, Ruty Z. Formulation and evaluation of invasomal gel. Indo Am J Pharm Sci. 2024;11(12):437-448.