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Development and Evaluation of Nanoparticles Based Topical Gel Containing Antifungal Drug Fluconazole

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ABSTRACT

The objective of this work was to prepare Fluconazole nanoparticles, and then incorporated into the freshly prepared gel for transdermal delivery, reducing the oral side effects of the drug and for enhancing stability. Fluconazole is commonly used antifungal agents for the treatment of local and systemic fungal infections. In this study Fluconazole nanoparticles was prepared by using Eudragit RL 100 by nanoprecipitation method with different drugs to polymer (1:1, 1:2 and 1:3) and stabilizer (Poloxamer 188) ratios (0.5%, 0.75% and 1%) and evaluated for various parameters. Drug-excipients compatibility was performed by FTIR study. The particle size, polydispersity index, Zeta potential, % Entrapment efficiency and % drug content of all the formulations were found in the range of 16.8 to 48.9nm, 0.229 to 0.558, -11.6 to -26.6 mv, 28.41% to 95.78% and 59% to 97.38%. From SEM studies it was revealed that Fluconazole nanoparticles particles are spherical in shape and without any agglomeration. From the *in-vitro* drug release study, it was revealed that sustained release of same formulation last up to 12 hours. From the stability study, it was revealed that the F5 formulation was stable at 40°C ± 2°C /75% ± 5%RH and 4°C. The optimised formulation F5 was selected to prepare Fluconazole loaded nanoparticles based topical gels using different concentration of Carbopol 934 and 940 and characterized for pH, spreadability, drug content, viscosity and in-vitro drug diffusion. Among the five formulations, G5 was selected as the best formulation. The pH of all formulations was found near to the skin pH value. The *in-vitro* diffusion study of Fluconazole gel (G5) showed 94.75%. The optimized formulation G5 was checked for mechanism and kinetics of drug release. It is found it following Zero order release and non-Fickian mechanism. The selected Gel formulation G5 was found to be stable at 40°C ± 2°C /75% ± 5%RH and 4°C, it is clear that the formulation did not undergo any chemical changes found more stable at room temperature.

KEYWORDS: Nanoparticles, Fluconazole, Eudragit RL 100, Poloxamer 188, Carbopol 934 and Carbopol 940.

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INTRODUCTION

Topical or transdermal drug delivery is challenging because the skin acts as a natural protective barrier. Several methods have been examined to increase the permeation of therapeutic molecules into and through the skin and one such approach is the use of Nanoparticulate delivery system. Drug delivery from colloidal systems such as nanoparticles dispersed in a gel appears to be unique when compared to the delivery from traditional topical and dermatological formulations. During the last decade, considerable attention has been paid to the development of new controlled drug delivery system, in order to supply a long-term drug release and therefore, increase patient's therapeutic compliance and acceptance. The transdermal drug delivery system can be used to deliver antifungal drug across the skin for the treatment of dermatological disease as well as skin care.

Fungal infections are very common in human beings, especially in the tropical regions. Fungi produce a wide spectrum of human infections ranging from superficial skin infections affecting the outer layers of skin, hair, nails and mucous membranes to systemic infections (internal organ invasion). The progression of fungal infections can be rapid

and serious due to compromising with immune function. Dermatophytes are one of the most frequent causes of tinea and Onychomycosis, and Candida infections are also among the most widespread superficial cutaneous fungal infections. Even, candida can invade deeper tissues as well as the blood which leads to life threating systemic candidiasis, when the system is weakened. Topical treatment of fungal infections has several superiorities including, targeting the site of infection, reduction of the risk of systemic side effects, enhancement of the efficacy of treatment and high patient compliance.

Fluconazole is a synthetic antifungal agent of the imidazole class. It works by slowing the growth of fungi that causes infection. It is used to treat fungal infection. Fluconazole remains one of the most frequent prescribed triazoles because of its excellent bioavailability, tolerability, and side-effect profile. It overcomes all the side effects of the other fungal drugs like, Ketoconazole, Amphotericin B, Clotrimazole, and Miconazole. When fluconazole overcomes side effects of other antifungal agents, it also has some side effects in the oral and parentals dosage forms as pass through the 1st pass metabolism through the liver and excretion through kidneys. Due to these side effects of tablet dosage of fluconazole drug the gel dosage form was formulated.

MATERIALS

Table no.1: List of materials

Sl. No.	Materials	Sources
1	Fluconazole	BMR Pharma and Chemicals.
2	Eudragit RL 100	Sigma Aldrich Pvt. Ltd
3	Ethanol	Merck specialities private limited
4	Poloxamer 188	Apotex India Pvt Ltd, Mumbai.
5	Carbopol 934	Central Drug House Pvt Ltd.
6	Carbopol 940	Central Drug House Pvt Ltd.
7	Propylene Glycol	Central Drug House Pvt Ltd.
8	Methyl paraben	NR Chemicals industries.
9	Propyl paraben	NR Chemicals industries.

METHODS

Formulation of fluconazole nanoparticles: The fluconazole nanoparticles were prepared by a nanoprecipitation method. The formulation plan is shown in table no.1. Drug and polymer were dissolved in Ethanol. The internal organic phase solutions were slowly injected at the rate of (1ml/minute) into the external aqueous solution containing stabilizing agent (Poloxamer 188) at various concentrations in double distilled water, and the mixtures were then stirred at 500 rpm for 4 hours at room temperature. The aqueous phase immediately turned into milky bluish opalescence due to the formation of the nanoparticle suspension. Ethanol was completely removed by rotary vacuum evaporation using a water bath maintaining at 32°C. The Fluconazole nanoparticles formed were isolated, washed three times with distilled water, and freeze-dried.

Table no. 2: Shows the formulation of fluconazole nanoparticles (F1- F9)

Formulation Code	Drug: Eudragit RL 100	Ethanol (ml)	Poloxamer 188 (%)	Distilled water (ml)
F1	1:1	3	0.5	20
F2	1:2	3	0.5	20
F3	1:3	3	0.5	20
F4	1:1	3	0.75	20
F5	1:2	3	0.75	20
F6	1:3	3	0.75	20
F7	1:1	3	1	20
F8	1:2	3	1	20
F9	1:3	3	1	20

EVALUATION OF FLUCONAZOLE NANOPARTICLES

Practical yield:

The prepared nanoparticles of all batches were accurately weighed. The weight of nanoparticles was divided by the total amount of all the excipients and drug used in the preparation of the nanoparticles, which gives the total percentage yield of nanoparticles. It was calculated by using the following equation,

$$\text{Percentage yield} = \frac{\text{Weight of nanoparticles obtained}}{\text{Weight of drug, polymer + other excipients used}} \times 100$$

Drug entrapment efficiency:

The encapsulation efficiency and loading capacity of the nanoparticles were determined by the separation of nanoparticles from the aqueous medium containing non-associated fluconazole by cold centrifugation (Eppendorf Centrifuge) at 11000 rpm for 30 minutes. The amount of free fluconazole in the supernatant was measured by Shimadzu 1800 UV-Visible Spectrophotometer at 261 nm. The entrapment efficiency (%) of drug was calculated by the following equation;

$$\text{Entrapment efficiency (\%)} = \frac{\text{Initial amount of drug added- Amount of drug actually present}}{\text{Initial amount of drug added}} \times 100$$

Drug content:

Accurately weighed 100mg of freeze-dried nanoparticles were dissolved in 2ml of ethanol and made up the volume to 100ml with saline phosphate buffer (PH 7.4) in 100ml volumetric flask. 1 ml of the above solution was further diluted to 10 ml with saline phosphate buffer (PH 7.4). The absorbance was measured using Shimadzu 1800 UV-Visible spectrophotometer at 261 nm.

Morphology:

Scanning electron microscopy (SEM) of the fluconazole nanoparticles was performed to examine the particle size and surface morphology. The nanoparticles were mounted on metal stubs and the stub was then coated with conductive gold with sputter coater attached to the instrument. The photographs were taken using a Jeol scanning electron microscope under magnification of 7500–20000 ×.

Particle size distribution and polydispersity index:

The mean size of the fluconazole nanoparticles was determined using Nano particle Analyzer SZ-100, HORIBA scientific. Each sample was appropriately diluted with double distilled water for analysis.

***In- vitro* diffusion studies:**

The *in-vitro* drug release of fluconazole nanoparticles was studied by using Franz diffusion apparatus. Freshly prepared pH 7.4 phosphate buffer was used as the diffusion medium. Cellophane membrane previously soaked overnight in the distilled water was tied to one end of a specially designed glass cylinder (open at both ends). Accurately measured 1ml of nanosuspensions was placed into this assembly. The cylinder was fixed to a stand and suspended above the receptor compartment containing 50 ml of diffusion medium maintained at 37± 0.5°C, so that the membrane just touched the receptor medium surface. The diffusion medium was stirred at 50 rpm using magnetic stirrer for 12h. Aliquots, each of 1 ml volume was withdrawn at regular time intervals and replaced with equal volume of receptor medium. The aliquots were suitably diluted with receptor medium and analysed by UV-Vis Spectrophotometer at 261 nm.

Stability Studies:

Stability studies were carried out on optimized formulation (F5) at 40°C ± 2°C /75% ± 5%RH in stability chamber (Thermo lab) and 4°C in refrigerator for 30 days. The optimized formulation stored in the sealed in aluminium foil. After 30 days, evaluation studies were carried out.

Preparation of nanoparticle-based gel:

Six formulations of fluconazole gel were prepared using Carbopol 934 and Carbopol 940 as a gelling agent with different ratios of 0.3%, 0.5% and 0.7 %. Specified quantity of Carbopol 934 and Carbopol 940 were soaked overnight as mentioned in the formulation chart shown in Table 3. Fluconazole nanoparticle slurry was prepared by dissolving in a mixture of propylene glycol (penetration enhancer) and glycerine (moistening agent) under continuous stirring. To the Carbopol slurry specified quantity of fluconazole nanoparticles slurry was slowly added with stirring. Propylene glycol (20 % w/v), Glycerine (10%), Methyl paraben (0.03% w/v) and Propyl paraben (0.01 % w/v) were added slowly with continuous stirring until the homogenous gel was formed. The gel was neutralized with sufficient quantity of Triethanolamine and final volume was made to 50 ml with distilled water.

Table no. 3: Shows the formulation of fluconazole nanoparticles gel (F5)

Formulation code	G1	G2	G3	G4	G5	G6
Fluconazole nanoparticles equivalent to 0.5% w/v of fluconazole(gm)	250mg	250mg	250mg	250mg	250mg	250mg
Carbopol 934 (gm)	0.3	0.5	0.7	0.3	0.5	0.7
Carbopol 940 (gm)	0.3	0.5	0.7	0.3	0.5	0.7

Ethanol (ml)	2	2	2	2	2	2
Propylene glycol (%)	20	20	20	20	20	20
Glycerine (%)	10	10	10	10	10	10
Methyl paraben (%)	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
Triethanolamine (ml)	0.2	0.2	0.2	0.2	0.2	0.2
Distilled water	q.s to make 50gm	q.s to make 50gm	q.s to make 50gm	q.s to make 50gm	q.s to make 50gm	q.s to make 50gm

Evaluation of gel:

Percentage yield:

The empty container was weighed in which the gel formulation to be stored and again the container was weighed with gel formulation. Subtract the empty weight of the container with the weight of container with gel formulation. Difference in weight was considered as the practical yield. The percentage yield was calculated by using;

$$\text{Percentage yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Measurement of pH:

The pH of gel formulation is determined by digital pH meter.1 g of gel is dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation is done in triplicate and average values are calculated.

Drug content studies:

Accurately weighed 1 g of gel was transferred into 10 ml volumetric flask containing 5 ml of saline phosphate buffer (pH 7.4) and stirred for 30 min followed by sonication. The volume was made up to 10 ml with saline phosphate buffer (pH 7.4). 5 ml of the above solution was further diluted to 10 ml with saline phosphate buffer (PH 7.4). The absorbance was measured using Shimadzu 1800 UV Visible spectrophotometer at 261 nm.

Spreadability:

The Spreadability of all formulations was determined by using horizontal plate method. 1 g of gel was placed between two horizontal glass plates and standard weight (125 g) was tied on the upper glass plate. The whole set was held in the vertical position. The time was noted for the plate to slide off from the other plate. The spreadability was calculated from the following formula,

$$S = (m \times l) / t$$

Where 'S' is the spreadability coefficient, 'm' is the weight tied to the upper slide, 'l' is the length of glass slide and 't' is the time taken.

Viscosity measurement:

Viscosity of the gel was determined by using Brookfield viscometer. Accurately weighed 25 gm of fluconazole gel was transferred to 50 ml glass beaker. Spindle no 6 was selected and it is immersed into the gel. The viscometer was operated at 10 rpm until the reading gets stabilized and reading was noted in centipoises. It was noted from the literature that the formulations after gelling should have a viscosity of 50 –50,000 cps.

***In-vitro* diffusion studies:**

In-vitro diffusion study was carried out in a Franz diffusion cell using cellophane membrane which is soaked overnight in distilled water. The membrane was tied to the donor compartment and mounted on the reservoir compartment of Franz diffusion cell containing 150 ml of pH 7.4 phosphate buffer. 1 gm of fluconazole gel was placed over the cellophane membrane of donor compartment. Whole set was placed on the magnetic stirrer. The study was carried out at 37±0.5 ºC and 100 rpm for 12 h. Samples were withdrawn from the sampling port of reservoir compartment at regular intervals and absorbance was measured using Shimadzu 1800 UV visible spectrophotometer at 261 nm.

Mathematical modelling of drug release profile:

The % Drug release from the Fluconazole nanoparticle gel at different time intervals were fitted to zero order kinetics and first order kinetics model, Higuchi model and Korsemeyer-Pappas model to characterize mechanism of drug release. To characterize the release mechanism, the diffusion data are evaluated.

Stability:

The stability study was carried out for the optimised formulation (G5), subjecting to a temperature of 40 ± 2°C and 75 ± 5% RH and 4°C in refrigerator for 1month. After 1 month the samples were analysed for the physical characteristics, drug content and *in-vitro* diffusion study.

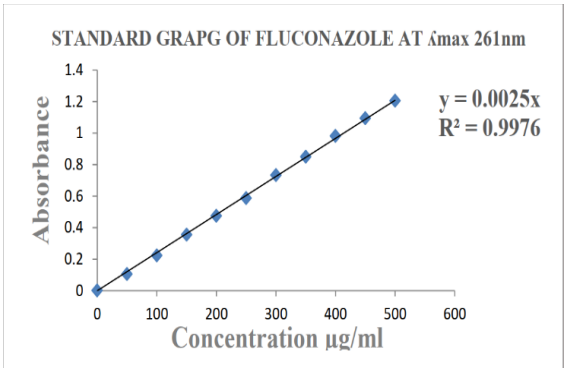
RESULTS AND DISCUSSION:

Standard calibration Curve of Fluconazole at λ max 261 nm in phosphate buffer (pH 7.4): Fluconazole obeyed Beer's law in the range from 50-500 µg/ml. The absorbance is shown in the table no.4 and standard graph in figure no.1.

Table no.4: Standard graph of fluconazole.

Sl. No.	Concentration (µg/ml)	Absorbance (MEAN±SD) n=3
1.	0	0±0
2.	50	0.105±0.004
3.	100	0.222±0.001
4.	150	0.355±0.0006
5.	200	0.474±0.0042
6.	250	0.587±0.006
7.	300	0.733±0.0021
8.	350	0.849±0.0043
9.	400	0.982±0.0005
10.	450	1.094±0.0051
11.	500	1.205±0.0065

Fig. no.1 Standard calibration curve of Fluconazole



Drug-Excipient Compatibility Studies: FTIR of fluconazole, Eudragit RL100, poloxamer 188, Carbopol 934 and Carbopol 940 was done for drug compatibility studies, showed that there is no interaction between the components when taken together

.Fig.no. –2 FTIR Characteristics Peaks of Pure Fluconazole Drug

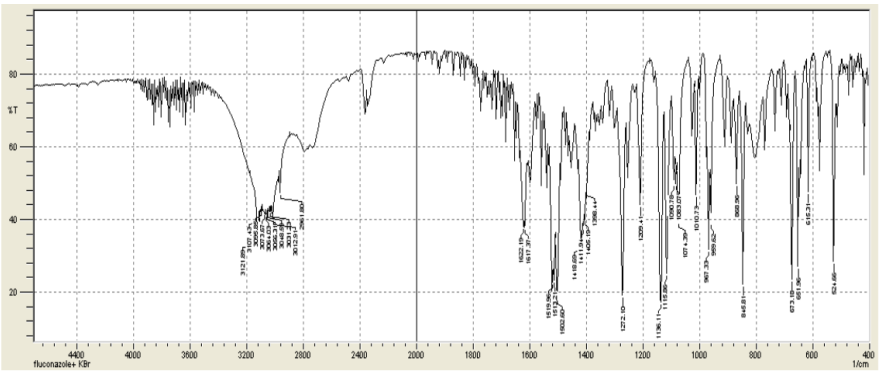


Table no. 5: FTIR Characteristics Peaks of Fluconazole:

Functional Group	Peak obtained in drug (frequency cm-1)	Actual values (cm-1)
OH Stretching	3424.38	3550-3200
CH2 Stretching	1217.36	1375
CH (Aromatic Stretching)	3013.20	3050-3010
C = N Stretch	1616.15	1650-1550
CH (Aromatic bending)	726.80	900-690
C - F Stretch	868.75	1400-1000

Evaluation of nanoparticles: The particle size and polydispersity index of best formulation (F5) was found in the range of 20.9nm and 0.337 respectively. The zeta potential of best formulation (F5) was found in the range of -26.6mv which indicate that the formulation was stable. The entrapment efficiency and drug content of the formulation (F5) was found in the range of 95.78% and 97.38%.

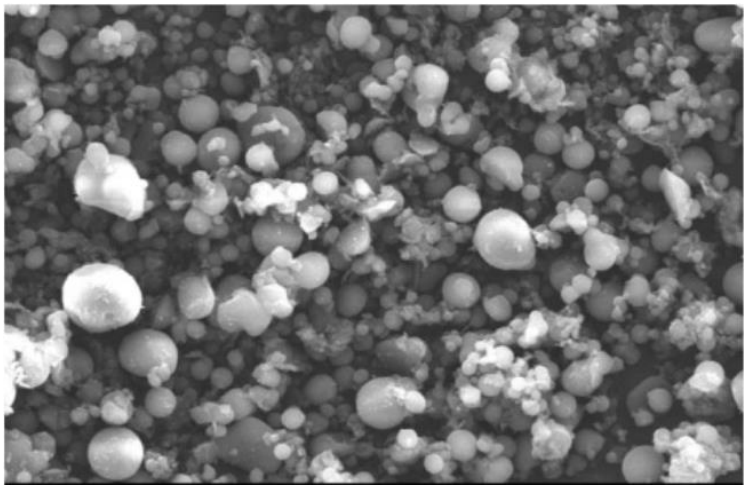
Table no.6: Shows evaluation of nanoparticles (F1 to F9)

Formulation code	Particle size (nm)	Polydispersity index	Zeta potential (mV)	Entrapment efficiency (%)	% Yield	Drug content
F1	47.7±2.05	0.558	-25.9	28.41±0.03	72.32	59±0.01
F2	34.3±1.98	0.338	-21.7	90.8±0.45	78.45	68±1.90
F3	42.0±2.09	0.345	-16.4	89.55±0.50	79.13	70±1.94

F4	48.9±1.94	0.229	-26.4	86.48±0.23	67.56	88±1.26
F5	**20.9±1.26**	**0.377**	**-26.6**	**95.78±0.37**	**94.25**	**97.38±1.40**
F6	40.5±1.16	0.461	-25.3	92.68±0.61	92.01	87±1.48
F7	16.8±1.21	0.342	-16.9	26.78±0.02	81.87	70.34±1.35
F8	43.6±1.28	0.406	-11.6	65.97±0.12	83.16	79±1.29
F9	28.3±1.34	0.555	-21.0	86.77±0.40	86.78	89±1.37

Scanning electron microscopy: The SEM was done for formulation F5 and was found that the particles are spherical in shape and without any agglomeration.

Fig no.3 Scanning electron microscopy of Fluconazole nanoparticles (F5)



***In-vitro* diffusion study (F5):** *In-vitro* diffusion studies of 9 formulations of Fluconazole nanoparticles were carried out by Franz diffusion cell using pH 7.4 phosphate buffer. The sample was withdrawn at regular time intervals of 1h and drug concentration was measured by UV-Visible spectrophotometer at 261nm. The percentage cumulative drug release of F5 after 12 h was found to be 95.5%.

Table no.7: Shows *In-vitro* diffusion release of fluconazole nanoparticle (F5)

% Cumulative Drug Release of F1 to F9									
Time (hr)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	**21.5±1.94**	**34.9±1.92**	**5.8±0.11**	**23.8±1.23**	**36.02±1.45**	**12.3±0.4**	**7.3±0.09**	**15.5±0.06**	**10.12±1.01**
2	**30.3±1.82**	**41.5±1.57**	**15.8±0.98**	**36.3±1.34**	**42.54±1.83**	**27.8±1.21**	**15.2±0.12**	**24.33±0.32**	**19.3±0.96**
4	**38.9±1.89**	**55.4±1.36**	**26.9±1.24**	**41.6±1.58**	**59.76±1.03**	**36.9±1.42**	**22.5±1.34**	**39.1±0.051**	**32.5±1.26**
6	**45.4±1.66**	**67.8±1.24**	**34.6±1.27**	**50.4±1.67**	**63.34±1.62**	**44.2±1.01**	**27.6±1.42**	**48±0.22**	**48.6±1.34**
8	**52.6±1.78**	**76.9±2.01**	**38.1±1.31**	**58.7±1.46**	**70.03±1.78**	**51.3±1.43**	**33.8±1.94**	**55.6±1.65**	**59.2±1.96**
10	**59.8±1.81**	**88.9±1.86**	**41.8±1.18**	**69.1±1.33**	**85.72±1.88**	**57.9±2.01**	**36.1±1.39**	**61.3±0.8**	**65.3±1.48**
12	**62.92±2.17**	**93.5±1.97**	**46.3±1.47**	**75.4±1.32**	**95.5±2.32**	**61.8±1.19**	**40.2±1.94**	**63.8±1.21**	**74.8±1.96**

Fig no.4: *In-vitro* diffusion release of fluconazole nanoparticle (F1 to F5)

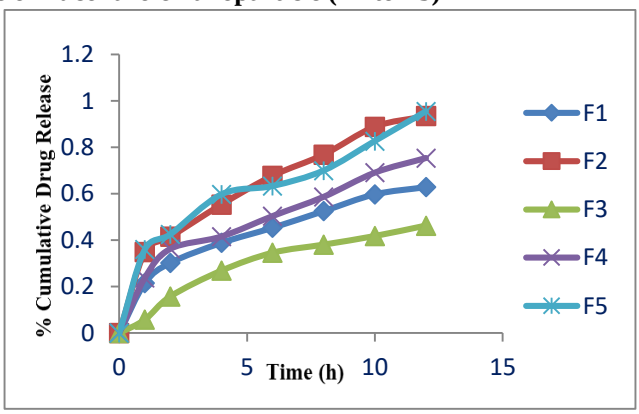
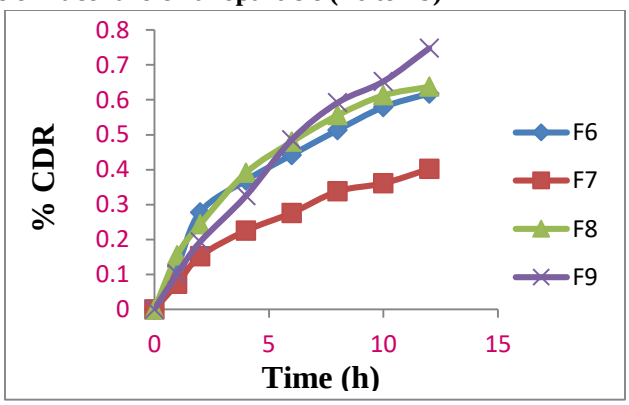


Fig no. 5: *In-vitro* diffusion release of fluconazole nanoparticle (F6 to F9)



Stability studies: The stability studies of the Fluconazole nanoparticles were carried out at 4ºC and 40°C ± 2°C /75% ± 5%RH for best formulation (F5) for 30 days. The results showed no significant difference in the particle size, polydispersity index, zeta potential, entrapment efficiency, drug content and cumulative drug release. The formulation (F5) was selected for the preparation of nanoparticle loaded gel based on the high % drug release, % drug entrapment, % drug content and high %yield.

Table 8: Stability studies of Fluconazole nanoparticles (F5)

At 40°C ± 2°C /75% ± 5%RH							
Formulation code	**Particle size (nm)**	**Polydispersity index**	**Zeta potential (mv)**	**Entrapment efficiency (%)**	**% Yield**	**Drug content**	**In-vitro drug release (%)**
F5	21.2	0.312	-26.8	95.45	93.42	97.12	95.31
At 4°C							
Formulation code	**Particle size (nm)**	**Polydispersity index**	**Zeta potential (mv)**	**Entrapment efficiency (%)**	**% Yield**	**Drug content**	**In-vitro drug release (%)**
F5	21.3	0.311	-26.5	95.42	93	97.3	95.19

Evaluation of Fluconazole nanoparticle gel:

Table 9: Evaluation of Fluconazole nanoparticle gel

Formulation code	**Percentage yield (%)**	**Drug content (%)**	**pH**	**Spreadability (gm.cm/sec)**	**Viscosity (cps)**
G1	91.5	89.9±0.900	6.8	11.0	6,900
G2	93.1%	90.31±0.412	7.1	11.1	8,300
G3	96.6%	93.0±0.996	6.9	10.8	7,115
G4	92.8%	91.11±0.339	6.85	11.7	9,200

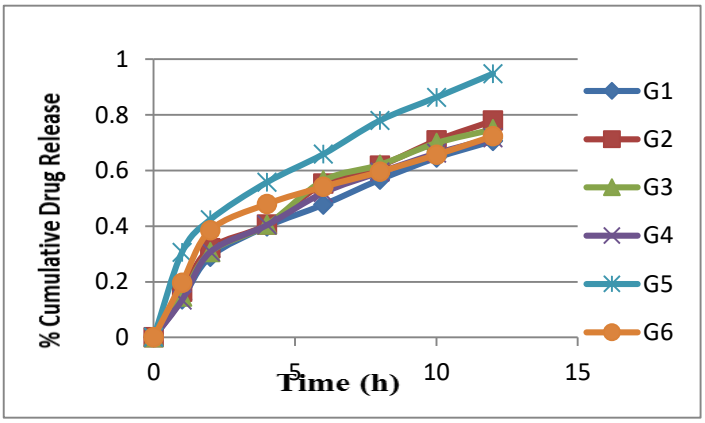
G5	98.7%	97.5±0.703	7.0	10.7	15,200
G6	98.0%	95.0±1.145	7.21	10.9	12,100

Table no. 10: *In-vitro* diffusion release of Fluconazole nanoparticle gel (G5)

% Cumulative Drug Release of G1 to G6						
Time (h)	**G1**	**G2**	**G3**	**G4**	**G5**	**G6**
0	0	0	0	0	0	0
1	13.65±0.015	16.42±0.763	14.66±0.712	13.42±0.669	30.54±0.824	19.56±1.611
2	28.96±1.24	32.07±0.489	30.69±0.834	30.71±0.445	42.32±0.511	38.46±1.21
4	39.89±1.35	40.54±2.322	40.5±1.232	40.37±0.473	55.70±1.011	47.89±2.211
6	47.71±2.205	55.3±1.018	56.4±1.240	52.04±0.714	65.85±0.251	54.1±1.121
8	56.7±1.103	61.7±1.705	62.10±0.313	59.4±0.282	77.92±1.411	59.5±0.285
10	64.53±0.221	70.8±0.706	69.9±0.386	66.21±0.190	86.26±0.339	65.6±0.634
12	70.61±1.269	77.9±1.411	74.81±0.493	71.71±0.200	94.75±0.703	72.3±0.035

In-vitro* diffusion release of fluconazole nanoparticles-based Gel*: *In-vitro* drug release of the 6 formulations was carried out using Franz diffusion cell. The amount of the drug released after 12 hours was in the range of 70.61 to 94.75% respectively. The formulation G5 showed better sustaining effect amongst all the formulations in the range of 94.75%.

Fig no.6. *In-vitro* diffusion release of fluconazole nanoparticle gel (G1 to G6)



Drug release kinetics of formulation G5: The values for the release rate constant (K0 and K1), the correlation coefficients (R2) were calculated using different equations. For the optimized formulation G5, the model that fits the data was zero-order model (R2=0.9739) and n value for Korsemeyer-peppas equation was found to be 0.6569 and mechanism of drug release follows non-Fickian.

Table no. 11: Kinetics of drug release of G5 Formulation

Formulation code	**Zero order kinetics**	**First order kinetics**	**Higuchi model**	**Korsemeyer peppas model**		**Mechanism of Drug Release**
	R^2	**R^2**	**R^2**	**R^2**	**N**	
G5	0.9731	-20.14	0.94	0.9879	0.6569	Non-Fickian

Fig no.7: Kinetics of drug release of G5 Formulation

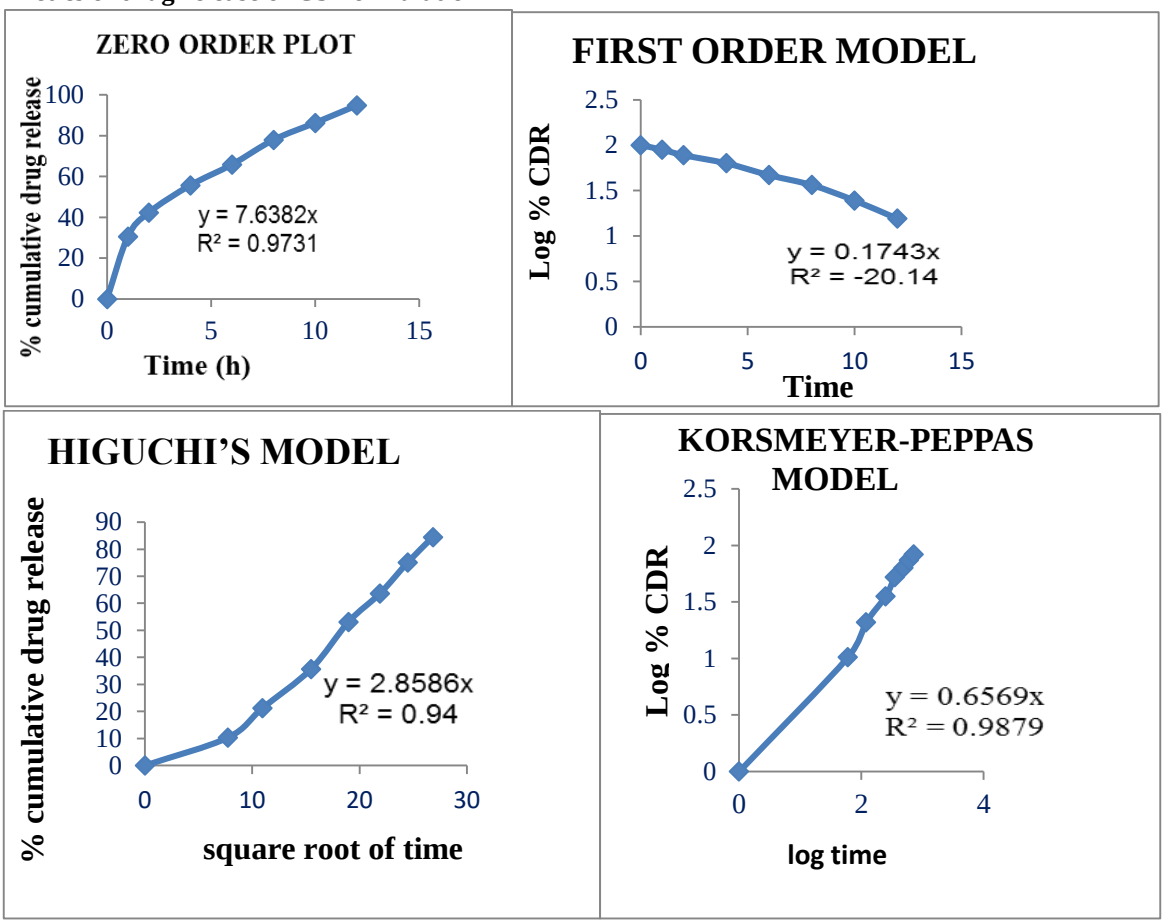


Table 12: stability studies of Fluconazole nanoparticle gel (G5)

At 40°C ± 2°C /75% ± 5%RH						
Formulation code	**Percentage yield (%)**	**Drug content (%)**	**pH**	**Spreadability (gm.cm/sec)**	**Viscosity (cps)**	***In-vitro* drug release**
G5	98.3	97.6	7.06	10.6	15,202	94.76
At 4°C						
Formulation code	**Percentage yield (%)**	**Drug content (%)**	**pH**	**Spreadability (gm.cm/sec)**	**Viscosity (cps)**	***In-vitro* drug release**
G5	98.2	97	7	10.5	15,200	94

CONCLUSION

- In the present study, an attempt was made to formulate nanoparticle-based fluconazole gel for efficient delivery of drug to the skin. Fluconazole nanoparticles were prepared by nanoprecipitation method using different ratios of drug and Eudragit RL100 and different concentration of poloxamer 188.
- Pre-formulation studies were carried out to check the purity of the drug. Fluconazole showed maximum absorption at a wavelength of 261 nm in alcohol and pH 7.4 phosphate buffer. The value of correlation coefficient was found to be $R^2 = 0.9976$, which showed linear relationship between concentration and absorbance. Thus, it can be concluded that, beer's law was obeyed.
- FTIR technology showed no interaction between the drug and the excipients.
- F1 to F9 Fluconazole nanoparticles formulations were prepared by varying the ratio and concentration of Eudragit RL100 and poloxamer 188 and evaluated for particle size, zeta potential, morphology, % yield, % drug entrapment efficiency, % drug content and *in-vitro* drug release studies. Based on the result formulation F5 was selected to be best formulation. The stability studies were also carried out for formulation F5 showed closeness in data of *in-vitro* release and particle size, zeta potential, % entrapment efficiency, % drug content

and % yield when compared to data at 40°C ± 2°C /75% ± 5%RH and 4°C. Thus, F5 was found to be the best formulation and the nanoparticles were found to be spherical, discrete, and free flowing and able to sustain the drugs release effectively.

- The optimised formulation of Fluconazole nanoparticles (F5) was formulated into gel using different concentration of Carbopol 934 and Carbopol 940 and subjected to physicochemical studies and in-*vitro* release studies. The pH of all the formulations was in the range of 6.8 to 7.21, which lies in the normal pH range of the skin. The spreading area was found to decrease with increase in viscosity. From the *in-vitro* drug release results it was found that, G5 shows highest drug release rate. The mechanism of the drug release for the formulation G5 was found to be Non-Fickian with Zero order kinetics. From the stability study, it is clear that the formulation did not undergo any chemical changes and found to be more stable at 40°C ± 2°C /75% ± 5%RH and 4°C. Thus, the objective of the present work of development and evaluation of nanoparticle based topical gel containing antifungal drug fluconazole has been achieved with success.

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