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Design, Development and in Vitro Characterization of Emulgels Loaded with Fluconazole Solid Dispersion and Various Oils for Synergestic Anti-Fungal Effect

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Abstract

Topical Fungal Infections are the most common types of skin infections. Nearly a billion people are suffering from fungal infections of different types. Early accurate diagnosis and treatments may lead to complete cure of such infections, which if left untreated may lead to deadly results. Our current Research topic includes designing of antifungal emulgels that contain oil base which already has proven its efficacy against fungal infections and Fluconazole as the main active ingredients. Three oils were selected namely Tea tree oil, Neem oil and Lemon grass oil. To enhance the efficacy of BCS class II drug fluconazole, solid dispersions of the drug were prepared(F1-F6). Twelve formulations (EGF1-EGF12) containing various combination of oils, gelling agents, API, Aloe vera gel were prepared. Which were then evaluated and characterized for properties like drug content, Rheological study, spread ability, Drug release, pH, stability analysis etc. Among all the formulations EGF2 and EGF5 showed optimum results for drug content and drug release kinetics. The Best selected formulations were then compared with marketed gel formulation of Fluconazole and were kept for stability study analysis. Preformulation studies of the drug, preparation of solid dispersions, incorporation of these solid dispersions into emulgels and characterization of prepared emulgels by comparing with marketed formulations are the main key points of our Research work.

Keywords: *Antifungal, Emulgels, Fluconazole, Solid dispersions*

1. Introduction

Emulsion-gels have been increasing their importance and popularity in both pharmaceutical and cosmetics topical semisolid dosage form as a direct effect of drug including medication to the skin to get the effect of drug or treatment of disorders. Emulsion is a controlled release system surrounded by biphasic liquid dosage form, means two immiscible liquid phases usually consist of organic solvent (oil) & aqueous phase (water), where drug particles are entrapped in internal phase & pass through the external phase towards the skin and gradually absorbed by skin. The current research work aims to design emulgels using different types of antifungal oils such as tea tree oil, lemon grass oil and neem oil along with an antifungal drug Fluconazole. All three oils selected has proven efficacy against various fungal infections. Fluconazole has High permeability and low solubility that is what makes it a good candidate for topical preparation. Twelve formulations (EGF1-EGF12)were prepared using different combinations of oils, sodium alginate, propylene glycol, Aloe Vera gel, glycerine, triethanolamine, methyl and propyl paraben. The drug incorporated in all the emulgels was in the form of solid dispersion. To enhance the solubility of fluconazole, six solid dispersions(F1-F6) were prepared using combination of beta cyclodextrin and PVP. The best solid dispersion was selected each of beta cyclodextrin and PVP and it was then incorporated in various formulation of emulgels. The prepared emulgels were then evaluated for various properties like pH, drug content, viscosity, spreadability,extrudability as well as in vitro release studies. Based on the Evaluation parameters the best formulations were selected. The selected emulgels were compared with marketed formulation Flucos^{TM}**.**

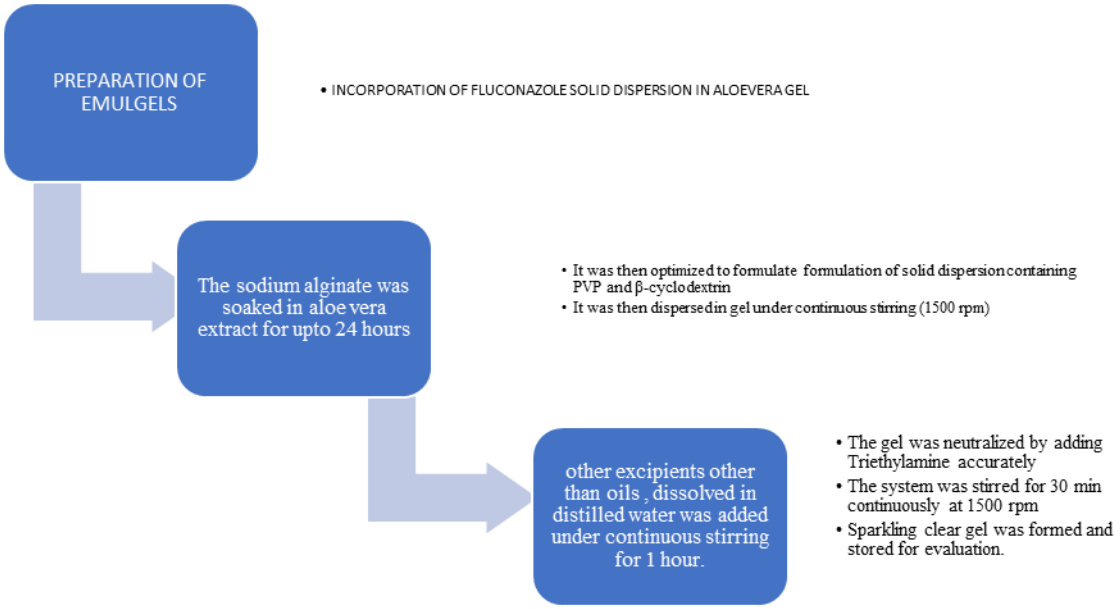

Figure 1 : Step By Step Process Forpreparation Of Emulgels

2. Materials And Methods

- The preparation method of emulgels is represented in figure I.
- To prepare emulgels firstly, the solid dispersion of fluconazole was incorporated in aloe vera gel. For this, sodium alginate was soaked in aloe vera extract for upto 24 hours. It was then optimized to formulate formulation of solid dispersion containing PVP and β-cyclodextrin
- The dispersionin gel was done under continuous stirring (1500 rpm)
- other excipients other than oils , dissolved in distilled water was added under continuous stirring for 1 hour.
- The gel was neutralized by adding Triethylamine accurately
- The system was stirred for 30 min continuously at 1500 rpm

Sparkling clear gel was formed and stored for evaluation.

Table No.1 : Polymers And Excipients Used in formulation.

POLYMERS & EXCIPIENTS USED	MANUFACTURER
Sodium alginate	Sd.-fine chem. Limited, Mumbai
Propylene glycol	Sd. Fine chem. Limited, Mumbai
Aloe vera	Botanical garden
Methyl paraben	Yarrow Chem. Products, Mumbai.
Propyl paraben	Yarrow Chem. Products, Mumbai.
Triethanolamine	Sd-fine chem. Limited, Mumbai
Ethanol	Merck ltd. Mumbai
Glycerine	Sd. Fine chem. Limited. Mumbai
Distilled water	From college lab.
Polyvinyl pyrrolidone	Sd. Fine chem. Limited. Mumbai
Beta-cyclodextrin	Sd. Fine chem. Limited. Mumbai

- **Preparation of Solid dispersion by solvent evaporation method**
  The drug and excipients were dissolved in required volume of methanol/solvent with continuous stirring.
- Once the solvent was completely evaporated fluconazole solid dispersion was obtained and it was then kept in dessicator for moisture removal.
- Prepared fluconazole solid dispersions was kept for further use.

Table No 2: Formulation Table For Different Solid Dispersion

FORMULATION	DRUG(mg)	β-CYCLODFEXTRIN(mg)	PVP(mg)
F1	200	200	-
F2	200	300	-
F3	200	400	-
F4	200	-	200
F5	200	-	300
F6	200	-	400

Extraction of Aloe Vera Gel-

- To extraxt aloe vera gel fresh leaves were collected from the plant. Then it was washed in the running tap water for around 15-20 mins and then it was rinsed with sterile distilled water and mild chlorine solution water
- The leaves were then cut/ dissected longitudinally section and the colourless paren-chymatous tissue i.e *Aloe* gel was scraped out using sterile knife.
- The thick epidermis was removed sectionally and gel like pulp separated with spoon, minced and homogenized in the mixer grinder

Table 3: Formulation Table For The Aloe-Vera Topical Gel Containing Solid Dispersion Of Fluconazole Using Factorial Design

	β-CYCLODEXTRIN			**PVP**								
Ingredients	EGF1	EGF2	EGF3	EFG4	EGF5	EFG6	EGF7	EGF8	EGF9	EGF10	EGF11	EFG12
SD containg drug equivalent to 1g Fluconazole	1 gm	1gm	1gm	1gm	1gm	1gm	1gm	1gm	1gm	1gm	1gm	1gm
LemonGrass oil	5ml	5ml	5ml	5ml	-	-	-	-	-	-	-	-
Neem oil	-	-	-	-	5ml	5ml	5ml	5ml	-	-	-	-
Tea Tree oil	-	-	-	-	-	-	-	-	5ml	5ml	5ml	5ml
Sodium alginate	0.5	1gm	1.5gm	2gm	0.5gm	1gm	1.5gm	2gm	0.5gm	1gm	1.5gm	2gm

Propylene glycol	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml	10ml
Aloe vera	60ml	60ml	60ml	60ml	60ml	60ml	60ml	60ml	60ml	60ml	60ml	60ml
Glycerine	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml
Triethanolamine	Q.S	Q.S.	Q.S.	Q.S.	Q.S.	Q.S	Q.S.	Q.S	Q.S.	Q.S.	Q.S.	Q.S
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propyl paraben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Water	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q,S	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S

Incorporation of Fluconazole Solid Dispersion in Aloe Vera gel :

- The sodium alginate was soaked in aloe vera extract for upto 24 hours.
- It was then optimized to formulate formulation of solid dispersion containing PVP and β-cyclodextrin .
- It was then dispersed in gel under continuous stirring (1500 rpm)
- Measured quantities of oils were taken in the suitable beaker.
- other excipients dissolved in distilled water was added under continuous stirring for 1 hour.
- The gel was neutralized by adding Triethylamine accurately.
- The system was stirred for 30 min continuously at 1500 rpm.
- Sparkling clear gel was formed and stored for evaluation.

3. Results and Discussion

Evaluation Parameter of Aloe Vera Topical Gel

5.6.3.1. Measurement of pH

The pH of gel formulations were determined by using electronic digital pH meter. About 1gm of prepared gel formulation was dissolved in around 10ml of distilled water.it was then kept almost for 2 hours.

The above step was followed for almost all formulations for pH determination.

Each formulation evaluation was done in triplet. At last the average value was calculated.

Drug content analysis

5gm of gel contain 100mg of drug was taken and transfer in to 100ml volumetric flask and volume made up with 5.5pH buffer. Sonicated for 30minutes and filtered further diluted it and absorbance was determined at 260nm by UV-Spectrophotometer. At last drug content was calculated.

Viscosity study

Rheological / Viscosity of this prepared formulation was determined by the using of rotational viscometer (fungi lab) with the spindle no. PA, PC, PB, PD, PE, PF.

- The range of viscosity was noted at a speed from 2-15rpm, at the individual rpm is higher torque was noted down and the mean calculated.

Spreadability

The evaluation of Spreadability of fluconazole Emulgels was detected by measuring the diameter when 2gm of gel placed between the two glass plates for upto 3 minutes.

- Gel made a uniform layer between two plates by the spreading, then after this a weight was tied with the upper plate and spreadability was calculated that by using formula mentioned :

$S=M\times L/T$

S= Spreadability (gcm^{-1}/sec)

M=weight of tied gel on the upper plate

L=length of glass slide

T=Time

Extrudability study

This is one of the most important parameter, The prepared formulation of emulgels was filled in the collapsible tube then after gel gets to stabilize in the container. The Extrudability was determine by the extruded the gel from tube..

In-vitro release study

In-vitro drug release study of the prepared fluconazole emulgels formulation were carried study by the diffusion cell.

Procedure

The diffusion cell release study of the emulgel formulations was carried out using by dual chamber. One chambered of donor and other receiver.

- Compartment model by the using of cellophane membrane or egg membrane. 5gm of gel sample was kept/hold on the membrane and fixed and one end of broken or two sided open glass tube and it was dispersed on the phosphate buffer pH 5.5 buffer as medium of diffusion .
- Then after regular interval samples was withdrawn at a constant interval time of 30 minutes,60,90,120,150, hours.
- Every sample was replaced with their equivalent volume of fresh buffer medium to maintain the sink condition.
- Every taken sample was analyzed by UV-spectrophotometer at 260 nm with the using of phosphate buffer.

Stability studies

Stability study and accelerated stability study is defined as the extent to which products retains its efficacy and activity within a specified limit & throughout its limited periods of storage and their uses. Shelf life, stability studies, were carried out in optimization formulation according to international conference on harmonization (ICH) guidelines.

- For this study A specific amount of formulation is previously sterilized was stored in desiccators, which give a relative humidity of $75\pm5\%$.
- The desiccators were then placed in a humidity chamber was maintained at a temperature $40\pm5^{o}C$ and at room temperature.
- These samples was withdrawn at 0 day, 14 days, 28days, 42 days, 56 days, 70 days, 90 days intervals.

The percentage drug remaining was calculated.

Preformulation Study

Organoleptic properties: The procured drug sample of as fluconazole was identified by organoleptic properties.

Table 4: Showing drug properties

ORGANOLEPTIC PROPERTIES	
Description	Fine powder
Colour	White
Odor	Odorless
Taste	Tasteless as per I.P

Solubility study

Solubility study is done in methanol, ethanol and distilled water

Table5: solubility profile in various solvents

S. No.	Solvents	Solubility
1	Methanol	Soluble
2	Ethanol	Soluble
3	Distilled water	slightly soluble

Partition coefficient

Partition coefficient (log P) of the drug was obtained 0.571 which indicates that the drug is lipophilic and very less soluble in aqueous media.

Melting point

Three time it is done to got different result and this by average is taken which is 137 where as reported value is 138.4

Table 6: Melting point of Fluconazole

Melting point(ºC)	Average(Mean)
132-135	
134-139	
133-142	137

Wavelength maximum of Fluconazole

The fluconazole solution of (6 µg/ml) was prepared in phosphate buffer 5.5 and then scanned using SHIMADZU, double beam UV-VIS Spectrophotometry 1700). The scanning range was between 200nm to 400nm. And it was obtained **260 nm.**

b. Standard calibration curve of fluconazole

the calibration curve of fluconazole in phosphate buffer 5.5 is done in different concentration of 5,10,15,20 and 25µg/ml in following table.

Table .8:Absorbance of Fluconazole

S. No.	Concentration (µg/ml)	Absorbance
1	5	0.0493
2	10	0.0729
3	15	0.0964
4	20	0.113
5	25	0.1257

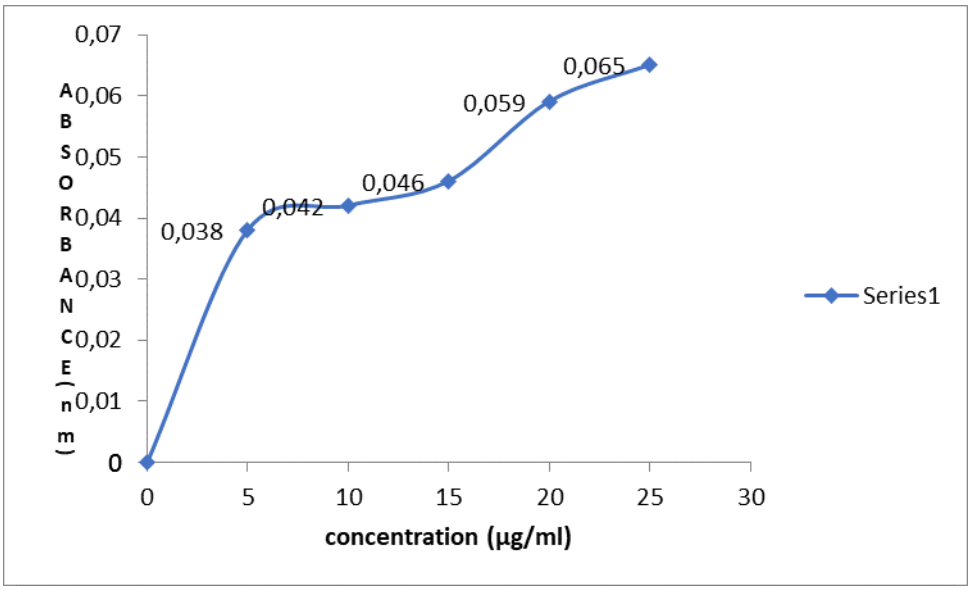

Fig 2 : Standard calibration cure of Fluconazole in Phosphate buffer 5.5

Standard curve in Distilled water

Table 9: Showing less absorbance in Distilled Water

s.no	µg/ml	Absorbance(nm)
1	5	0.038
2	10	0.042
3	15	0.046
4	20	0.059
5	25	0.065

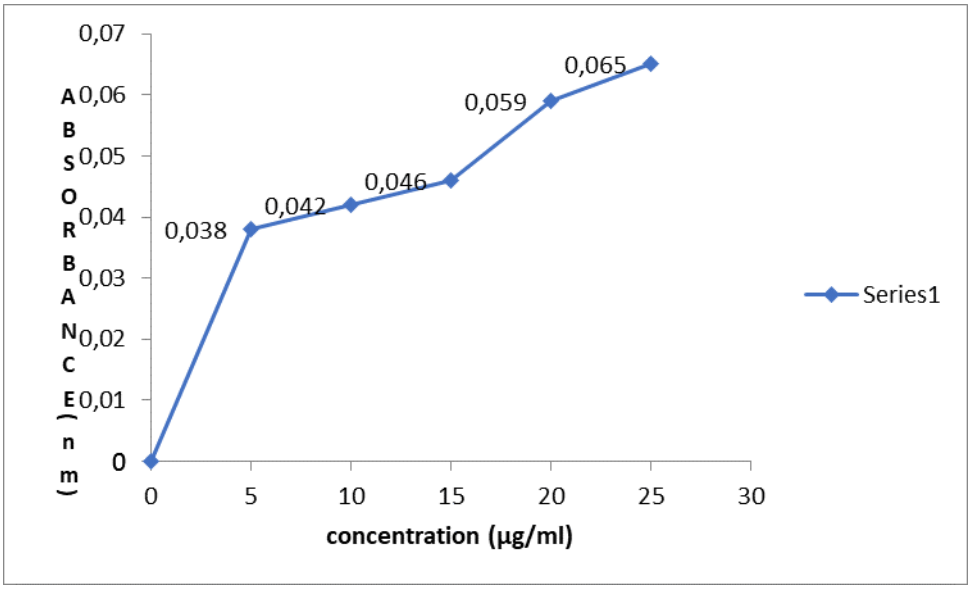

Figure 3: Calibration curve of fluconazole in water

Drug Excipients Comptability Study

The fluconazole drug and other excipients were taken in ratio 1:1 and well mixed and kept in poly bags. Then mixture of drug and excipients was transferred from poly bag to glass vials & sample was put in to the stability chamber at 40°C for 21days

Through Fourier transform Infrared Spectroscopy: The compatibility study of drug excipients was done by FTIR analysis.

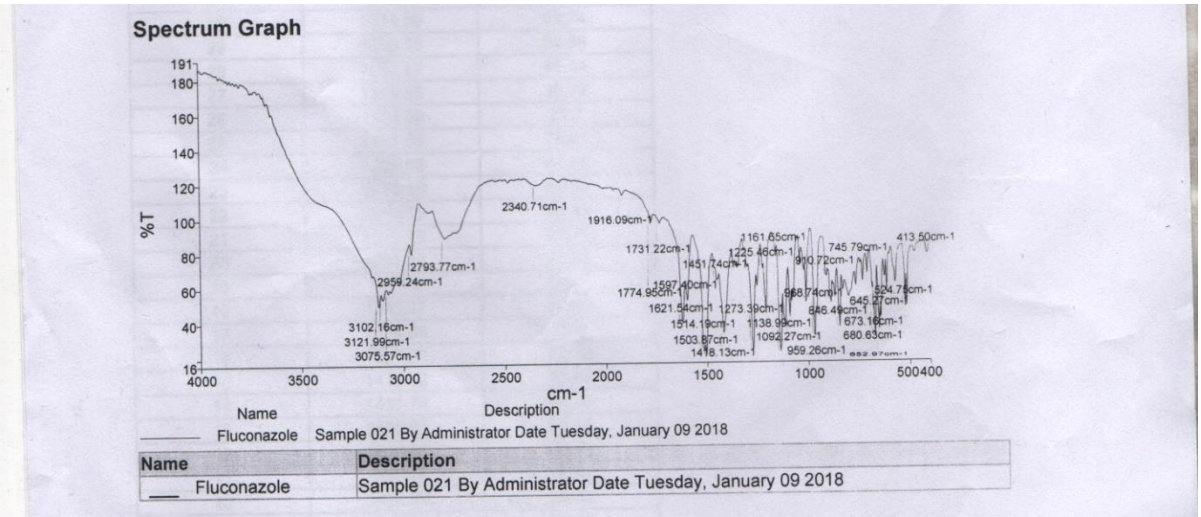

Figure 4 : FTIR of Fluconazole (pure drug).

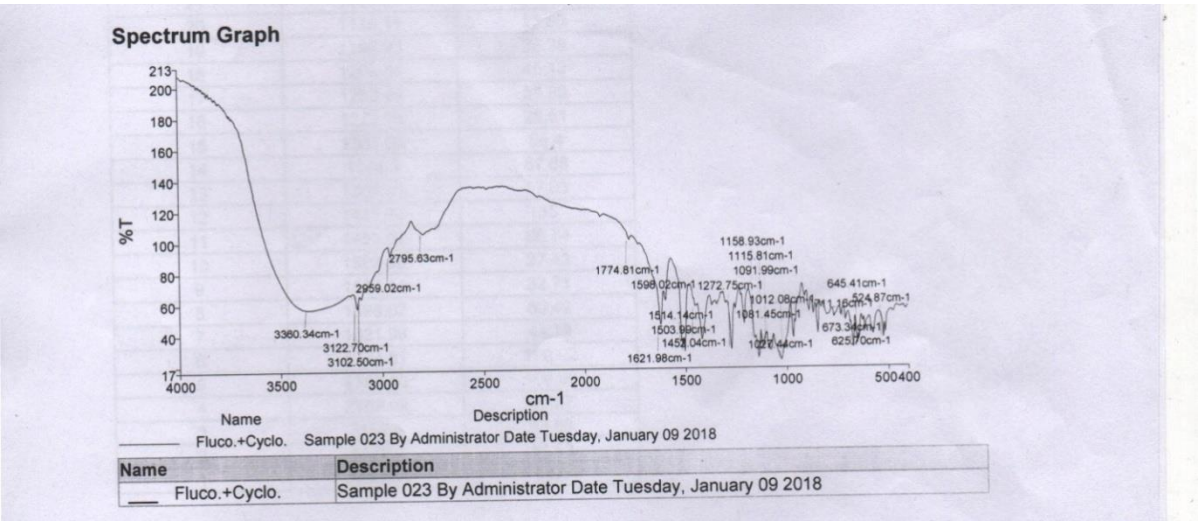

Figure 5: FTIR of fluconazole + β- cyclodextrin

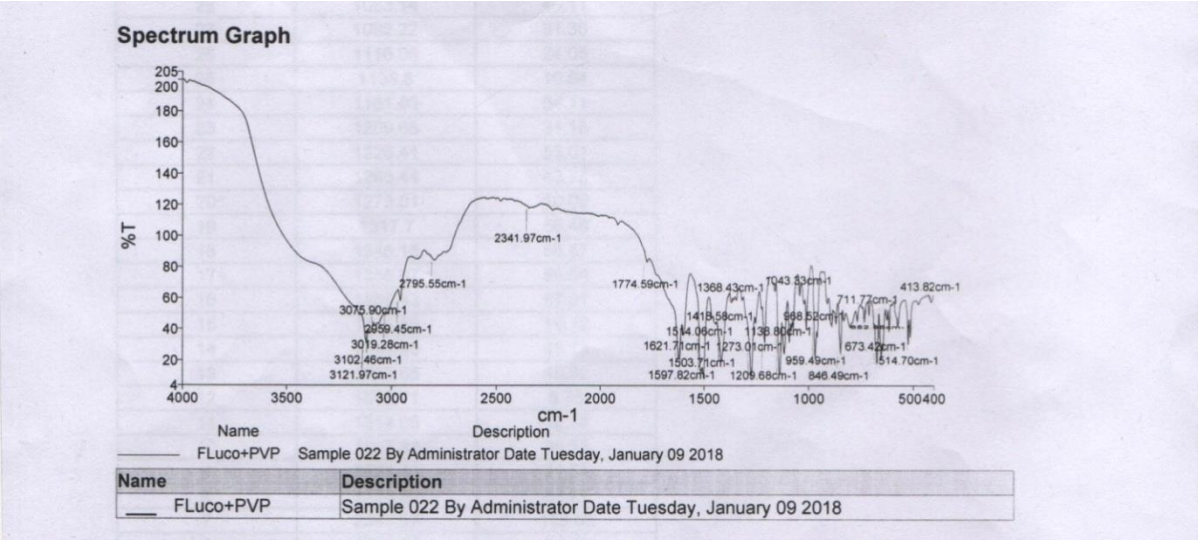

Figure 6: FTIR of fluconazole+ PVP

Discussion: FTIR is done of fluconazole alone and between fluconazole and β-cyclodextrin, fluconazole and PVP and this is showing not any changes in functional group .so there is no any compatibility and we can use these combination further in various formulation.

Evaluation of Fluconazole Solid dispersion

Solubility Studies of Fluconazole solid dispersion

Solubility of the fluconazole solid dispersion in water was performed and it was found that aqueous solubility of all solid dispersion formulation was enhanced when compared to pure drug.

Among all the formulation aqueous solubility of formulation F2 (1:2) prepared by β-cyclodextrin showed higher aqueous solubility of around 78.41%

Table 9: Showing different solubility according to polymer ratio changes

S.NO	FORMULATION	% AQUEOUS SOLUBILITY
1.	F1	70.22
2.	F2	78.41
3.	F3	72.32
4.	F4	68.45
5.	F5	56.42
6.	F6	65.25
7.	Pure drug	34.11%

Drug content of Fluconazole solid dispersion

Drug content of Different formulation of solid dispersion of fluconazole with β-cyclodextrin and PVP is done in phosphate buffer 5.5 and it is observed that the F2 have highest 98.6 drug content among all formulation

Table 10: drug content of different solid dispersion formulation

Formulation	Drug content (%)
F1	92.78
F2	98.68
F3	94.56
F4	97.53
F5	96.91
F6	93.67

Dissolution rate studies of fluconazole solid dispersion

It was performed in phosphate buffer 5.5 for 2.3 hours using USP type II apparatus.

From the table given below it is observed that dissolution rate of solid dispersion prepared using β-cyclodextrin have higher dissolution rate than that of those formulated PVP as carrier. the

Formulation F2 showed higher dissolution rate of 99.23 afetr 150 minutes.

Table11: Release of all solid dispersion formulation

Formulation	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
30	22.04	20.46	27.75	13.78	17.64	11.6
60	32.96	36.54	37.75	36.67	34.75	29.57
90	55.45	58.84	44.7	51.34	48.62	45.74
120	78.35	85.98	67.84	70.01	66.39	65.97
150	93.64	99.23	89.3	94.86	92.4	86.57

Evaluation Of Fluconazole Emulgels

All the developed formulation of gels of fluconazole was evaluation parameter detected by such as measurement of visual appearance, pH and drug content. The pH of prepared formulation was found to be 5.7 to 6.2. All formulation was prepared in distilled water.

Table no. 12: Preliminary evaluation of visual appearance, pH and drug content

Formulation code	Visual appearance	pH	Drug content (%)
EGF1	light green	5.8	93.16%
EGF2	Green	6.1	97.31%
EGF3	Dark green	6.5	91.53%
EGF4	Light green	5.9	87.10%
EGF5	Green	5.7	95.76%
EGF6	Dark green	6.2	92.32%

Formulation code	Visual appearance	pH	Drug content (%)
EGF7	Green	5.7	92.56%
EGF8	Green	6.6	95.21%
EGF9	Light green	6.2	93.93%
EGF10	Light green	5.7	93.10%
EGF11	Green	6.0	92.66%
EGF12	Dark green	6.3	95.32%

Spreadability And Extrudability Test

Table 13: Spreadability and Extrudability of different formulation

S. No.	Formulation code	Spreadability (in cm^2)	Extrudability
1	EGF1	123.04	+++
2	EGF2	115.47	+++

3	EGF3	98.84	++
4	EGF4	120.57	++
5	EGF5	112.66	+++
6	EGF6	95.27	++

+++ Excellent

++ Good

Figure 8: Testing for exturdability of gel

Viscosity Studies

The viscosity of various formulation is done with the spindle PF in different shear rate (2,5,10,15,20,25) and approx. all the formulation have good viscosity which is decreasing with respect to increasing of shear rate.

Table 14: Viscosity study of fluconazole gel

Shear rate (RPM)/ST	**Viscosity of the formulation in centipoises**					
	EGF1	**EGF2**	**EGF3**	**EGF4**	**EGF5**	**EGF6**
2	6252.55	5492.31	7057.28	7582.39	7800.12	7308.81
5	6343.4	6617.22	7125.38	7389.53	7798.39	7289.90
10	5998.51	5771.32	7748.48	7393.25	7787.20	7271.92
15	6393.25	5561.31	7142.29	7447.92	7782.98	7262.18
20	6126.41	5471.47	7452.30	7452.84	7757.81	7229.21
25	6225.54	5682.82	7525.48	7501.76	7723.25	7216.20

Time (minute)	EGF1	EGF2	EGF3	EGF4	EGF5	EGF6	Marketed formulation	
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	
30	**16.41**	**38.91**	**10.51**	**14.11**	**23.12**	**14.65**	**33.95**	
60	**26.31**	**46.34**	**31.97**	**35.67**	**47.11**	**23.45**	**46.12**	
90	**36.27**	**55.73**	**44.35**	**49.11**	**55.21**	**33.72**	**68.46**	
120	**45.31**	**79.13**	**58.27**	**59.31**	**67.41**	**45.11**	**78.21**	**Drug**
150	**55.67**	**89.12**	**63.32**	**65.31**	**75.21**	**49.57**	**89.81**	**Releas**
180	**77.29**	**95.61**	**65.32**	**74.45**	**80.25**	**59.51**	**94.88**	**e**
								Study

Drug release study of gel is done in phosphate buffer 5.5 and among all formulation GF2 is the best release of 96.5 for 150 minutes

Table 15: Different gel formulation release

TIME (MINS)	E G F1	EGF2	EGF3	EGF4	EGF5	EGF6
0	0	0	0	0	0	0
30	15.2	17.6	14.78	13.78	12.64	13.6
60	37.1	40.2	35.89	36.67	34.75	29.57
90	54.7	63.7	55.8	51.34	48.62	45.74
120	75.6	81.8	72.89	70.01	66.39	65.97
150	84.2	96.5	85.7	80.86	82.4	76.1

TABLE 16: Formulation showing drug release in which EGF2 is showing highest CDR%

In vitro drug release study and kinetic release

Formulations shows the drug release in descending order EGF2>EGF1>EGF3 where the amount of drug released after 180 minutes (3 hrs) was 95.61%, 77.29%, 65.32% respectively, and for the formulations with carbopol 940 the drug release in descending order EGF5>EGF4>EGF6 where the amount of drug released after 180 minutes (3 hrs) was 80.25%, 74.45%, 59.51%respectively. And marketed formulation aroxia emulgel shows the drug release after 180 minutes (3 hrs) was 94.88 which is comparable with the EGF2 formulation of carbopol 934 (1.5%). It has been concluded that the carbopol 934 emulgel with 1.5% concentration of polymer EGF2 shows maximum release. The release pattern with carbopol 934 emulgel was better than that of carbopol 940. It shows carbopol 934 is better polymer or gelling agent than carbopol 940 for formulating emulgel. Formulation EGF2 from carbopol 934 polymer and formulation EGF5 from carbopol 940 polymer shows the best result. And finally it has been concluded that EGF2 formulation from carbopol 934 shows better result than marketed emulgel formulation. The cumulative % drug release profile of all the formulation batches has been shown in fig. 7 [16].

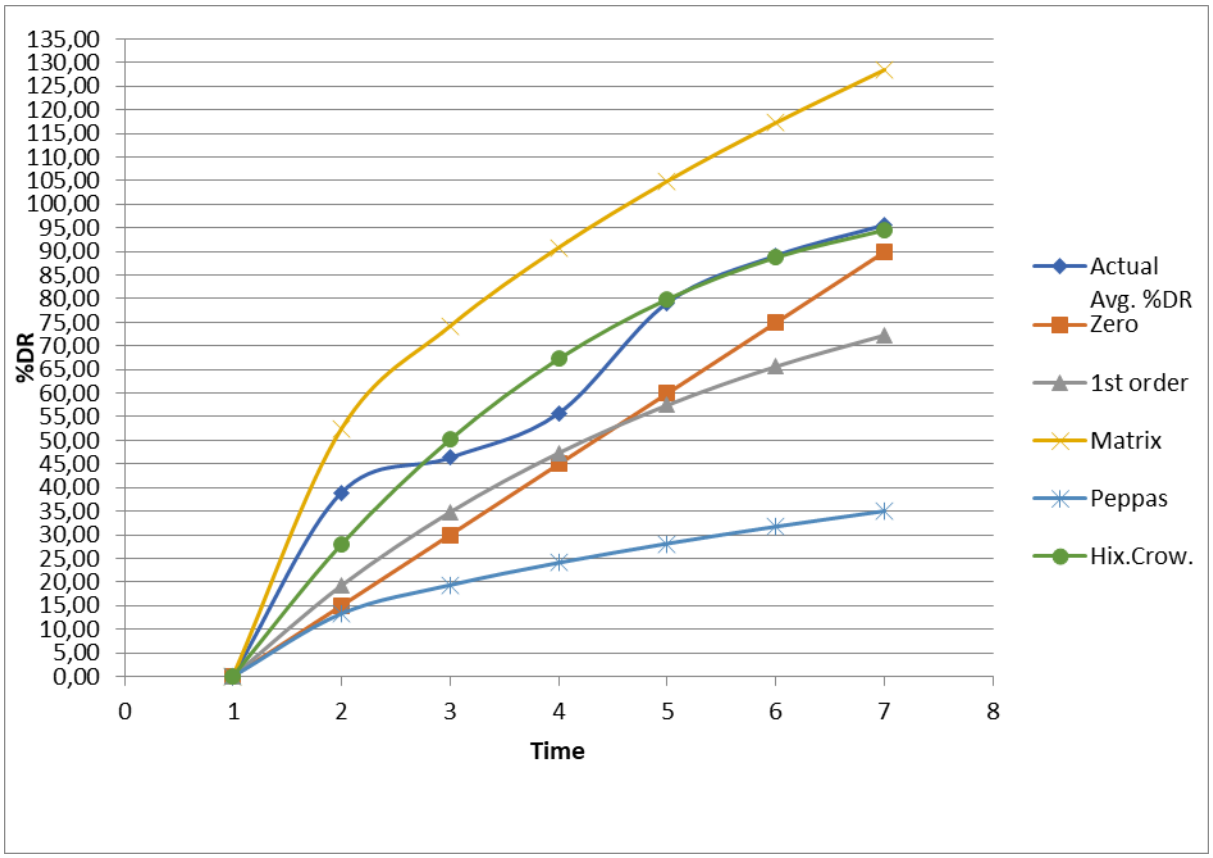

Figure 7: Cumulative Drug Release Data

Release kinetic result of selected best drug release emulgel formulations and marketed formulation

Formulation	Zero order R^2	1st order R^2	Higuchi Matrix R^2	Peppas R^2	Hix.Crow. R^2	Parameters for korsmeyer-peppas eqn.	Best fit model
EGF2	0.9406	0.9313	0.9177	0.9329	0.9720	n =0.5402 K= 2.1169	Hixon-Crowell
EGF5	0.9321	0.9957	0.9303	0.9652	0.9849	n = 0.6809 K= 0.6809	First order
Marketed emulgel formulation	0.9278	0.9734	0.9296	0.9946	0.9967	n =0.5793 K=1.9877	Hixon-Crowell

Stability Studies

Stability study of the formulated gel was following the ICH stability guidelines. Total prepared formulation was studied their stability and also their appearance, clarity, pH, % drug content. This study was follow up by the pH study at different room temperature and also 45°C. Such study was carried out up to 90 days and the all product maintained their limits. After the study observed result was show slightly changing in the pH and also in % drug released but that was in their changed was acceptable.

S.N	Number of days	pH(EGF1)		pH(EGF2)		pH(EGF3)		pH(EGF4)		pH(EGF5)		pH(EGF6)	
		RT	45^0C	RT	45^0C	RT	45^0C	RT	45^0C	RT	45^0C	RT	45^0C
1	0	5.8	5.8	6.1	6.1	6.5	6.5	5.9	5.9	5.7	5.7	6.2	6.2
2	14	5.8	5.8	6.06	6.06	6.47	6.47	5.88	5.88	5.68	5.68	6.19	6.19
3	28	5.78	5.78	5.96	5.96	6.45	6.42	5.87	5.76	5.74	5.64	6.11	6.10
4	42	5.71	5.70	5.95	5.91	6.42	6.40	5.85	5.71	5.72	5.61	6.10	6.8
5	56	5.70	5.69	5.92	5.90	6.40	6.38	5.82	5.68	5.69	5.59	6.9	6.7
6	70	5.68	5.65	5.89	5.88	6.35	6.33	5.80	5.79	5.65	5.64	6.89	6.87
8	90	5.65	5.60	5.7	5.69	6.2	6.19	5.73	5.67	5.57	5.52	6.82	6.75

4. Conclusion

In the present study,fluconazole using to its low aqueous solubility is formulated as solid dispersion,β-cyclodextrin & PVP was chose as carrier for the solid dispersion formulation . among all six formulation F2 was obtained as best formulation as is showed higher aq. Solubility (78.41) higher drug content (98.68) and also faster dissolution rate (99.23).

The optimized solid dispersion formulation was then incorporated in gel prepared by aloe-vera. all six formulations (GF1-GF6) were evaluated for various parameter such as pH, Viscosity, spreadibility, extrudability, drug content, diffusion studies. GF2 was obtained as best formulation with very high drug content & higher drug release through the formulation.

Thus, from above study, it can be concluded that solubility of a poorly soluble drug can be enhanced by preparing its solid dispersion using β-cyclodextrin and also by incorporating the solid dispersion in gel formulation exhibits better result in treatment of various antifungal disease.

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