Research Article

Development and Characterization of Fluconazole loaded Emulgel for the treatment of Cutaneous Candidiasis

Vishakha Soni, Harshita Jain, Mansha Singhai, Sunil K. Jain, Amit Verma*

Adina Institute of Pharmaceutical Science, NH, Bhopal Road, Sagar (M.P.), India – 470001

Received: 25 October 2023 Revised: 12 November 2023 Accepted: 12 December 2023

Abstract

Cutaneous candidiasis (CC) is an opportunistic fungal infection of the skin generally caused by the yeast-like fungus Candida albicans. It is a secondary yeast infection that can be either sub-acute or chronic in nature. In human beings, Candida species is a part of the normal flora of human skin and gastrointestinal and genitourinary systems. Overgrowth of Candida species is disturbed by normal bacterial Flora. The present study was focused on formulating and evaluating the antifungal drug fluconazole-loaded emulgel with a gelling agent such as carbapol-940 and guar-gum for effective delivery i.e., modifying the release rate of a drug on target infective site. Four formulations of fluconazole-loaded emulgel were prepared. Natural polymer guar gum and Synthetic polymer carbapol 940 were used as gelling agents. All the formulations of emulgel were evaluated for visual examination, phase separation, spreadability, and pH, and drug content, in-vitro diffusion study. On the basis of the finding of the study, amongst all the developed formulation F2 showed highest drug release and highest drug content and formulation F3 showed good spreadability because in these formulation carbapol 940 is used and while guar gum loaded emulgel formulation F5 showed highest content and highest drug release, respectively.

***Keywords*:** Cutaneous candidiasis, Emulgel, Fluconazole, Carbapol-940, Guar-gum

Introduction

Cutaneous candidiasis (CC) is an opportunistic fungal infection of the skin generally caused by the yeast-like fungus Candida albicans. It is a secondary yeast infection that can be either sub-acute or chronic in nature (Zarei Mahmoudabadi, 2006).

In human beings, Candida species is a part of the normal flora of human skin and gastrointestinal and genitourinary systems. Overgrowth of Candida species is disturbed by normal bacterial Flora (Martins et al., 2014).

The Candida species is one of the fungi that cause the most superficial cutaneous infection. Fungal infections, such as cutaneous candidiasis are thought to impact 20 to 25% of the world's population, making them a rather common occurrence (Kühbacher et al., 2017).

Under certain conditions, these candida species overgrow and become pathogens. Warmth and moisture of the intertriginous skin (axilla, inguinal folds, abdominal creases, inframammary creases), an increased skin pH, and the administration of antibiotics can disrupt the normal bacterial flora, allowing Candida to proliferate. (Martins et al., 2014). Young children and infants frequently experience cutaneous candidiasis, which can affect the skin, nails, or hair.

One of the most frequent candidiasis infections in infants and young children is diaper rash. This rash often lasts longer than three days and is typically red with a distinct border. Treatment includes changing the child's diaper frequently and allowing them to wear loose-befitting clothes on top of the diaper (Bryant, 2017).

Cutaneous candidiasis is particularly common in people with diabetes and in those who are obese. Other predisposing factors are antibiotics and oral contraceptives.

Topical fungal therapy is usually preferred because of its targeted topical therapy and fewer side effects. A topical drug delivery system (TDDS) gives a greater chance of success of drug delivery over traditional methods like used injections and oral formulation. Topical drug administration is the simplest and easiest route of localized drug delivery anywhere in the body by route as skin, ophthalmic, rectal, and

Address for Corresponding Author:
Dr. Amit Verma
Department of Pharmaceutics
Adina Institute of Pharmaceutical Science,
NH, Bhopal road, Sagar (M.P.), India – 470 001
E-mail: draverma1783@gmail.com

DOI: https://doi.org/10.31024/ajpp.2023.9.6.1

vaginal. These are applied as a wide spectrum of preparations in case of both cosmetic and dermatological, to healthy or diseased skin.

Topical drug delivery can be defined as the application of the drug-containing formulation to the skin to directly treat cutaneous e.g., Acne or cutaneous candidiasis, cutaneous manifestations of a general disease e.g., psoriasis. A variety of pharmaceutical dosage forms, such as semisolid, liquid preparations, sprays, and solid powders, are included in topical drug delivery systems. The most popular semisolid topical drug delivery formulations includes, gels, creams, and ointments. The main advantage of topical delivery is to bypass first-pass metabolism (Sabalingam and Siriwardhene, 2022).

Emulgels are considered emulsions of both oil-in-water (O/W) and water-in-oil (W/O) types in which the gels are incorporated. Emulgels have emerged as drug delivery systems for the administration of lipophilic or hydrophobic drugs, particularly as a boon for cutaneous health and cosmetic science. The emulgels not only increase the stability of the bioactive that is entrapped but also regulate its release (Verma et al., 2018).

Emulgels are most commonly used in the cosmetics and pharmaceutical science for the local and systemic effects of the entrapped drug. It is also a better carrier for hydrophilic drugs as it facilitates drug penetration into the skin (Verma et al., 2018). The O/W type of emulgel systems can be simply removed with water when it is required. It is also known as a water-washable emulgel system for this reason. (Khunt et al., 2012; Singla et al., 2012).

Emulgel can be delivered both in oil-in-water and water-in-oil type emulsion mixed with gel. Oil-in-water type is used for lipophilic drug and water-in-oil type is used for hydrophobic drug delivery and these are biphasic systems that have better drug loading capacity and better stability.

The emulgel has several good properties, such as good spreadability, greaseless, thixotropic, easily removable, emollient, non-staining, bio-friendly, odourless, pleasing appearance, transparent and cosmetically acceptable, which also have a good skin penetration and long shelf life. The emulsion also acts as a controlled release drug delivery system in which drug particles entrapped in the internal phase goes through the external phase to the skin and slowly gets absorbed. The drug reaches the external phase of the skin in a controlled manner through the internal phases which act as a reservoir of the drug. Gel captures small drug particles and provides its release in a controlled manner because of a cross-linked network.

A gel is a colloid that is normally 99% liquid and is immobilized by surface tension between it and a macromolecular network of fibres made from a small amount of a gelatin substance present.

Despite the many benefits of gels, a major limitation is in the delivery of hydrophobic drugs. Hence, to overcome this limitation, an emulsion-gel based technique is being developed, allowing even a hydrophobic therapeutic moiety to be directly incorporated and delivered through gels (Akki et al., 2019).

A number of medicated products are applied to the skin or mucous membrane that either improves or restores a fundamental function of the skin or pharmacologically modifies activity in the tissues specified is applied to the skin or mucous membrane. These products are known as topical or dermatological products.

Cutaneous candidiasis (CC) is an opportunistic fungal infection of the skin generally caused by the yeast-like fungus Candida albicans. It is a secondary yeast infection that can be either sub-acute or chronic in nature.

Fluconazole is a hydrophobic, triazole antifungal drug that is used in the treatment of candidiasis and it is used in opportunistic fungal infection in people with HIV, superficial and systemic fungal infection.

Fluconazole is available commercially in oral, suspension, and parenteral dosage forms which can be associated with serious adverse effects nausea, vomiting, abdominal discomfort, bloating, gastric irritation, rash, and headache. Oral therapy of azoles should be avoided in lactating mothers and pregnant women. It may birth defects in new born babies. Oral delivery of FCZ is associated with teratogenicity effects.

The bioavailability of conventional forms is less in comparison with topical forms. Oral formulations require high dosage formulations, which may be expensive and unrealistic and it has a less localized effect but more side effects, which need to be overcome as well as it has altered gastrointestinal drug absorption caused by gastrointestinal pH and enzymatic activity and drug interaction with food and drinks. More than 80 % of the orally ingested drug has been found in the circulation, 60 to 70% is excreted in the urine and only 10% of fluconazole is protein-bound. Thus, it is metabolized in the liver there is an incidence of hepatotoxicity.

There are different forms of transdermal like cream, ointment, lotion, and spray. Other trimming methods include niosomes, and liposomes, which are nano, sized and may leak due to their vesicular structure, resulting in less effective entrapment but Emulgel is effective due to its combined property.

Emulgel, which contains a System for double release

control that includes both a gel and an emulsion, has become one the important promising topical delivery systems.

In semisolid preparation, the gel is the newer class of dosage form that is widely used in both pharmaceutical and cosmetic preparation. In gel dosage form, a large aqueous and hydroalcoholic liquid in a network of colloidal solid particles may be inorganic or organic polymers of natural or synthetic origin. In comparison with another topical dosage form, the drug-releasing capacity of gel is fast but the major limitation associated with the gels is in the delivery of hydrophobic drugs.

Gels are mostly used for the delivery of hydrophilic drugs; hydrophobic drugs cannot be easily incorporated into the gel system because solubility act as a barrier and problem arises during the release of the drug profile. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in the aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into a gel base. This may provide better stability and release of drugs than simply incorporating drugs into a gel base.

Material and methods

Material

Fluconazole (FLZ) was procured as a gift sample from Micro Labs Ltd, Bangalore. Rest of Other chemicals and regents were used of pure analytical grade.

Preparation of Fluconazole loaded Emulgel

Step 1

Preparation of Carbopol gel: The carbopol gel was prepared by adding the calculated amount of carbopol in the warm water with continuous stirring on a magnetic stirrer at moderate speed. The pH of the Carbopol gel was adjusted by using TEA.

Preparation of guar gum gel: The guar gum gel was prepared by adding a calculated amount of guar gum in warm water with continuous stirring on a magnetic stirrer at moderate speed.

Step 2

Preparation of aqueous phase: The aqueous phase was prepared by dispersing the calculated amount of tween 20 in purified water and heating separately at 70ºc. Propylparaben and methylparaben are used as preservatives and are dissolved in propylene glycol. On the other hand, fluconazole was dissolved in ethanol. Both the mixture was added to the aqueous phase.

Step 3

Preparation of oil phase: The oil phase was prepared by dispersing the calculated amount of span 20 in light liquid paraffin and heating separately at 70ºc.

Step 4

Emulsification: After the heating process, the oil phase is added to the aqueous phase with continuous stirring until it cools. The prepared emulsion was a type of oil in water.

Step 5

Formation of emulgel: The prepared emulsion was mixed with both gel bases separately with an appropriate ratio with continuous stirring to obtain the emulgel. The prepared emulgel was packed in a wide-mouth glass jar covered with a secure capped plastic lid.

Optimization of various Parameters

Visual Examination

In the visual examination, we inspected for the color, phase separation, and homogeneity of emulgel.

Table 1. Composition of Fluconazole loaded Emulgel

Ingredients	Purpose	Formulations					
		F1	F2	F3	F4	F5	F6
Fluconazole	Drug	1	1	1	1	1	1
Carbopol 940	Gelling agent	1	1	1.5	-	-	-
Guar gum (gm)	Gelling agent	-	-	-	1	1	1.5
Light liquid paraffin	Oily phase	5	7.5	5	5	7.5	5
Span 20	Emulsifier	1	1.5	1	1	1.5	1
Tween 20	Emulsifier	1	1.5	1	1	1.5	1
Ethanol	Solvent	2.5	2.5	2.5	2.5	2.5	2.5
Propylene Glycol	Humectant	5	5	5	5	5	5
Methylparaben	Preservative	0.03	0.03	0.03	0.03	0.03	0.03
Propylparaben	Preservative	0.01	0.01	0.01	0.01	0.01	0.01
Purified water	Aq. Solvent	100	100	100	100	100	100

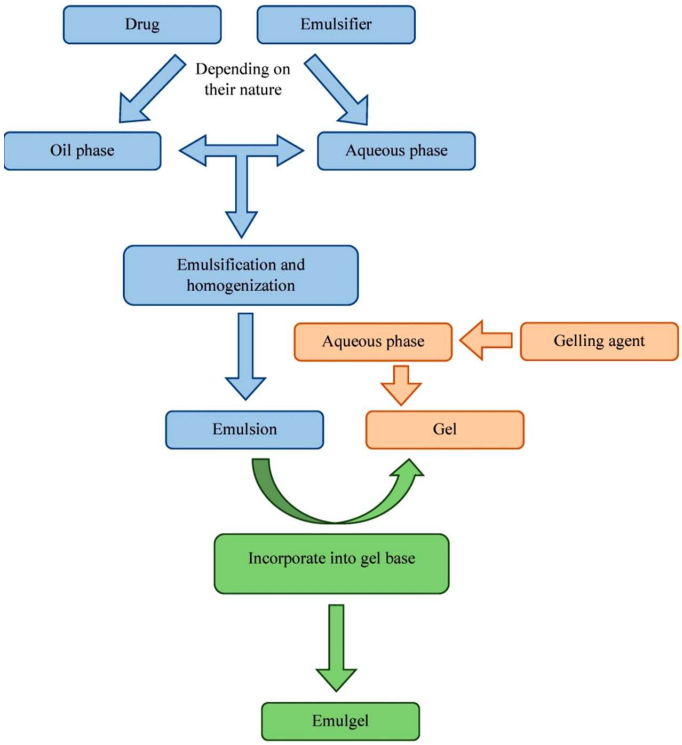

Figure 1. Flow chart of Emulgel formulation

pH Determination

The pH of emulgel formulations is determined by using a digital pH meter. The readings were taken for an average of 3 times.

Extrudability

For a good emulgel formulation, it should be extruded easily from the container. In this test, the sample is extruded from the tube by the usual procedure. It is an empirical test to measure the force required to extrude the material from the collapsible tube. A closed collapsible tube containing gel was passed firmly at the crimped end. When the cap was removed, the gel extruded until the pressure dissipated. The weight in grams required to extrude a 0.5 cm ribbon of gel for 10 seconds was determined. The results for each formulation were recoded as extrusion pressure in grams. More quantity extruded better was extrudability. The measurement of the extrudability of each formulation was in triplicate and the average values are presented.

The extrudability was then calculated by using the following formula:

$$\text{Extrudability} = \frac{\text{Weight applied to extrude emulgel from tube (in gm)}}{\text{Area(in } cm^2\text{)}}$$

Spreadability test

The spreadability of the formulations was determined by measuring the spreading diameter of 0.5g of sample (an excess of emulgel about 2gm) between two horizontal glass plates for 5 minutes or the time when spreading stops. The diameter of the spread circle was taken in cm and shows the comparative value for spreadability.

The standard weight applied to the top plate was 25 gm, 80 gm, or 1kg. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicates better spreadability. Each formulation was tested three times. Spreadability was calculated by using the formula,

$$S = M \times L/T$$

Where,

S= Spreadability, M= Weight tied to upper slide,

L= Lenght of glass slides, T= time taken to separate the slides

Drug content determination

A calculated quantity of emulgel formulation was taken and dissolved in a phosphate buffer of pH 7.4 in a volumetric flask. The volumetric flask is shaken for about 2 hours and kept for 24 hours aside. After 24 hours, the solution was filtered out. The appropriate number of dilutions drug absorbance was recorded by using UV at λ_{max} 260 nm with the use of phosphate buffer.

Drug content = (Concentration x D.F. x V.T.)x C.F.

Where,

D.F. = Dilution factor, V.T. = Volume taken , C.F. = Conversion factor

In–vitro permeation studies

In-vitro permeation studies of emulgel formulations were performed by using an eggshell membrane with a receptor compartment. With the help of a thread, the eggshell membrane was fixed at the end of the hollow tube as a donor compartment and the beaker was present as a receptor compartment. A specific quantity of prepared emulgel was applied onto the surface of the eggshell membrane and the eggshell membrane clamped between the donor and receptor chamber. The receptor compartment was filled with phosphate buffer solution pH 7.4 to solubilize the drug. On the magnetic stirrer, the whole assembly was placed and the solution was continuously stirred with the help of a magnetic bead. The temperature was maintained at 37±0.5ºC at a suitable interval, a 1ml sample was withdrawn and analysed for drug content spectrophotometrically at 260 nm.

Kinetic of Drug Release

One of the most important and challenging areas in the drug delivery field is to predict the release of the active agent as a function of time using both simple and sophisticated mathematical models. The importance of such models lies

in their utility during both the design stage of a pharmaceutical formulation and the experimental verification of a release mechanism. To identify a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model. To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted into zero-order, first-order, Higuchi matrix, and Korsmeyer-Peppas model.

Results and Discussion

Visual Examination

The prepared emulgel formulae were inspected visually for their color and phase separation is shown in Table 2. All emulgel formulations were light yellowish to white viscous creamy with a smooth homogeneous texture without lumps and glossy appearance.

pH Determination

The pH was found to be in the range from 5.9 – 4.3 which is considered acceptable to avoid the risk of irritation upon application to the skin because adult skin pH is 5.5. The results are shown in Table 2.

Spreadability test

An emulgel should possess good spreadability representing its ideal property. Spreadability is the term expressed to denote the extent of the area to which gel spreads on application to the skin or the affected area. The therapeutic efficacy of a formulation also depends upon its spreadability. The spreadability is very important as shows the behavior of the emulgel coming out from the tube. The results are shown in Table 2.

Extrudability

The extrusion of the emulgel from the tube is important during its application and in patient acceptance. The extrudability of all formulations was found to be good and compatible as shown in Table 3.

Drug content

For all fluconazole-loaded emulgel formulations, drug content determination was done using PBS (pH 7.4) as the medium, and the results are shown in Table 3.

Table 2. Physiochemical properties of Fluconazole loaded Emulgel

Formulations	color	Phase Separation	pH	Spreadability (cm)
F_1	Milky	No	5.7	5
F_2	Milky	No	4.3	4.5
F_3	Milky	No	5.9	5.9
F_4	Light yellow	No	5.2	4.3
F_5	Light yellow	No	5.3	4.1
F_6	Light yellow	No	5.5	4.2

Table 3. Extrudability and percent drug content of emulgel formulation

Formulations	Extrudability	Drug content (%)
F_1	+++	63.7
F_2	+++	70.2
F_3	+++	59.6
F_4	+++	72.9
F_5	+++	75.2
F_6	+++	68

In-vitro permeation studies

In-vitro permeation study of fluconazole loaded emulgel by using PBS medium at pH 7.4 performed for up to 10hrs by using UV spectrophotometry at 260 nm wavelength. Formulation of carbapol gelling agent, F2 shows maximum drug release and formulation F3 shows minimum drug release. Formulation of guar gum, F5 shows maximum release of drug. Over a period of 10 Hours, the drug release was slow and constant in all the emulgel formulation of various polymers.

Kinetic of Drug Release

To analyse the mechanism for the release and release rate kinetics of the dosage form, the data obtained was fitted into zero-order, first-order, Higuchi matrix, and Korsmeyer-Peppas model were used. Linear regression analysis applied on the data and the model shows highest regression coefficient (r^2) value as selected as the best fit model for drug release for particular formulation. Kinetics model indicate that drug release from emulgel formulation shows Higuchi as a best fit model. The value of 'n' for all the fluconazole emulgel formulations (F1 to F6) lies in between 0.5483-0.6508 which shows that the release mechanism drug is non-fickian. The results are concluded by comparing all the model dataand results are shown in Table 4.

Zero-order release kinetics

% Cumulative drug release v/s time data used for plotting zero-order release kinetics and result shows in Figure 2 graphically.

Equation, $Q_t=Q_0+K_0t$

Where Q_t and Q_0 is the amount of drug released at time t and time zero, respectively, and K_0 is the zero-order release constant.

First-order release kinetics

Log % drug remaining v/s time used to develop the first-order release curve and result shows in Figure 6 graphically.

Table 4. In-Vitro Cumulative release data of Fluconazole loaded emulgel formulation

Table	% Cumulative drug release					
(min)	F1	F2	F3	F4	F5	F6
0	0.00	0.00	0.00	0.00	0.00	0.00
15	10.296	13.640	11.400	38.58	21.600	19.320
30	13.8696	18.408	13.870	44.863	27.600	28.702
60	16.3599	31.191	19.738	46.74	30.334	29.175
120	43.7939	47.542	34.760	47.496	30.826	30.788
180	51.3047	51.737	42.167	50.532	32.458	40.340

Equation, $\ln Q_t = \ln Q_0 + K_1 t$

Where, Q_t and Q_0 is the amount of drug released at time t and time zero, respectively, and K_1 is the first-order release constant.

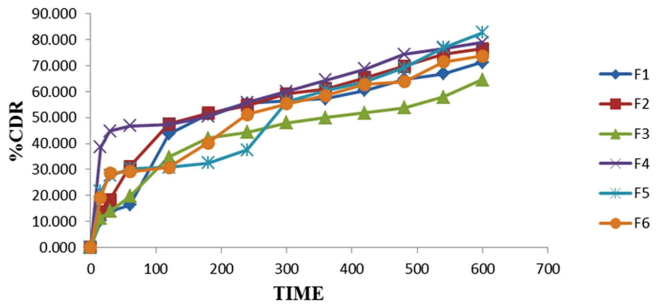

Figure 2. Comparative in- vitro cumulative drug release graph of all formulation for zero-order release kinetics

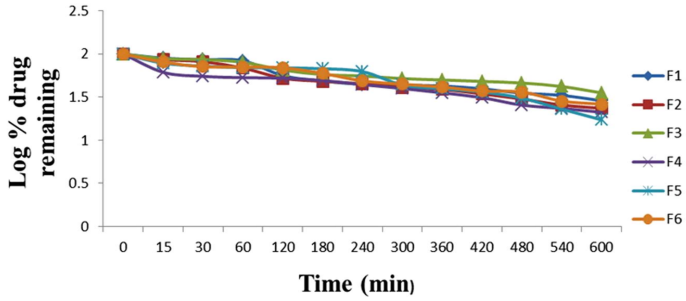

Figure 3. Comparative in- vitro permeation study data graph of all formulation for first-order release kinetics

Higuchi's equation

Equation, $Q = K_H\sqrt{t}$

Where, Q is the amount of drug released at time t and K_H is the higuchi diffusion rate constant.

Korsmeyer-Peppas equation

Equation, $M_t / M\infty = KKP \times t_n$

Where, $M_t / M\infty$ is the fraction of drug released at time t, KKP is the Korsmeyer-Peppas release constant and n is the drug release exponent which describes drug release mechanism. The model that fit best was selected by comparing R^2 values obtained from all the models (Table 5).

Discussion and Conclusion

Emulgel are relatively newer and better topical drug delivery systems since they enjoy the advantages of both emulsion and gel. They enable the poorly aqueous-soluble drugs to be loaded into a hydrophilic gel base. Fluconazole-loaded emulgel were prepared and optimized. All the physicochemical properties of the emulgels were checked and were found to be good.

In the present work, four formulations of fluconazole-loaded emulgel were prepared. Natural polymer guar gum and Synthetic polymer carbapol 940 were used as gelling agents. All the formulations of emulgel were evaluated for visual examination, phase separation, spreadability, and pH, and drug content, in-vitro diffusion study. The result of

Table 5. Drug release kinetics parameters for different emulgel formulation

Formulations	Zero-order release	First-order release	Higuchi'srelease kinetics	Korsmeyer-Peppas release kinetics		Best fit model	Release mechanism
	R^2	R^2	R^2	R^2	n value		
F1	0.8258	0.9429	0.9461	0.9691	0.65086	Higuchi	Non-Fickian diffusion
F2	0.8507	0.9842	0.9722	0.9493	0.6304	Higuchi	Non-Fickian diffusion
F3	0.8702	0.9662	0.9765	0.9661	0.6089	Higuchi	Non-Fickian diffusion
F4	0.746	0.946	0.8673	0.7758	0.5903	Higuchi	Non-Fickian diffusion
F5	0.9312	0.9236	0.9428	0.8868	0.5842	Higuchi	Non-Fickian diffusion
F6	0.8996	0.9813	0.9735	0.9003	0.5852	Higuchi	Non-Fickian diffusion

all the formulations was found to be in favourable parameters.

The present study was focused on formulating and evaluating the antifungal drug fluconazole-loaded emulgel with a gelling agent such as carbapol-940 and guar-gum for effective delivery i.e., modifying the release rate of a drug on target infective site.

The drug content of all the formulations was analyzed using a phosphate buffer of pH 7.4 as medium λmax 260nm. In the prepared formulations of carbapol F2 shows the highest drug content and formulation F3 shows the lowest drug content. In the formulations of guar gum F4 shows, the highest drug content. All the formulations are found in the pH range of 6.1 – 5.9 and are compatible with the skin. The spreadability was found in a range of 4.1-5.9. Formulation F3 shows good spreadability.

In the in-vitro drug permeation study of fluconazole was performed by using a phosphate buffer of pH 7.4 for 10 hours. The formulation of Carbopol F2 shows the highest drug release and formulation F3 shows the lowest drug release. In the formulation of guar gum formulation, F4 shows the highest drug release and formulation.

Among all the prepared formulations of loaded emulgel, formulation F5 shows the highest drug content, and formulation F3 shows good spreadability. Formulation F2 and F5 shows the highest drug release and drug content because of the increasing concentration of light liquid paraffin in the oil phase. In the future, in-vitro diffusion studies and other evaluations will be performed based on these formulation parameters.

The present was an effort to develop and evaluate fluconazole loaded emulgel formulations with a view to use topically. On the basis of the previous finding we can concluded that fluconazole drug was successfully incorporated into the different topical emulgel preparations. Amongst, all the developed formulation F2 showed highest drug release and highest drug content and formulation F3 showed good spreadability because in these formulation carbapol 940 is used and while guar gum loaded emulgel formulation F5 showed highest content and highest drug release, respectively.

Conflict of Interest: None

References

Akki R, Susmitha B, Kiranmai J. 2019. A novel approach for topical delivery using emulgel. The Pharma Innovation Journal 8(4):35-42

Bryant M. 2017. Fungal infections. InnovAiT. 10(7):417-24.

Khunt DM, Mishra AD, Shah DR. 2012. Formulation design & development of piroxicam emulgel. International Journal of PharmTech Research. 4(3):1332-44.

Kühbacher A, Burger-Kentischer A, Rupp S. 2017. Interaction of Candida species with the skin. Microorganisms. 5(2):32.

Mahmoudabadi AZ. 2006. Clinical characteristics and mycology of cutaneous candidiasis in Ahwaz (Iran). Pakistan Journal of Medical Sciences. 22(1):43.

Martins N, Ferreira IC, Barros L, Silva S, Henriques M. 2014. Candidiasis: predisposing factors, prevention, diagnosis and alternative treatment. Mycopathologia. 177:223-40.

Patel BM, Kuchekar AB, Pawar SR. 2021. Emulgel Approach to Formulation Development: A Review. Biosciences Biotechnology Research Asia. 18(3):459-65.

Sabalingam S, Siriwardhene MA. 2022. A review on emerging applications of emulgel as topical drug delivery system. World Journal of Advanced Research and Reviews. 13(1):452-63.

Singla V, Saini S, Joshi B, Rana AC. 2012. Emulgel: A new platform for topical drug delivery. International Journal of Pharma and Bio Sciences. 3(1):485-98.

Verma A, Jain A, Tiwari A, Jain SK. 2018. Emulgels: application potential in drug delivery. Functional biopolymers. 2018:343-71.