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Formulation And Characterization Of Polymeric Emulgel Of Flucytosine For Effective Topical Fungal Treatment

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Abstract
The present study aimed to develop and characterize a polymeric emulgel formulation of Flucytosine for effective topical treatment of fungal infections, overcoming the limitations associated with conventional formulations. Flucytosine-loaded emulsions were prepared using cholesterol as the oil phase and incorporated into a Carbopol 934P gel base to obtain the emulgel. The formulations were evaluated for physical appearance, washability, spreadability, extrudability, viscosity, pH, drug content, in-vitro drug release, release kinetics, and antimicrobial activity against Candida albicans*. All formulations exhibited good homogeneity, acceptable pH (6.15–6.80), excellent washability, and shear-thinning behavior. Drug content ranged from 95.58 ± 0.74% to 99.85 ± 0.15%, indicating uniform drug distribution. In-vitro release studies demonstrated a sustained release pattern, with the optimized formulation (F3) showing 86.53% cumulative release over 240 minutes. Kinetic modeling suggested a first-order release profile with a non-Fickian diffusion mechanism. Antimicrobial studies confirmed potent antifungal activity of the optimized formulation, with the highest inhibition zone of 24.65 ± 0.86 mm at 100 mg/ml. These findings suggest that Flucytosine-loaded polymeric emulgel is a promising topical delivery system for effective management of fungal infections, offering improved patient compliance and therapeutic efficacy.*
Keywords: *Flucytosine, Polymeric emulgel, Antifungal activity, Sustained drug release,* Candida albicans, *Topical drug delivery, Carbopol 934P, Release kinetics*

INTRODUCTION

Fungal infections of the skin are among the most prevalent superficial mycoses, affecting millions worldwide and posing significant therapeutic challenges due to recurrence, drug resistance, and limited penetration of topical agents (Gupta & Cooper, 2008). These infections, caused primarily by dermatophytes, yeasts, and molds, can lead to discomfort, disfigurement, and in severe cases, systemic spread in immunocompromised individuals (Havlickova et al., 2008).

Flucytosine (5-fluorocytosine) is a synthetic fluorinated pyrimidine analog with potent antifungal activity against *Candida* species, *Cryptococcus neoformans*, and some molds. Its mechanism involves intracellular conversion by fungal cytosine deaminase into 5-fluorouracil, which is subsequently incorporated into fungal RNA, disrupting protein synthesis, and inhibiting DNA synthesis through thymidylate synthase inhibition (Vermes et al., 2000). While flucytosine is clinically effective, its use is largely restricted to systemic infections in combination therapy, due to poor stability in conventional topical formulations and systemic toxicity risks when used orally (Vermes et al., 2003).

The development of polymeric emulgels offers a promising approach for topical delivery of antifungal drugs. Emulgels combine the advantages of emulsions (enhanced solubilization of hydrophobic drugs) and gels (favorable rheology, ease of application, and non-greasy nature), making them suitable for sustained and localized drug release at the site of infection (Sharma et al., 2014). The polymeric network in emulgels can improve drug stability, enhance skin retention, and provide controlled release properties while reducing systemic exposure (Joshi & Patravale, 2006).

Given the increasing resistance to standard antifungal agents and the need for patient-friendly, effective topical formulations, formulating a polymeric emulgel of flucytosine could significantly improve therapeutic outcomes for superficial fungal infections. The characterization of such a formulation encompassing physical properties, pH, viscosity, spreadability, drug content, and in-vitro release will be critical in ensuring optimal performance and stability (Patel et al., 2011). Therefore, the present study aims to formulate and characterize a polymeric emulgel of flucytosine to achieve enhanced topical antifungal activity, sustained drug release, and improved patient compliance.

Materials and Methods

Materials

The formulation of the flucytosine-loaded polymeric emulgel was developed using pharmaceutical-grade ingredients sourced from reputed suppliers. Flucytosine was obtained as a gift sample from a pharmaceutical company, while cholesterol was procured from Ash Chemie India, Thane. Analytical-grade disodium hydrogen phosphate, dipotassium hydrogen orthophosphate, sodium chloride, carbopol 934P, methyl paraben, propyl paraben, and propylene glycol were supplied by S. D. Fine Chem. Ltd., Mumbai. Methanol, ethanol, and chloroform of analytical grade were obtained from Qualigens Fine Chemicals, Mumbai. All chemicals and reagents used were of analytical or pharmaceutical grade and were employed without further purification to ensure formulation quality and reproducibility.

METHODS

Preparation of Carbopol 940

Fifty grams of the Carbopol gel was prepared by dispersing one gram of carbopol powder in50 ml purified water with aid of moderate speed stirrer (50 rpm), and then the pH was adjusted to 6-6.5 using 0.5N of sodium hydroxide.

Preparation of emulsion

The emulsions for Flucytosine emulgel formulations (F1–F8) were prepared using a modified general method as follows:

The oil phase was prepared by dissolving Span 20 (0.45%) in liquid paraffin, the concentration of which varied between 5% and 7.5% depending on the formulation (as shown in Table 7.1). Simultaneously, the aqueous phase was prepared by dissolving Tween 20 (0.3%) in purified water. Separately, 1 g of Flucytosine was dissolved in 2.5 g of ethanol, and a preservative solution was prepared by dissolving 0.15 g of methylparaben and 0.05 g of propylparaben in 5 g of propylene glycol. Both these solutions were mixed with the aqueous phase to form a homogenous aqueous component.

The required quantity of Carbopol 940 or Carbopol 934 (ranging from 0.25% to 1%, depending on the formulation) was dispersed in the aqueous phase before emulsification.

Both the oil phase and aqueous phase were separately heated to 70–80°C to ensure complete dissolution and uniformity. The oil phase was then slowly added to the aqueous phase with continuous stirring at 500 rpm using a mechanical stirrer. Stirring was continued until the emulsion cooled to room temperature, leading to the formation of a uniform emulsion base. This emulsion was further used to prepare the emulgel by adjusting the pH to 6.8–7.0 using triethanolamine, leading to the final Flucytosine emulgel formulations (F1–F8).

Formulation of Flucytosine emulgel

Eight formulation of Flucytosine were prepared by dispersing the obtained emulsions with the gel in 1:1 ratio with gentle stirring until get homogenous emulgel (Khullar *et al.,* 2012).

Table 1: Different formulas of Flucytosine emulgel (% w/w)

F. code	Flucytosine (%)	Carbopol 940 (mg)	Carbopol 934 (mg)	Liquid Paraffin (%)	Span 20 (%)	Tween 20 (%)	Propylene glycol (%)	Water (ml)
F1	1	0.25	-	5	0.45	0.3	5	100
F2	1	0.5	-	5	0.45	0.3	5	100
F3	1	0.75	-	5	0.45	0.3	5	100
F4	1	1	-	5	0.45	0.3	5	100
F5	1	-	0.25	7.5	0.45	0.3	5	100
F6	1	-	0.5	7.5	0.45	0.3	5	100
F7	1	-	0.75	7.5	0.45	0.3	5	100
F8	1	-	1	7.5	0.45	0.3	5	100

Evaluation of emulgel

Physical characteristic

The Physical characteristic was checked for gel formulations (colour, clogging, homogeneity and texture) (Patel *et al.*, 2014).

Determination of pH

The pH of the gels was determined by digital pH meter. One gram of gel was dissolved in 25 ml of distilled water and the electrode was then dipped in to gel formulation for 30 min until constant reading obtained. And constant reading was noted. The measurements of pH of each formulation were replicated two times (Single *et al.*, 2012).

Washability

Formulations were applied on the skin and then ease and extent of washing with water were checked manually.

Extrudability study

The gel formulations were filled into collapsible metal tubes or aluminium collapsible tubes. The tubes were pressed to extrude the material and the extrudability of the formulation was checked (Mundada *et al.*, 2013).

Spreadability

An important criterion for gels is that it must possess good spreadability. Spreadability is a term expressed to denote the extent of area to which the gel readily spreads on application to skin. The therapeutic efficacy of a formulation also depends on its spreading value. A special apparatus has been designed to study the spreadability of the formulations. Spreadability is expressed in terms of time in seconds taken by two slides to slip of from formulation, placed between, under the application of a certain load. Lesser the time taken for the separation of two slides, better the spreadability.

Two glass slides of standard dimensions (6×2) were selected. The gel formulation whose spreadability had to be determined was placed over one of the slides. The second slide was placed over the slide in such a way that the formulation was sandwiched between them across a length of 6 cms along the slide. 100 grams of weight was placed up on the upper slide so that the gel formulation between the two slides was traced uniformly to form a thin layer.

The weight was removed and the excess of the gel formulation adhering to the slides was scrapped off. The lower slide was fixed on the board of the apparatus and one end of the upper slide was tied to a string to which 20 gram load could be applied 50with the help of a simple pulley. The time taken for the upper slide to travel the distance of 6 cms and separate away from lower slide under the direction of the weight was noted. The experiment was repeated and the average of 6 such determinations was calculated for each gel formulation.

$$\text{Spreadability} = \frac{m.l}{t}$$

Where, S=Spreadability (gcm/sec)
m = weight tied to the upper slide (20 grams)
l= length of glass slide (6cms).
t = time taken is seconds.

Viscosity

The measurement of viscosity of the prepared gel was done using Brookfield digital Viscometer (Khunt *et al.*, 2012). The viscosity was measured using spindle no. 6 at 10 rpm and 25^{0}C. The sufficient quantity of gel was filled in appropriate wide mouth container. The gel was filled in the wide mouth container in such way that it should sufficiently allow to dip the spindle of the Viscometer. Samples of the gels were allowed to settle over 30 min at the constant temperature (25 ±/1^{0}C) before the measurements.

Drug content determination

Drug concentration in emulgel was measured by UV spectrophotometer. Flucytosine content in emulgel was measured by dissolving Known quantity of emulgel in solvent (Phosphate Buffer pH 7.4) by

Sonication. Absorbance was measured after suitable dilution at 284nm in UV/VIS spectrophotometer (Labindia 3000+) (Zhang *et al.,* 1995).

***In-vitro* drug release studies using the prehydrated cellophane membrane**

Preparation of cellophane membrane for the diffusion studies:

The cellophane membrane approximately 25 cm x 2cm was taken and washed in the running water. It was then soaked in distilled water for 24 hours, before used for diffusion studies to remove glycerin present on it and was mounted on the diffusion cell for further studies (Rutrer, 1987).

Diffusion Studies:

The *in-vitro* diffusion of drug from the different gel preparations were studied using the classical standard cylindrical tube fabricated in the laboratory; a simple modification of the cell is a glass tube of 15mm internal diameter and 100mm height. The diffusion cell membrane was applied with one gram of the formulation and was tied securely to one end of the tube, the other end kept open to ambient conditions which acted as donor compartment. The cell was inverted and immersed slightly in 250 ml of beaker containing neutralizing phthalate buffer, freshly prepared (pH 5.4)as a receptor base and the system was maintained for 2 hrs at 37± 0.5°C. The media was stirred using magnetic stirrer. Aliquots, each of 5 ml volume were withdrawn periodically at predetermined time interval of up to 12 hrs and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium and analyzed by UV-Vis spectrophotometer at 284 nm using neutralizing phthalate buffer as blank.

***In vitro* antifungal activity of optimized emulgel formulation**

The well diffusion method was used to determine the antifungal activity of the emulgel prepared from of Flucytosine using standard procedure (Bauer, 1966). There were 3 concentration used which are 25, 50 and 100 mg/ml in studies. It's essential feature is the placing of wells with the antibiotics on the surfaces of agar immediately after inoculation with the organism tested. Undiluted over night broth cultures should never be used as an inoculums. The plates were incubated at 37°C for 24 hr. and then examined for clear zones of inhibition around the wells impregnated with particular concentration of drug.

RESULTS AND DISCUSSION

The prepared Flucytosine-loaded polymeric emulgel formulations were evaluated for their physical and performance-related parameters. Washability studies (Table 2) revealed that all formulations demonstrated good to excellent washability, with F2 and F3 exhibiting excellent (+++) washability, indicating ease of removal from the skin surface, which is desirable for patient compliance.

Extrudability and spreadability results (Table 3) showed that F3 and F4 had excellent (+++) extrudability, suggesting better ease of application from the container. Spreadability values ranged from 9.87 ± 0.14 g·cm/sec (F8) to 14.45 ± 0.25 g·cm/sec (F1). A decrease in spreadability was observed with increasing polymer concentration, which can be attributed to the higher viscosity of these formulations.

Viscosity measurements (Table 4) indicated that all formulations exhibited shear-thinning behavior, with viscosity decreasing at higher spindle speeds (from 10 to 100 rpm). This pseudoplastic behavior is characteristic of topical gels and supports ease of application without compromising formulation stability.

The pH values (Table 5) of the formulations ranged from 6.15 ± 0.03 to 6.80 ± 0.02, which is within the acceptable range for topical applications, thereby minimizing the risk of skin irritation.

Drug content analysis (Table 6) demonstrated uniform distribution of Flucytosine in the formulations, with drug content ranging from 95.58 ± 0.74% (F6) to 99.85 ± 0.15% (F3). The high drug content in F3 suggests superior formulation uniformity, possibly due to optimized mixing conditions and excipient compatibility.

In-vitro drug release studies (Table 7) revealed that all formulations showed a sustained release profile over 240 minutes. Among them, F1 exhibited the highest cumulative drug release (98.89%), followed by F2 (93.58%) and F3 (86.53%). The differences in release rates may be attributed to variations in polymer type and concentration, which influence the gel matrix structure and drug diffusion rate.

Kinetic modeling of the optimized formulation F3 (Table 8) showed the highest correlation coefficient (R^2 = 0.9332) for the First-order model, indicating that the drug release was concentration-dependent.

The Korsmeyer–Peppas model (R^2 = 0.894) suggested a non-Fickian diffusion mechanism, implying that both diffusion and polymer relaxation contributed to the release process.
The antimicrobial activity of the optimized formulation (Table 9) against *Candida albicans* demonstrated a concentration-dependent increase in the zone of inhibition, with the maximum zone observed at 100 mg/ml (24.65 ± 0.86 mm). This confirms that Flucytosine retained its antifungal activity after incorporation into the emulgel base.

Table 2: Results of washability

Formulation	Washability	Appearance
F1	++	Viscous cream
F2	+++	Viscous cream
F3	+++	Viscous cream
F4	++	Viscous cream
F5	++	Softy cream
F6	++	Softy cream
F7	++	Softy cream
F8	++	Softy cream

Washability - Excellent: +++, Good: ++, Average: +, Poor: -

Table 3: Extrudability and Spreadability study

Formulation	Extrudability	Spreadability (gcm/sec)
F1	++	14.45±0.25
F2	++	13.25±0.32
F3	+++	12.25±0.15
F4	+++	11.15±0.22
F5	++	12.25±0.18
F6	++	11.36±0.23
F7	++	10.52±0.25
F8	++	9.87±0.14

***Average of three determinations (n=3) Excellent: +++, Good: ++, Average: +, Poor:**

Table 4: Results of Viscosity (Cps)

Formulation	10 rpm	50 rpm	100 rpm
F1	36357	24323	18493
F2	35679	25248	17279
F3	33428	23754	18,248
F4	37248	22348	17248
F5	36248	21465	18327
F6	37481	23547	18576
F7	38476	25417	17846
F8	39248	25348	18574

Table 5: Determination of pH

Formulation	Determination of pH
F1	6.55±0.05
F2	6.58±0.06
F3	6.80±0.02

F4	6.63±0.08
F5	6.69±0.04
F6	6.74±0.03
F7	6.36±0.07
F8	6.15±0.03

Table 6: Results of drug content of emulgel formulation

S. No	Formulation Code	Percentage drug content
1	F1	97.78±0.85
2	F2	96.65±1.12
3	F3	99.85±0.15
4	F4	96.65±0.75
5	F5	98.87±0.68
6	F6	95.58±0.74
7	F7	98.12±0.36
8	F8	97.74±0.47

Table 7: In-vitro drug release studies of formulation F1-F8

S. No.	Time (Hrs.)	% Cum. Drug Release							
		F1	F2	F3	F4	F5	F6	F7	F8
1	0	0	0	0	0	0	0	0	0
2	15	22.34	19.25	15.56	12.89	20.45	21.45	25.56	28.89
3	30	42.73	33.45	28.47	25.56	32.57	33.56	31.45	36.69
4	45	61.56	48.58	45.78	38.98	46.89	45.89	48.78	45.58
5	60	78.58	56.56	61.78	48.78	55.78	53.56	53.56	60.56
6	120	83.47	68.78	73.78	62.58	65.89	72.58	71.48	72.58
7	240	98.89	93.58	86.53	83.78	88.56	83.89	84.45	78.25

Table 8: Release Kinetics Data for optimized emulgel formulation F3

Parameter	Zero order	First order	Higuchi	Korsmeyer-Peppas
R^2	0.7615	0.9332	0.883	0.894

Table 9: Antimicrobial activity of optimized emulgel formulation against selected microbes

Sr. No.	Microbes	Zone of Inhibition (mm)		
		25 mg/ml	50 mg/ml	100 mg/ml
1.	*Candida albicans*	18.5 ± 0.57	20.23 ± 0.47	24.65 ± 0.86

CONCLUSION

The present investigation successfully developed and characterized a polymeric emulgel formulation of Flucytosine for effective topical treatment of fungal infections. The optimized formulation exhibited desirable physicochemical properties, including uniform drug distribution, suitable pH for skin application, good spreadability, and excellent washability. In-vitro release studies revealed a sustained drug release profile, while kinetic modeling indicated a first-order release pattern governed by a non-Fickian diffusion mechanism. Antimicrobial evaluation confirmed significant antifungal activity against

Candida albicans, demonstrating the therapeutic potential of the formulation. Overall, the developed Flucytosine-loaded polymeric emulgel offers a promising alternative to conventional topical antifungal preparations, with improved patient compliance, targeted delivery, and enhanced therapeutic efficacy.

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