

Development and characterization of fluconazole-loaded spanethosomal gel for topical antifungal therapy

Saja Taher SAHIB¹, Lubna A. SABRI^{2*}

¹ University of Misan, College of Pharmacy, Misan, Iraq

² University of Baghdad, College of Pharmacy, Department of Pharmaceutics, Baghdad, Iraq

ABSTRACT

Fluconazole (FLC) is a commonly used antifungal drug with broad-spectrum activity. However, its traditional topical application is often hindered by limited skin penetration and low drug retention, which can reduce therapeutic effectiveness. This study aimed to develop an FLC-loaded spanethosomal gel capable of sustaining drug release and improving antifungal activity while maintaining safety. FLC-loaded spanethosomes dispersions were prepared using the ethanol injection method with Span 60 and sodium deoxycholate. These vesicles were incorporated into a gel base formulated with either xanthan gum or carboxymethyl cellulose (CMC) as the gelling agent. The prepared gels were evaluated for their physical characteristics, pH, drug content, viscosity and *in vitro* release profile. In addition, the optimized FLC-spanethosomal gel was examined for skin irritation potential and antifungal performance. The optimized formulation, containing 2% xanthan gum, demonstrated desirable properties, including high spreadability (5.17 ± 1.26 g-cm/sec), appropriate viscosity, acceptable drug content ($95.83 \pm 1.04\%$), and a pH of 5.8 ± 0.1 . *In vivo* skin irritation studies confirmed that the formulation was non-irritant. The release profile showed sustained drug release, reaching $88.25 \pm 2.21\%$ after 9 hours. FTIR analysis indicated no significant interaction between FLC and the polymers in the gel base. Antifungal testing against *Candida albicans* showed a

* Corresponding author: Lubna A. SABRI

E-mail: lobna.sabri@copharm.uobaghdad.edu.iq

ORCID:

Saja Taher SAHIB: 0009-0008-7765-2871

Lubna A. SABRI: 0000-0001-7729-6645

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significant improvement ($p < 0.05$) in activity compared with both the plain FLC gel and control formulations. Overall, the findings emphasize the possible use of spanethosomal gel systems as an effective approach for topical antifungal therapy.

Keywords: fluconazole, spanethosomes, gel, antifungal activity, spreadability

INTRODUCTION

Fungal infections have become increasingly prevalent and are now considered a significant global health concern. Superficial infections affecting the skin, hair, and nails, primarily caused by dermatophytes and *Candida* species are the most common¹. Conditions such as athlete's foot, scalp ringworm, and onychomycosis are widespread, particularly in developing regions, where an estimated 40 million people are affected. Immunocompromised individuals are at greater risk, as fungal infections can progress rapidly and, in the case of candidiasis, may lead to invasive and potentially fatal systemic infections². Triazole medications constitute a class of pharmaceuticals that specifically target the cell membrane of *Candida* cells. FLC is one of the preferred treatments for all types of *Candida* infections in both immunocompetent and immunocompromised individuals³. Fluconazole exhibits distinct pharmacokinetic characteristics compared to other azole antifungals, primarily due to the presence of two triazole rings, which contribute to its relatively low lipophilicity ($\log P \approx 0.5$). This limited lipophilicity affects its permeability across biological membranes, including the skin⁴. Recent progress in nanotechnology-based topical formulations has demonstrated improved skin penetration and pharmacokinetic performance of FLC, enhancing its therapeutic potential in cutaneous fungal infections⁵. Topical drug delivery systems offer numerous benefits, including the capacity to deliver drugs more selectively to a specific site and the prevention of problems associated with the gastrointestinal system^{6,7}. Spanethosomes are vesicular nanocarriers structurally related to spanlastics and niosomes but differ in composition, stability, and storage properties. They are typically composed of Span 60, ethanol and bile salts or ions which act as edge activators. Compared to conventional spanlastics, spanethosomes offer enhanced flexibility, improved stability and better biocompatibility⁸. The majority of topical dermatological formulations, including creams and ointments, are characterized by a sticky nature, a lower dispersal coefficient and the necessity of rubbing during application. By employing a gel formulation, these constraints may be mitigated⁹. Currently, there is a significant focus on the formulation of gels, particularly those that are attractive and induce an appealing cool sensation¹⁰. Therefore,

the objective of this investigation was to develop an FLC-loaded spanethosomal gel capable of sustaining drug release and improving antifungal activity while maintaining safety.

METHODOLOGY

Materials

Fluconazole was donated by the Sama-alfayhaa Pharmaceutical Industry in Iraq. Sodium deoxycholate (SDC) and Phosphate buffer (pH 5.5) were purchased from HIMEDIA Laboratories, India. Span 60, methylparaben and ethanol were from Alpha Chemika, India. Carboxymethyl cellulose and xanthan were purchased from LOBA CHEMIE PVT LTD, India.

Preparation of fluconazole-spanethosome

Ethanol injection method using a homogenizer (Homogenizer HG 150, Witeg Labortechnik, Germany) operating for 10 min at 2000 rpm was carried out for the preparation of formulas fluconazole-spanethosomes⁸. The ethanol injection approach is preferred over the thin-film hydration method due to its speed, safety, and reproducibility. Nine formulas (F1-F9) were prepared as shown in Table 1 by mixing three different amounts of Span 60, FLC was kept at 0.5% w/v and SDC was added at three different amounts. The prepared dispersions were subjected to probe sonication (QSONICA Sonicator, Qsonica, USA) for 5 min (50 seconds on and 10 seconds off with 30% amplitude) at room temperature, approximately 20°C¹². Ultimately, the obtained milky dispersions were refrigerated overnight to facilitate the maturation of the vesicles. Refrigeration overnight allows for the stabilization and complete formation of spanethosome vesicles, promoting uniform size distribution, improved encapsulation efficiency, and enhanced formulation stability. It was maintained in this location until the formulations were subjected to additional physicochemical evaluation.

Table 1. Composition of different FLC-spanethosomes formulations

Formula Code	FLC (mg)	Span 60 (mg)	Ethanol (mL)	SDC (mg)	Deionized Water (mL)
F1	50	100	3	5	7 mL
F2	50	100	3	10	7 mL
F3	50	100	3	15	7 mL
F4	50	200	3	5	7 mL
F5	50	200	3	10	7 mL
F6	50	200	3	15	7 mL
F7	50	300	3	5	7 mL
F8	50	300	3	10	7 mL
F9	50	300	3	15	7 mL

Evaluation of the prepared spanethosomes

Particle size and size distribution

Distilled water was used to dilute each of the prepared formulations at a ratio of 1:10. The mean droplet size of the spanethosome was determined using a laser particle size analyser (Malvern Instrument Ltd., UK)¹³.

Fluconazole entrapment efficiency (EE%)

By quantifying the un-entrapped FLC in the dispersion medium, the EE% of FLC in the spanethosome was measurable. Utilizing a cooling centrifuge, 1 mL of spanethosome was introduced into a centrifugation tube and spun at 15,000 rpm for 1 hour at 7°C. Cold centrifugation was employed for all formulations to separate free drug from spanethosomes. Following the separation and dilution of the resultant supernatant with ethanol, the drug concentration was quantified utilizing a UV-VIS spectrophotometer at 261 nm. As a result, the EE% was derived from the subsequent equation. ($y=0.0021x-0.0114$, $R^2=0.9993$). Calculation of EE% was conducted according to the following equation¹⁴:

$$EE\% = \frac{\text{Rheum } L.}{\text{Total amount of drug}} \times 100 \text{ [Eq 1]}$$

Drug release profile

The dissolution apparatus type II (paddle type) was utilized for the *in vitro* FLC release investigation. Each formulation was put within a dialysis membrane (molecular weight cut-off 8000 Dalton), which had been immersed in phosphate buffer at pH 5.5 overnight. The membrane bag was thereafter affixed to the paddle shaft, rotated at 100 rpm, and maintained at a temperature of $32 \pm 1^\circ\text{C}$. A volume of 3 ml was withdrawn at specified time intervals of 0.5, 1, 2, 3, 4, 5, 6 and 7 hours, and replaced with 3 ml of fresh PBS to maintain the sink condition. The samples were analyzed for fluconazole concentration in withdrawn sample by the UV spectrophotometry at 260 nm against blank formula which had the same prepared spanethosomes components except FLC¹⁵.

Preparation of FLC spanethosomal gel and FLC plain gel

Fluconazole-loaded spanethosomal gels were formulated using varying concentrations (1% and 2% w/w) of carboxymethyl cellulose (CMC) and xanthan gum as gelling agents (Table 2). The predetermined quantities of CMC and xanthan were gradually dispersed into the FLC-spanethosomal dispersion under continuous stirring at 800 rpm for 2 hours then methylparaben was incorporated with stirring for another half hour to ensure its uniform distribution followed by standing to allow for complete gel formation. For comparison of antifungal activity with the optimized formulation, a plain gel was prepared using the same procedure, replacing the spanethosomal dispersion with a solution of pure FLC dissolved in ethanol. A control gel was also prepared following the same method as the spanethosomal gel, but without incorporating FLC.

Table 2. Composition of FLC spanethosomal gel formulations

Formula Code	CMC (w/w %)	Xanthan (w/w %)	Methylparaben (mg)
F1cmc1%	1%		0.18
F1cmc2%	2%		0.18
F6 cmc1%	1%		0.18
F6 cmc2%	2%		0.18
F1 xan1%		1%	0.18
F1 xan2%		2%	0.18
F6 xan1%		1%	0.18
F6 xan2%		2%	0.18

Evaluation of fluconazole spanethosomal gel

Physical appearance

Visual inspection was performed to evaluate the homogeneity of all prepared gels after being transferred into their respective containers. The appearance of the gels and the presence of any visible aggregates were also assessed¹⁶.

pH measurement

To minimize the risk of skin irritation, it is crucial to evaluate the pH of topical formulations to ensure compatibility with the natural pH of the skin. The pH values of the FLC gel formulations were measured using a calibrated digital pH meter¹⁷.

Evaluation of spreadability

The spreadability of the gel formulations was determined by placing 0.5 grams of gel in a circular area with a diameter of 2 cm on a glass plate. A second glass plate was carefully placed over the gel, and a weight of 0.5 kg was applied to the top plate for 5 minutes. After the specified time, the diameter of the spread gel was measured in centimeters to assess its spreadability¹⁸.

Viscosity measurement

The viscosity of the prepared FLC-loaded spanethosomal gel was evaluated using a digital rotational viscometer (Myr Rotational Viscometer, Spain) equipped with spindle number R7. Measurements were conducted at room temperature. The spindle was immersed in the sample, and viscosity readings were recorded at rotational speeds of 6, 12, 30, 50, 60, 100, and 200 rpm. The resulting viscosity values were expressed in centipoise (n=3)¹⁹.

Drug content determination

The quantity of FLC in the prepared spanethosomal gels was quantified using a validated UV-spectrophotometric method. The drug content was expressed as a percentage of the theoretical amount initially incorporated into the system. For analysis, approximately 0.5 gram of the spanethosomal gel was dissolved in ethanol, and the absorbance of the resulting solution was measured at 261 nm using a UV-Visible spectrophotometer²⁰.

***In vitro* drug release**

The *in vitro* release profile of FLC from the gel formulations was evaluated using a Franz diffusion cell apparatus. One gram of the FLC spanethosomal gel was placed in the donor compartment, while the receptor compartment

was filled with 25 mL of phosphate buffer (pH 5.5). A synthetic semipermeable membrane (molecular weight cut-off: 8000 Da) was used to separate the donor and receptor chambers. The receptor medium was maintained at a constant temperature of $32 \pm 0.5^\circ\text{C}$ and agitated continuously at 250 rpm. At predetermined time intervals, 1 mL aliquots were withdrawn from the receptor compartment and immediately replaced with an equal volume of fresh buffer to maintain sink conditions. The concentration of FLC in the samples was determined spectrophotometrically at 260 nm using phosphate buffer as the blank. The release kinetics were further analyzed using the Korsmeyer–Peppas model to characterize the drug release mechanism²¹.

FTIR spectrum for the optimum FLC-spanethosome gel

The compatibility between the active pharmaceutical ingredient and the selected excipients was assessed through a comparative analysis of their Fourier-transform infrared (FTIR) spectra. The spectrum of the pure drug was analyzed alongside those of its physical mixtures with the excipients used in the formulation, as well as the spectrum of the selected optimized formulation²².

Skin irritation test

A skin irritation test was conducted on rats divided into three groups (n=3 per group): a control group (no treatment), a group treated with blank gel, and a group treated with FLC-loaded spanethosomal gel. A defined amount of gel was applied to a shaved area of the dorsal skin of each animal. The application site was examined at the time of application, and subsequently after 1 hour and 24 hours, for any signs of irritation, including erythema, lesions, or necrosis. The purpose was to assess the potential dermal toxicity or irritancy of the formulations²³.

Antifungal activity of optimum FLC spanethosome gel

The antifungal efficacy of the optimum gel formulation was assessed *in vitro* using the Mueller-Hinton agar well diffusion method. *Candida albicans* cultures were standardized to a concentration of 1.5×10^8 CFU/mL. Agar plates were prepared, and wells with a diameter of 6 mm were carefully bored into the inoculated media²⁴. The selected gel formulation, a control gel (blank gel) containing all components of spanethosomal gel except fluconazole, a plain gel (fluconazole and gelling agent 2% xanthan), and a negative control (phosphate buffer) were accurately introduced into the respective wells. The plates were then incubated at 37°C for 48 hours. Following incubation, the diameter of the inhibition zones surrounding each well was measured to evaluate antifungal activity.

Statistical analysis

All evaluation test results were conducted in triplicate and presented as the mean \pm standard deviation (SD). Data were analyzed using GraphPad Prism 10 and due to our small sample size ($n=3$), normality testing was not possible. Therefore, we assumed that our data were normally distributed, and we performed a one-way ANOVA test for the statistical analysis. Statistical significance was established by p values of 0.05 or lower, whilst values above 0.05 were deemed statistically insignificant²⁵.

RESULTS and DISCUSSION

Preparation and evaluation of FLC spanethosomes

Nine prepared formulations exhibited a homogeneous, milky-white liquid dispersion. The physicochemical characteristics of the spanethosomal vesicles are summarized in Table 3, which presents the results of the investigation into the effects of varying concentrations of Span 60 and SDC. The particle size of the spanethosomes ranged from 185.00 ± 5.00 nm to 277.17 ± 18.41 nm, with polydispersity index (PDI) values between 0.23 ± 0.03 and 0.42 ± 0.02 (Table 3). The entrapment efficiency (EE%) varied from $79.79 \pm 8.36\%$ to $95.92 \pm 3.42\%$, depending on the formulation parameters.

Table 3. The Entrapment Efficiency (EE)%, vesicular size (VS), and PDI of the spanethosomal prepared formulas

Formula Code	EE%*	VS (nm)*	PDI*
F1	95.92 ± 3.42	189.33 ± 14.01	0.23 ± 0.03
F2	92.37 ± 2.68	207.00 ± 9.85	0.41 ± 0.01
F3	92.90 ± 8.69	187.33 ± 7.77	0.37 ± 0.02
F4	95.46 ± 0.68	277.17 ± 18.41	0.41 ± 0.01
F5	90.87 ± 0.45	185.00 ± 5.00	0.38 ± 0.01
F6	91.91 ± 0.80	188.7 ± 1.8	0.25 ± 0.01
F7	79.79 ± 8.36	242.53 ± 7.53	0.42 ± 0.02
F8	87.24 ± 2.81	229.00 ± 6.24	0.35 ± 0.01
F9	91.31 ± 1.34	188.00 ± 6.24	0.38 ± 0.02

*The results were presented as the mean \pm standard deviation.

A significant reduction in mean vesicle size ($p < 0.05$) was observed with increasing concentrations of SDC when span 60 was 200 and 300 mg, as illustrated in Figure 1. Similar findings were reported by Leonyza A²⁶. This reduction in vesicle size may be attributed to the anionic nature of SDC, which promotes steric and electrostatic repulsion between adjacent vesicles, thereby contributing to size minimization²⁷.

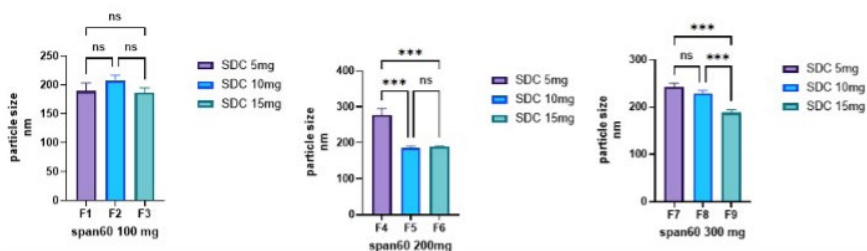


Figure 1. The impact of SDC amount on FLC-loaded spanethosomes vesicles size (ns, *, **, and *** represent non-significant, $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively), $n=3$, mean values \pm SD

Based on the results of the ANOVA analysis, the amount of SDC had a statistically significant effect ($p < 0.05$) on the PDI values of the FLC-loaded spanethosomes, as shown in Figure 2. A PDI value of 0.3 or below is generally considered acceptable, indicating a uniform and homogeneous colloidal dispersion²⁸. Among the tested formulations, F1, F3, F5, F6 and F9 demonstrated PDI values consistent with a nearly monodisperse system.

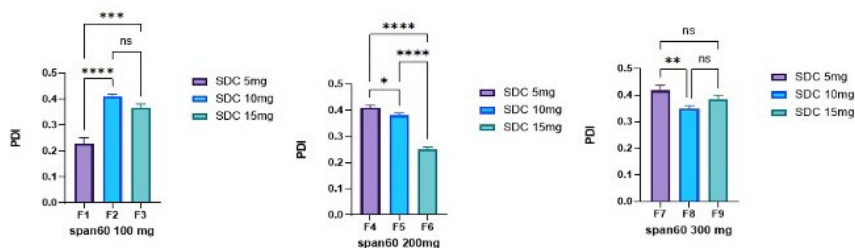


Figure 2. The impact of SDC amount on polydispersity index value of FLC-loaded spanethosomes, (ns, *, **, and *** represent non-significant, $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively), $n=3$, mean values \pm SD

The incorporation of SDC, as an edge activator, contributed to high entrapment efficiencies (EE%) across all formulations, with values consistently exceeding 79.7% (Table 3). No statistically significant variation in EE% was observed at Span 60 concentrations of 100 mg and 300 mg, despite increasing SDC levels. However, at a Span 60 concentration of 200 mg, a statistically significant decrease in EE% ($p < 0.05$) was detected when the amount of SDC was increased from 5 mg in formulation F4 ($95.46 \pm 0.68\%$) to 10 mg in F5 ($90.87 \pm 0.45\%$) and 15 mg in F6 ($91.91 \pm 0.80\%$), as illustrated in Figure 3.

Although the EE% decreased slightly at higher SDC levels, the values remained within an acceptable range. The observed reduction may be due to excessive membrane fluidization caused by higher SDC concentrations, which can compromise bilayer stability and promote drug leakage. This effect appears to be more pronounced at intermediate Span 60 levels, possibly due to an imbalance between membrane-forming components and surfactant concentration²⁹.

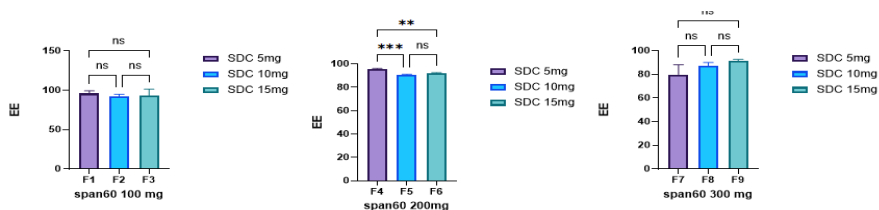


Figure 3. The impact of SDC amount on entrapment efficiency percentage of FLC-loaded spanethosomes (ns, *, **, and *** represent non-significant, $p < 0.05$, $p < 0.01$, and $p < 0.001$, respectively), $n = 3$, mean values \pm SD

***In vitro* release profile**

The *in vitro* release profiles of formulations F1, F3, F5, F6, and F9 were compared based on their favorable physicochemical characteristics, specifically: EE% greater than 90%, vesicle size below 200 nm, and PDI less than 0.4, as presented in Table 3. After 6 hours, the cumulative percentage of FLC released from the spanethosomal formulations followed the descending order: F1 ($100 \pm 0.37\%$) > F5 ($97.24 \pm 1.20\%$) > F6 ($94.60 \pm 1.64\%$) > F3 ($92.92 \pm 1.70\%$) > F9 ($64.08 \pm 0.47\%$), as shown in Figure 4.

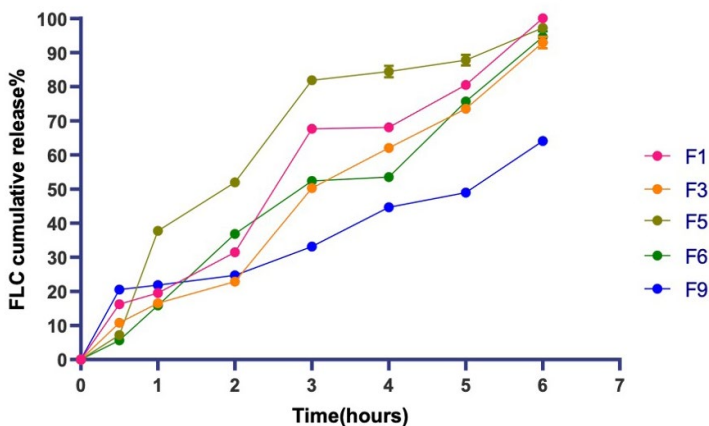


Figure 4. The dissolution profile of the selected FLC-loaded spanethosomes formulations

Evaluation of FLC spanethosomal gel

Physical characteristics

The prepared FLC spanethosomal gel formulations were evaluated for their physical appearance, including texture, clarity, and homogeneity. All formulations demonstrated a smooth, uniform texture and an off-white color, with no evidence of phase separation, grittiness, or particulate matter, indicating good physical stability³⁰.

pH measurement

As shown in Table 4, the pH values of gel formulations ranged from 5.8 ± 0.1 to 7.2 ± 0.1 , which falls within the physiologically acceptable range for topical application and minimizes the potential for skin irritation³¹.

Spreadability

The spreadability of topical formulations is a critical parameter influencing both ease of application and therapeutic efficacy, as inadequate spreadability may prevent uniform dosing across the intended site of application¹⁷. As presented in Table 4, the spreadability values of gel formulations ranged from 4.0 ± 1.0 to 7.83 ± 0.76 . These findings are consistent with Nurman et al. (2019), who reported that a spreadability diameter of approximately 5–7 cm is suitable for topical gels and indicative of good patient usability³². Notably, the spreadability of xanthan-based gel formulations was lower than that of CMC-based gels. This difference can be attributed to the intrinsic properties of the polymers used. In general, an increase in polymer viscosity whether due to higher concentration or increased cross-linking, results in reduced spreadability of semisolid preparations³³.

Drug content

The fluconazole content in all gel formulations ranged from $83.78 \pm 5.57\%$ to $99.61 \pm 3.95\%$, indicating uniform drug distribution throughout the gels. These values were in close agreement with the theoretical drug content, confirming the consistency and accuracy of the formulation process.

Table 4. The pH, spreadability, and drug content % evaluation of the prepared FLC spanethosomal gel

Spanethosomal Gel	pH	Spreadability (g·cm/sec)	Drug Content %
F1 cmc1%	7.2 ± 0.1	7.83 ± 0.76	84.08 ± 5.25
F1 cmc2%	7.0 ± 0.1	6.0 ± 1.0	83.78 ± 5.57
F6 cmc1%	7.1 ± 0.1	6.5 ± 0.5	90.91 ± 2.01
F6 cmc2%	7.2 ± 0.1	5.0 ± 0.5	95.29 ± 2.25
F1 xan1%	6.2 ± 0.1	6.0 ± 1.0	92.3 ± 0.98
F1 xan2%	5.8 ± 0.1	5.17 ± 1.26	95.83 ± 1.04
F6 xan1%	6.4 ± 0.1	5.17 ± 0.76	91.94 ± 1.82
F6 xan2%	6.1 ± 0.1	4.0 ± 1.0	99.61 ± 3.95

Viscosity

Viscosity measurements were performed to evaluate the rheological properties of the gel formulations and to examine the influence of polymer type and concentration. As revealed in Figure 5, the viscosity of the gels decreased with increasing shear rate, demonstrating shear-thinning (pseudoplastic) behavior, which is typical of semisolid polymeric systems. This behavior facilitates easier application under mechanical stress (during spreading on the skin) while maintaining structural integrity at rest. Among the evaluated formulations, the F6 xan2% gel formula exhibited the highest viscosity, reaching approximately 11687.76 centipoise (cP) at a shear rate of 200 rpm. The increase in viscosity with higher polymer concentration is attributed to the greater extent of molecular entanglement and network formation within the gel matrix³⁴.

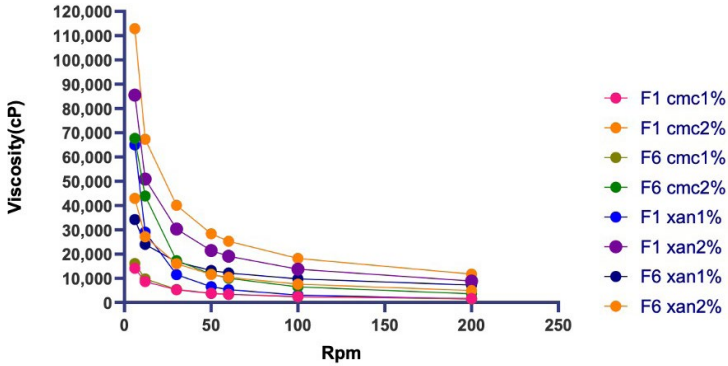


Figure 5. Viscosity analysis of FLC-loaded spanethosomal gel formulations

***In vitro* FLC release from spanethosomal gel**

The *in vitro* release profiles of FLC from various spanethosomal gel formulations were evaluated, and the results are presented in Figure 6. Among the tested formulations, F6 Xan 2% and F6 cmc2% formula exhibited the highest cumulative drug release at 4 hours. In contrast, formulation, such as F1 Xan 2% demonstrated comparatively slower release rates extended for 9 hours. These findings highlight the critical role of both the type and concentration of the gelling polymer in modulating drug release rate. Differences in polymer structure, viscosity, and interaction with the vesicular system likely contribute to the observed variations in release behavior.

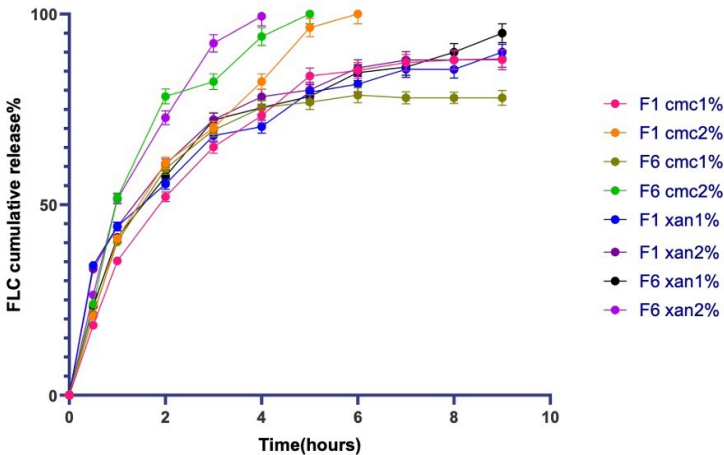


Figure 6. Released profiles analysis of FLC-loaded spanethosomes gel formulations

FTIR spectrum

The FTIR spectra of the optimum formula (F1 xan2%), unadulterated FLC and the physical mixture were illustrated in Figure 7. The FTIR spectrum of fluconazole exhibited key characteristic bands at approximately 3115.04 cm^{-1} (O–H and aromatic C–H stretching), 1618.28 cm^{-1} (aromatic C=C stretching), 1417.68 cm^{-1} (triazole ring stretching) and 1141.86 cm^{-1} (C–O tertiary alcohol stretching). These results are consistent with the spectra that have been previously reported and confirm the presence of fluconazole's functional groups^{35,36}. The optimum formula (F1 xan2%) and the physical mixture's FTIR spectra showed all of the characteristic peaks of FLC and the used excipients, without the appearance of any new bands, which suggests that there was no chemical interaction²², as shown in Figure 7.

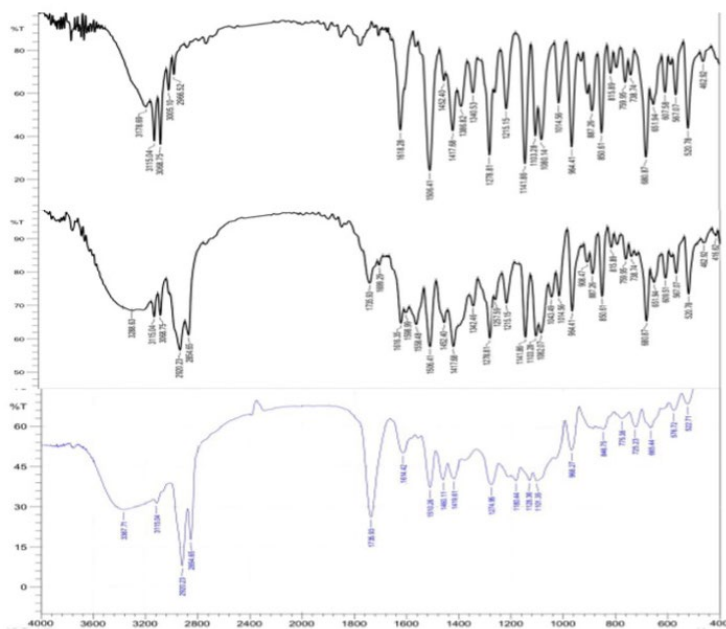


Figure 7. The FTIR spectra of fluconazole, physical mixture, and formula F1 xan2% for up to down, respectively

Skin irritation test

To ensure the dermatological safety of the optimized gel formulation (Formula F1 xan2%), a skin irritation study was conducted using rats, no visible signs of irritation or erythema were observed, indicating that the formulation was well-tolerated and safe for topical application.

Antifungal activity of optimum gel loaded with fluconazole spanethosomes

The control gel (without fluconazole) exhibited no inhibition zone against *C. albicans*, while formula F1xan2% exhibited an inhibition zone of 12.75 ± 1.26 mm, plain gel (pure fluconazole with gelling agent) has no activity, as illustrated in Figure 8.

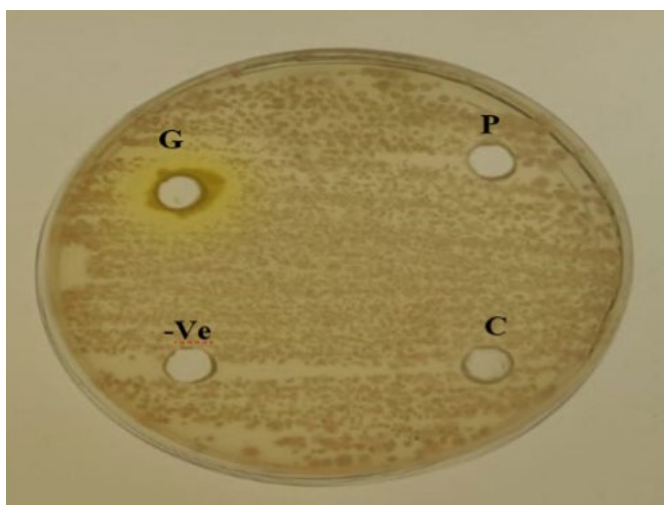


Figure 8. Photo illustrated; G: FLC-spanethosomal gel, P: plain gel, C: control gel, -Ve: negative control

The optimized fluconazole spanethosomal gel (containing 2% xanthan gum) showed high drug content, favorable viscosity, extended drug release, and good spreadability. Polymer type and concentration significantly influenced the gel's physical and release properties. *In vitro* antifungal testing demonstrated enhanced activity of the optimized gel, as evidenced by a larger inhibition zone compared to the plain gel. Additionally, the absence of skin irritation in animal studies confirmed its suitability for topical use.

STATEMENT OF ETHICS

The investigation was conducted in accordance with all applicable ethical standards. Research Ethics Committee at the University of Baghdad/College of Pharmacy has assigned the research ethical approval form number RECO32431R on 20/10/2024.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

The authors certify their contribution to the paper in the following manner: Design and conception of the study: LAS; data collection: ST; analysis and interpretation of results: LAS, ST; draft manuscript preparation: LAS, ST. The final version of the manuscript was endorsed by both authors after the results were reviewed.

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