WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 8, 2084-2098. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF FLUCONAZOLE EMULGEL BY USING DIFFERENT POLYMERS

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Article Received on
15 June 2020,

Revised on 06 July 2020,
Accepted on 27 July 2020,

DOI: 10.20959/wjpr20208-18316

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ABSTRACT

In present work, emulgel of fluconazole were prepared by using two polymers Carbopol 940 and Guar-Gum as a gelling agent. Fluconazole is hydrophobic and emulgel has potential, which makes it the most suitable delivery system for hydrophobic drugs. In the preparation of fluconazole emulgel, light liquid paraffin used as an oily phase in different concentrations, and an emulsifying agent such as Tween 20 and Span 20 were used. All the prepared emulgel formulation were analyzed for FTIR analysis for the compatibility of drug and excipients. Further, all the formulation evaluated for their pH, physical properties, spreadability, phase separation, stability study, and *in-vitro* permeation study. By all the results it was observed that formulation F2 shown the highest drug content and highest drug release and formulation F3 shown good spreadability because in these formulation carbopol 940 is used and while Guar-gum emulgel formulation F5 showed highest drug content and highest drug release respectively.

KEYWORDS: Emulgel, Gelling agents, Carbopol-940, Guar-Gum, *In-vitro* permeation.

1. INTRODUCTION

Fluconazole is a hydrophobic, synthetic antifungal drug belonging to the group of triazole and is used to treat superficial and invasive fungal infection. Fluconazole with long term therapy on high dose causes less patient compliance and oral drug delivery often produces gastric irritation, bloating, vomiting, and abdominal discomfort. To overcome these side effects, topical therapy of fluconazole can help to minimize systemic side effects and to target

infection sites with modifying release rate.[1,2] From the past few years, topical drug delivery is used for the treatment of local infection of vagina, nose, skin, and other dermatological diseases. The drugs are mainly administered through the topical route for local action includes anti-septic, anti-fungal, and skin emollients for protective effect.[3] Topical drug delivery systems have several key advantages including targeting to site of infection, reducing systemic side effects, increasing efficacy, and high patient compliance.[4] The penetration through the target tissue influences the ability of topical treatment and therefore last few years emulsion-based gels have been growing importance in the field of the semisolid dosage form.[5]

The various pharmaceutical dosages form are used for topical drug delivery systems are semisolid, gels, creams, ointments, and sprays. In semisolid preparations, the gel is the newer class of dosage form that widely used in both pharmaceutical and cosmetic preparation. In gel dosage form a large amount of hydroalcoholic and aqueous liquid are entrapped in a colloidal solid particle network. 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.[6-8] Therefore to overcome these limitation an emulsion-based approach is used. Emulgel is a combined form of emulsion and gel. In emulgel, the water phase is converted into the classical emulsion in the presence of a gelling agent. Lipophilic drugs are entrapped into O/W system whereas the hydrophilic drugs are in W/O system.[9] It is a stable and effective vehicle for the delivery of hydrophobic drugs. Emulgel shows a more effective mechanism than a gel because the permeation depth of the drug is more in emulgel.[10] The emulsion has a greater affinity to penetrate the skin as well as to possess a certain degree of elegance and is easily washable. Emulgel has several properties like easily removable, spreadable, greaseless, nonstaining, longer shelflife, transparent, thixotropic, emollient, bio-friendly, and water-soluble.[6,11] Synthetic polymer Carbopol 940 and natural polymer Guar-Gum is used because of their gelling capacity which decreases in surface and interfacial tension and increases aqueous phase's viscosity by allowing the formulation of a stable emulsion.[8] In emulgel both aqueous and oily ingredients incorporated properly, that's why antifungal agents are hydrophobic or poorly water-soluble, by the correct choice of oily phase suitably incorporated in such type of vehicles.[7,12]

Advantages of Emulgel[12,13]

Emulgel has many advantages such as:

- An easy method for target drug delivery on the body.
- It is suitable for self medications.
- It is helpful in inpatient acceptability.
- Emulgel can be used to prolong the effect of the drug having a shorter half-life.
- They are suitable to apply on hairs because of the absence of greasiness.

2. MATERIAL AND METHODOLOGY

2.1. Materials

Fluconazole was provided as a gift sample from HAB Pharmaceuticals and Research Limited Dehradun. Carbopol-940 purchased from HiMedia Laboratories Pvt. Ltd. while Guar-Gum, Light liquid paraffin, Tween 20, Span 20, Propylene glycol, Methylparaben, Propylparaben purchased from Central Drug House Pvt. Ltd.

2.2. Preparation of Fluconazole Emulgel[11,14,15]

Step 1

Preparation of gel base

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 carbopol gel was adjusted by using TEA.
2. **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 heat separately at 70ºc. Propylparaben and methylparaben are used as preservatives and were 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 heat separately at 70ºc.

Step 4

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

Step 5

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

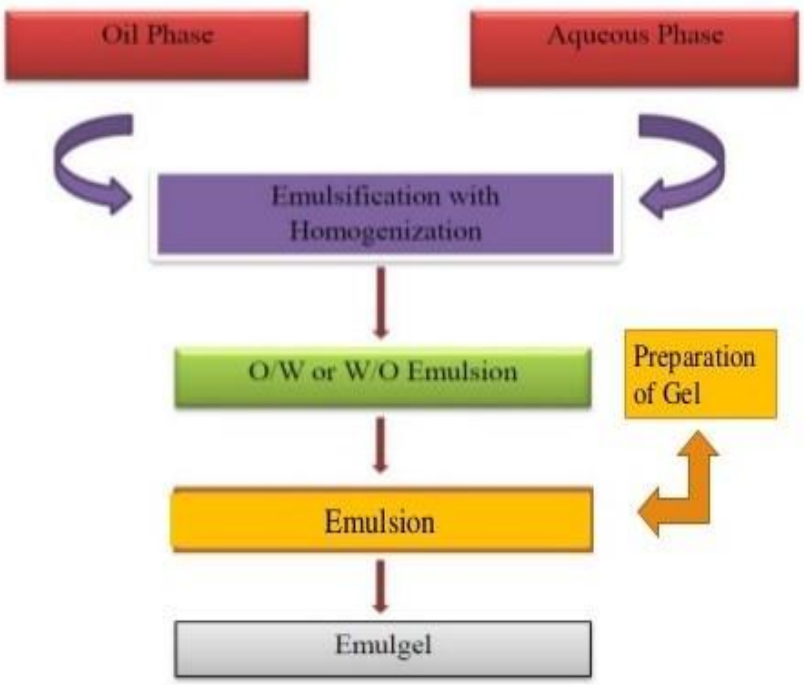


Figure 1: Flow chart of Emulgel formulation.[7,11]

Table 1: Composition of Emulgel of Fluconazole.

Ingredients	Formulations					
	F1	F2	F3	F4	F5	F6
Fluconazole (gm)	1	1	1	1	1	1
Carbopol 940 (gm)	1	1	1.5	-	-	-
Guar gum (gm)	-	-	-	1	1	1.5
Tween 20 (ml)	1	1.5	1	1	1.5	1
Span 20 (ml)	1	1.5	1	1	1.5	1
Light liquid paraffin (ml)	5	7.5	5	5	7.5	5
Ethanol (ml)	2.5	2.5	2.5	2.5	2.5	2.5
Propylene glycol (ml)	5	5	5	5	5	5
Methylparaben (mg)	0.03	0.03	0.03	0.03	0.03	0.03
Propylparaben (mg)	0.01	0.01	0.01	0.01	0.01	0.01
Purified water (ml)	100	100	100	100	100	100

2.3. EVALUATION PARAMETERS

2.3.1. Visual examination

In the visual examination, we inspected for the color, phase separation, and homogenecity of emulgel and also examine the color, appearance and odor of fluconazole.[10]

2.3.2. Spreadability test

From each formulation, a sample of 0.5gm was taken. The sample was pressed between the two slides for 5 minutes or the time where spreading stops. The diameter of the spread circle was taken in cm and shows the comparative value for spreadability.[16]

2.3.3. pH determination

By using a digital pH meter, the pH of each formulation is calculated. The readings of pH will be taken an average of 3 times.[17,18]

2.3.4. Drug content

A calculated amount of emulgel formulation was taken and was dissolved in phosphate buffer of pH 7.4 in a volumetric flask. The 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 was made and analyzed in the UV at λmax.260nm with the use of phosphate buffer.[16,19]

2.3.5. Stability studies

For more satisfactory formulation, the stability study was performed. The formulation was packed in collapse tubes and stored for three months at room temperature. The formulations were analyzed after every one month for physical properties, spreadability, pH, and drug content (12, 20).

2.3.6. FTIR analysis

In FTIR analysis compatibility of drugs with other components was identified. All the formulations of the emulgel were checked out in the wavenumber range of 1000-4000cm^{-1}. FTIR spectrum of all the formulations of emulgel was compared with the standard spectrum of the drug.[21]

2.3.7. *In-vitro* permeation study

By using an eggshell membrane with a receptor compartment (80ml capacity) *in-vitro* permeation studies were performed. With the help of a thread, the eggshell membrane was fixed at the end of the hollow tube as a donor compartment and beaker present as a receptor

compartment. a specified quantity of prepared emulgel was applied on to the surface of the eggshell membrane and eggshell membrane clamped between the donor and receptor chamber. Receptor compartment 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 analyzed for drug content spectrophotometrically at 260nm.[16,22]

3. RESULT AND DISCUSSION

3.1. Visual examination

In visual examination of drug, the physical characteristics of drug are shown in table 2. Table 3 shows that the color of first three formulations in which carbopol 940 used as gelling agent appear as milky and while rest of three formulations in which guar gum used as gelling agent appears as a light yellow, which indicates that first three formulations same in color and rest three are same in color. All emulgel formulation was viscous with a smooth homogeneous texture and glossy appearance.[10]

Table 2: Physical description of Fluconazole drug.

Characteristics	Description	
	As per IP	As per drug sample
Colour	White	White
Appearance	Crystalline powder	Crystalline powder
Odor	Odorless	Odorless

Table 3: Physiochemical properties of Fluconazole emulgel (color, phase separation, pH, & spreadability).

Formulation	Color	Phase separation	pH	Spreadability (cm)
F1	Milky	No	5.8	5
F2	Milky	No	4.3	4.5
F3	Milky	No	5.9	5.9
F4	Light Yellow	No	5.2	4.3
F5	Light Yellow	No	5.3	4.1
F6	Light Yellow	No	5.5	4.2

3.2. Spreadability

An emulgel should possess good spreadability representing its ideal property. Spreadability is used to denote the area to which gel spreads on the skin or the affected area. The spreadability shows the therapeutic efficacy of the formulation. Both the polymers used for

the preparation of emulgel spread by a small amount of shear.[16] The results are shown in Table 3.

3.3. pH determination

pH was found to be ranged between 5.9 - 4.3 which indicates that all the formulation is compatible with skin pH. Spreadability was found to be in a range between 5.9 – 4.1 cm which indicates that all the formulation evenly spreadable.[17,18] The results are shown in Table 3.

3.4. Drug content analysis

For all the fluconazole formulation, drug content analysis was done using the PBS (pH7.4) as the medium and the result are given in table 4.

Table 4: Percent drug content of emulgel formulation.

Formulation	Percent of drug content (%)
F1	64.7
F2	70.2
F3	59.6
F4	71.9
F5	75.1
F6	69

3.5. Stability study

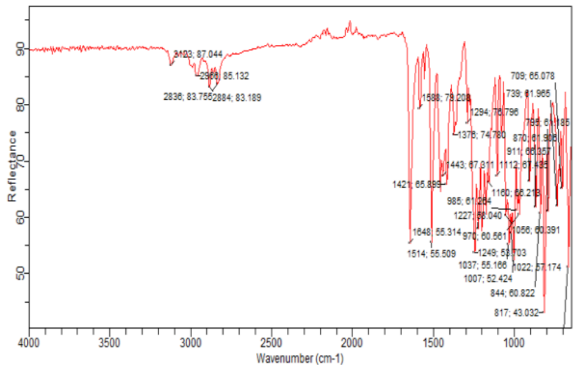
All the formulations of fluconazole emulgel were found to be stable after 3 months at room temperature. No change was recorded in parameters like visual appearance, pH, spreadability, and drug content. Syneresis is the main drawback of gel; also, there was no presence of syneresis effect.[12]

3.6. FTIR analyses

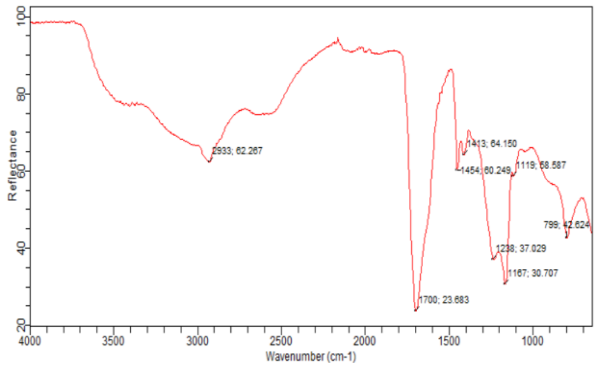
In FTIR analysis drug in alone and in combination with other excipients were subjected to analyze the compatibility of drugs with other excipients. The resulting spectrum was analyzed by Agilent technology.[21] Figure 2 (a) shows that IR of fluconazole shows absorption peak with –OH stretching at 3133cm^{-1}. The absorption peak at 2988cm^{-1} and 1514cm^{-1} shows –CH and triazole ring stretching mode. The absorption peak at 1112cm^{-1} represent C-F bending and at peak 1378cm^{-1} represent –OH bending of phenyl. Figure 2 (b) depict that IR of Carbopol absorption peak with –CH stretching at 2933cm^{-1}. The absorption

peak at 1700cm^{-1} and 1454cm^{-1} shows C=O and O-H bending of acids which shows that phenyl and carboxylic acid group are present in carbopol.

The absorption peak at 3272cm^{-1} and 2955cm^{-1} shows N-H stretching and C-H stretching represents amine and alkane groups are present in guar-gum. The absorption peak at 1640 and 1380cm^{-1} shows C=C stretching and C-H bending in sample of guar-gum which indicates that the alkene and aldehyde groups are present in guar-gum shows in figure 2 (c). The peaks are observed from the mixture of drug and polymers have no chemical interactions and don not have any interference. It was concluded that all the excipients are compatible with each-other which are shows in figure 2 (d) and (e).



(a)



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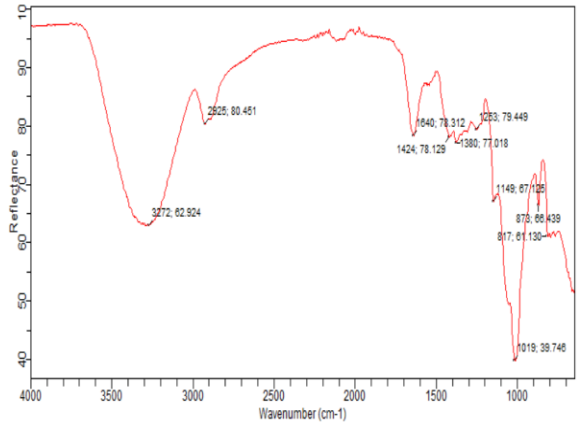
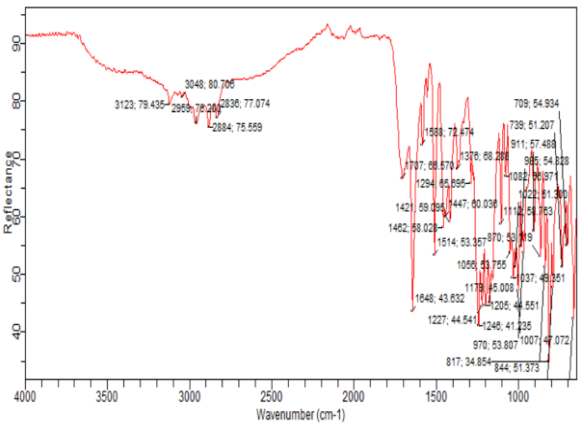
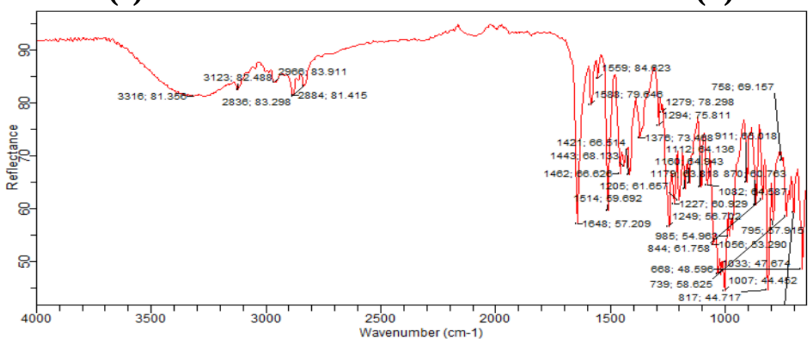


(c)



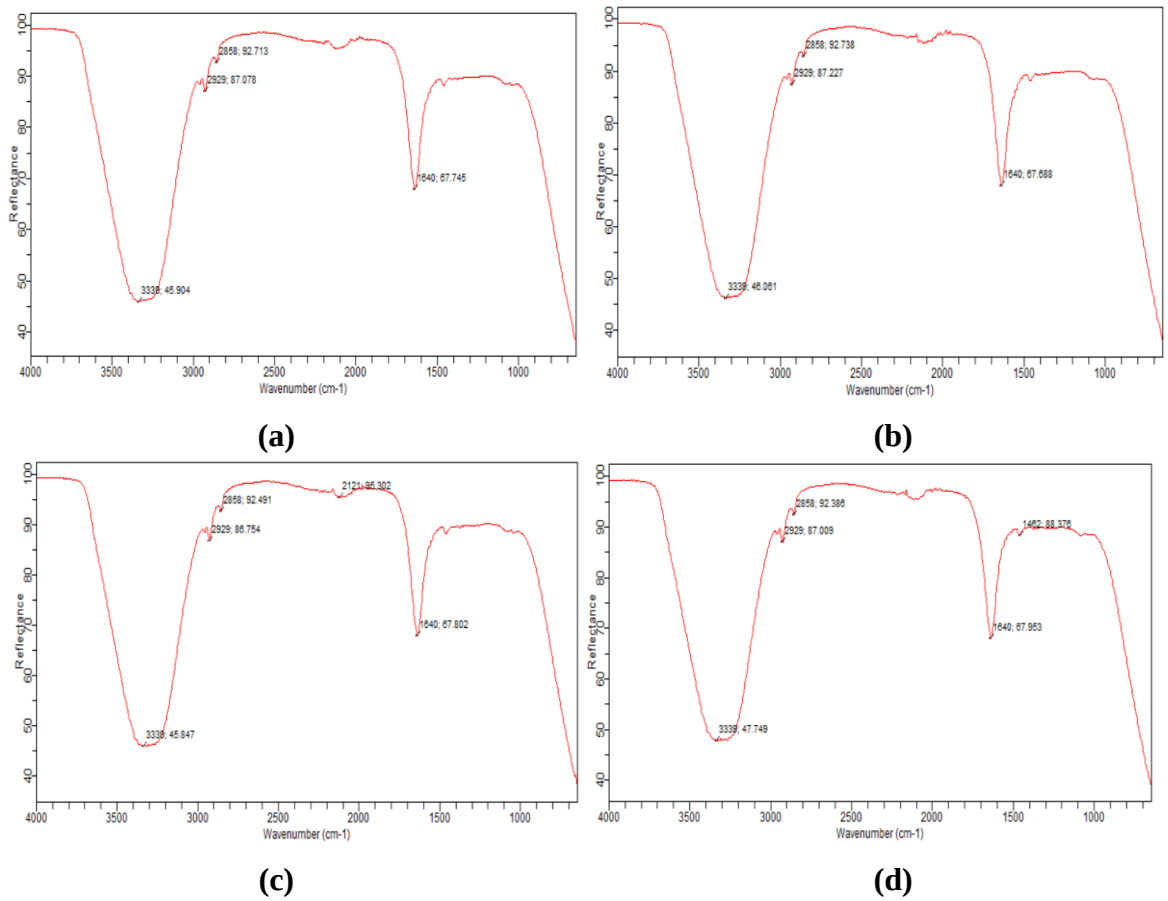
(d)

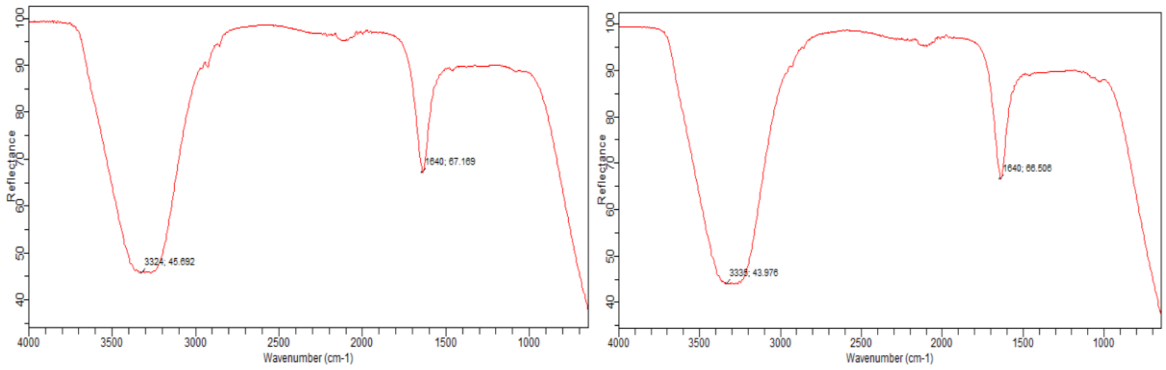


(e)

Figure 2: FTIR spectrum of samples shows compatibility between drug and polymers. In which graph (a) represent FTIR spectrum of fluconazole, (b) FTIR spectrum of carbopol, (c) FTIR spectrum of guargum, (d) FTIR spectrum of fluconazole with carbopol, and (e) FTIR spectrum of fluconazole with guargum.

For checking any incompatibilities during the process of formulation of emulgel all the prepared formulation subjected for FTIR analysis and are shown as figure 3 (a) for formulation F1, figure 3 (b) for formulation F2, figure 3 (c) for formulation F3, figure 3 (d) for formulation F4, figure 3 (e) for formulation F5 and figure 3 (f) for formulation F6. The Infrared spectrum (IR) of various formulations shows characteristics absorption peaks at 3331cm^{-1}, 2929cm^{-1} and 2858cm^{-1} denoting stretching vibration of —OH stretching, —CH stretching and CH stretching respectively. The absorption peaks at 1640cm^{-1} and 1462cm^{-1} due to the C=C and —CH aromatic stretching. As per the observation from FTIR spectra, there was no shifting or no major changes in the drug's peaks were observed, which shows that there is no chemical interaction between drug and polymer mixture. It was concluded that in all the formulation irrespective of the various excipients with the composition of drug are present in free form.





(e) **(f)**

Figure 3: FTIR spectrum of prepared formulations of fluconazole with various excipients in which graph (a) represent formulation F1, (b) formulation F2, (c) formulation F3, (d) formulation F4, (e) formulation F5, and (f) formulation F6.

3.7. *In-vitro* permeation study

In-vitro permeation study of fluconazole emulgel by using PBS medium at 7.4 pH performed for up to 10hrs by using UV spectrophotometry at 260 nm wavelength (16, 22). Table no. 5 shows that the formulation of carbopol gelling agent, F2 shows maximum drug release and formulation F3 shows minimum drug release. Where in formulation of guargum, F5 shows maximum release of drug and F6 shows minimum drug release. Over a period of 10 Hours, the drug release was slow and constant in all the emulgel formulation of various polymers.

Table 5: *In-Vitro* Cumulative release data of Fluconazole from emulgel formulation.

Time (minutes)	% Cumulative drug release					
	F1	F2	F3	F4	F5	F6
0	0.000	0.000	0.000	0.000	0.000	0.0
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
240	55.5327	54.789	44.387	55.826	37.469	51.183
300	56.4213	59.078	48.066	60.115	56.175	55.356
360	57.3099	61.144	49.962	64.461	60.483	58.505
420	60.4665	65.449	51.877	68.804	63.708	62.832
480	64.7889	69.870	53.811	74.403	69.191	63.796
540	66.8519	74.348	57.984	76.598	77.029	71.540
600	71.2729	76.543	64.553	78.871	82.760	73.757

Furthur to determine the drug release mechanism and kinetics of release rate, mathematical model like zero order, first order, Higuchi model, and Korsmeyer-Peppas 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 perticular 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 compairing all the model data which are shows in table no. 6.

Zero-order release kinetics

% Cumulative drug release v/s time data used for plotting zero-order release kinetics and result shows in figure 4 graphically.

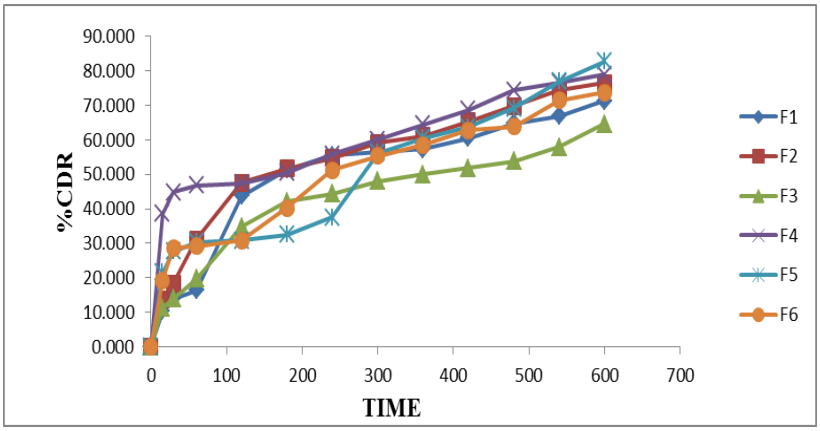


Figure 4: Comparative *in-vitro* cumulative release graph of all formulation F1-F6.

First-order release curve

Log % drug remaining v/s time used to develop the first-order release curve and result shows in figure 5 graphically.

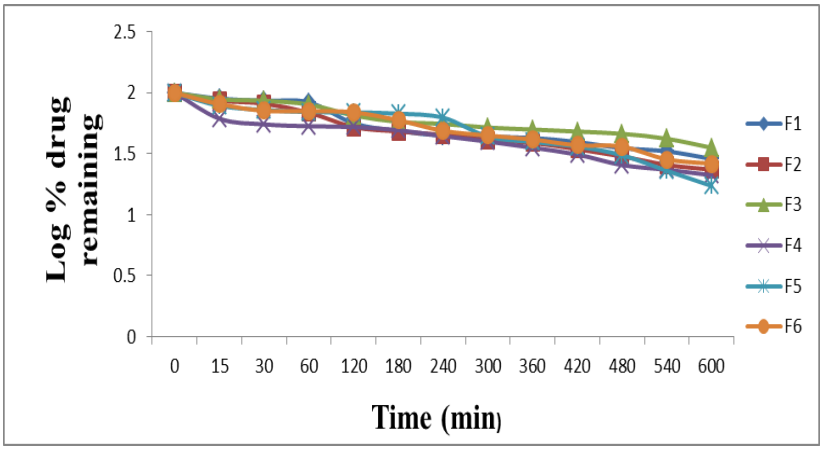


Figure 5: Comparative in vitro permeation study data graph of formulation F1-F6 for first-order release kinetics.

Table 6: Drug release mechanism by various kinetic models which shows the value of 'n' for the all fluconazole formulations (F1 to F6).

Formulations	Zero order release	First order release	Higuchi release kinetics	Korsmeyer-peppas release kinetics		Best fit model	Release mechanism
	R^2	R^2	R^2	R^2	n value		
F1	0.8259	0.9429	0.9462	0.9692	0.6508	Higuchi	Non-Fickian diffusion
F2	0.8507	0.9842	0.9724	0.9492	0.6304	Higuchi	Non-Fickiandiffusion
F3	0.8702	0.9663	0.9765	0.9661	0.6089	Higuchi	Non-Fickian diffusion
F4	0.747	0.945	0.8673	0.7758	0.5904	Higuchi	Non-Fickian diffusion
F5	0.9312	0.9237	0.9328	0.8868	0.5842	Higuchi	Non-Fickian diffusion
F6	0.8997	0.9813	0.9735	0.9001	0.5851	Higuchi	Non-Fickian diffusion

4. CONCLUSION

Fluconazole belongs to the group of triazole and shows fungistatic activity. It inhibits the main component of fungal enzyme 14α-demethylase and is used in the treatment of candida tropicalis, cryptococcus neoforneans, and Candida Albicans. The problem with fluconazole is that it is poorly water-soluble or hydrophobic in nature and long term therapy on a higher dose causes less patient compliance. Oral delivery of fluconazole often produces gastric irritation, bloating, abdominal discomfort, etc. The present study was focused to formulate and evaluate emulgel containing antifungal drug fluconazole with two gelling agents such as guar-gum and carbopol-940 for effective delivery i.e., modifying the release rate of a drug on target infective site.

In the present work, six formulations of emulgel were prepared. Synthetic polymer carbopol 940 and natural polymer guar gum were used as a gelling agent. The different pre-formulation studies were performed before the formulation of emulgel. All the formulations of emulgel were evaluated for visual examination, phase separation, spreadability, pH, drug content, kinetic study, and in-vitro diffusion study. The result of all the formulations was found to be in favorable parameters.

The drug content of all the formulations was analyzed using a phosphate buffer of pH 7.4 as medium λ_{max} 260nm. In the prepared formulations of Carbopol F2 shows the highest drug content and formulation F3 shows the lowest drug content. In the formulations of guar gum

F5 show, the highest drug content and formulation F6 shows the lowest drug content. All the formulations found in the pH range of 4.3-5.9 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 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. Where in the formulation of guar gum formulation F5 shows the highest drug release and formulation F6 shows the lowest drug release.

Among all the prepared formulation of 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 as the oil phase. In the future, in-vitro diffusion study and other evaluations will be performed based on these formulation parameters.

ACKNOWLEDGEMENT

Authors are thankful to the HOD and management of department of Pharmaceutical Sciences, H.N.B. Garhwal University (A Central University) Srinagar (Garhwal), Uttarakhand, for providing necessary facilities and support for conducting the research.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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