Original Article

EMERGING IMPLEMENTATION OF DRUG LOADED WITH MICROSPONGES TECHNOLOGY AND THEIR ANTIFUNGAL ACTIVITY

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Abstract

The main objective of this investigation was to formulate Fluconazole microsponge by quasi emulsion solvent diffusion technique in order to provide sustained release. Microsponge was formulated by quasi emulsion solvent diffusion technique with varied drug–polymer ratios. Ethyl cellulose and Eudragit L-100 was used as a polymers and polyvinyl alcohol was used as a surfactant for the preparation of external phase. The prepared microsponges were characterized by Fourier transform infrared spectroscopy, particle size analysis, and evaluated for pH, spreadability, viscosity, surface morphology, drug content, entrapment efficiency, in vitro drug release, skin irritation test, antifungal activity as well. The formulated microsponges are spherical with a porous surface and 6.8 µm of mean particle size. The microsponges were then integrated into the carbopol gel. The In vitro drug release results showed that microsponges with 1:1 drug–polymer ratios were more effective to make a prolonged drug release of 89.318 % at the end of 8 hours. Consequently the formed microsponge-based gel of fluconazole would be a confident decision for formal treatment for protected and powerful treatment of fungal infections.

Keywords: Microsponge, Target release, Topical formulation, Solvent diffusion method, Scanning electron microscopy, drug delivery, control release.

INTRODUCTION

Fluconazole is an engineered antifungal specialist having a place with the gathering of triazole. It is one of the ordinarily involved antifungal specialists for most sorts of contagious diseases; including shallow and intrusive parasitic contaminations. Lamentably fluconazole oral organization has constraints like queasiness, regurgitating, swelling and stomach uneasiness. Close by more often than not the parenteral organization of fluconazole prompted skin rashes and tingling.1 Thus, presently a day's development limited and transdermal conveyance has acquired a ton of significance. The customary gel definition of fluconazole causes cutaneous aggravation and delayed utilize prompted dermal extreme touchiness. Thus, a clever framework requires which will build the presence of dynamic specialists either on the skin surface or inside the epidermis, simultaneously lessening hurried transdermal entrance. Numerous analysts have endeavored to foster novel transdermal plans of fluconazole. Likewise, the goal of our exploration is to form and assess fluconazole microsponge stacked carbopol gel for protected, successful and stable gel and assess the in-vitro supported discharge execution.2 Microsponge-based conveyance frameworks (MDS) give confirmation of medication sanctioning on the skin surface and inside the epidermis without going into the foundational flow in more noteworthy degree; accordingly decreasing fundamental and neighborhood cutaneous afflictions. They likewise offer a benefit of programmable delivery and are naturally protected. Moreover, this innovation presents a considerable amount of advantages through drug capture through better plan adaptability, shortened incidental effects, further developed class and predominant solidness.3, 4

MATERIALS AND METHODS

Materials

Fluconazole was purchased from Balaji drugs, B-28, Thakordwar Soc, B/h. Spinning Mill, Varachha Road, Surat – 395010 (Gujarat). Ethyl cellulose was obtained from Pallav Chemicals & Solvents Pvt. Ltd. N-226, Near Kumbhavali Naka, MIDC,

Tarapur, Boisar– 401 506. INDIA. Eudragit L-100 was obtained from Chemdyes Corporation, 'Rasayan Ghar' Kotharia Naka Chowk, Rajkot-360001. (Gujarat). Ethyl acetate was obtain from Pallav Chemicals & Solvents Pvt. Ltd. N-226, Near Kumbhavali Naka, MIDC, Tarapur, Boisar– 401 506. INDIA. PVA was obtained from Pallav Chemicals & Solvents Pvt. Ltd. N-226, Near Kumbhavali Naka, MIDC, Tarapur, Boisar– 401 506. INDIA. Carbapol 934 was obtained from Pallav Chemicals & Solvents Pvt. Ltd. N-226, Near Kumbhavali Naka, MIDC, Tarapur, Boisar– 401 506. INDIA. Triethanolamine was obtained from Chemdyes Corporation, 'Rasayan Ghar' Kotharia Naka Chowk, Rajkot-360001. (Gujarat).

Methods

Formulation of Fluconazole Microsponges:

- Quasi-emulsion solvent diffusion method

Fluconazole loaded microsponges were prepared by quasi-emulsion solvent diffusion technique. The internal phase was encompassed ethyl cellulose and triethylcitrate (TEC) both were dissolved in 10 ml of ethyl acetate. TEC was used as plasticizer. This was, trailed by addition of fluconazole with mixing. The inner phase was then filled polyvinyl alcohol (PVA) arrangement in water, the outer phase. Then the final mixture was filtered through filter paper with a pore size of 0.45 µm to separate formed microsponges and dried at room temperature.5

Table No.1: Formulation batches of Fluconazole microsponges

Ingredient	**Formulation batches of Fluconazole microsponges**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
Fluconazole : Ethyl Cellulose	1:1	1:2	1:3	-	-	-
Fluconazole : Eudragit L-100	-	-	-	1:1	1:2	1:3
Ethyl Acetate	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml
Triethyl Citrate	1 ml	1 ml	1 ml	1 ml	1 ml	1 ml
PVA (% w/v)	0.75	0.75	0.75	0.75	0.75	0.75
Water	90 ml	90 ml	90 ml	90 ml	90 ml	90 ml

- Evaluation of fluconazole microsponges formulations

1) Production yield

Microsponge's production yield is determined by following formula.6

$$\textbf{Production yield (PY)} = \frac{\textbf{Practical mass of microsponges}}{\textbf{Theoretical mass (Drug + Polymer)}} \textbf{ X 100}$$

2) Actual drug content

Precisely weighed quantity (100 mg) of microsponges containing drug was kept in 100 ml PBS (pH 6.8) for 12 hr with continuous stirring. Samples were filtered using 0.45 µm membrane filter and further analyzed at 210 nm next to blank using ultraviolet-visible (UV) spectrophotometer. The drug content for all batches was done by using following equation.7

$$\text{Actual drug content} = \frac{\text{Actual Fluconazole Content}}{\text{Weighed quantity of microsponges}} \times 100$$

3) Entrapment efficiency

Microsponge (0.1g) was reconstituted with 10 ml of pH 6.8 phosphate buffer in a glass tube. The fluid suspension was sonicated in a sonicator bath for 30 min. The suspension centrifuging at 14,000 rpm at 40 0C for 30 min.The supernatant was taken and diluted with ethyl acetate and the drug concentration in the resulting solution was assayed by spectrophotometrically using UV spectrophotometer.8

$$\text{Entrapment efficiency} = \frac{\text{Total amount of drug} - \text{Un-entrapped drug}}{\text{Total amount of drug}} \times 100$$

4) Particle size determination

Molecule size investigation of arranged microsponges was concentrated by utilizing zeta molecule size analyzer. Microsponges were scattered in twofold refined water prior to running the sample in the instrument to guarantee that light dissipating signal (as shown by particles count each second) was inside the delicate scope of the instrument. The examination was completed at room temperature. The standard particle size range of microsponges is 5µm - 300µm.9

5) FT – IR Spectrophotometric studies

Infra-red spectrum of any compound gives information about the group present in particular compound in particular compound small quantity of drug was mixed with the excipient and spread uniformly. The pellets were set in holder and infrared spectra was taken different tops in infrared range were deciphered for presence of various gathering in the design of medication.10

- Preparation of fluconazole microsponges gel

0.5 gm of Carbapol 934 was uniformly dispersed in beaker containing a sufficient quantity of water & was allowed to hydrate overnight. Then it was mixed with 5 gm of glycerin to form a paste, 95 ml water was added slowly to paste under constant stirring. Then add drop wise tri-ethanolamine to adjust the pH. To this gel prepared fluconazole microsponges were added with stirring.11

- Evaluation of fluconazole microsponge loaded Carbapol gel

1) Visual inspection

The organoleptic properties, like tone, surface, consistency, homogeneity, and actual appearance of gel containing microsponges were really looked at by visual perception.12

2) pH measurement

Gel plan pH was recorded utilizing advanced pH meter. 5 g gel was dispersed in 45 ml distilled water at 27°C and solution pH was measured.13

3) Spreadability studies

One of the essential characteristics for an ideal gel is to seek after magnificent Spreadability. Spreadability is utilized to communicate the degree of the area of skin or impacted part to which gel promptly spreads. A spreading esteem fundamentally influences remedial viability of the definition. Articulation of Spreadability is given concerning time (in a flash) taken by two slides to sneak off from gel in the middle of between under use of explicit burden. Better Spreadability is shown by least time expected for slides partition. Numerical articulation utilized for Spreadability computation was: 14

$$S = \frac{M\,L}{T}$$

Where,

M = weight (in gm) connected to upper slide,

L = Glass slide length

T = time (in sec) taken to isolate the slides

Wooden block-glass slides mechanical assembly was utilized and by applying weight around 20 gm, time for complete partition of the upper slide (mobile) from lower slide (fixed) was assessed.

4) Viscosity

The viscosity of the gel formulation was measured with a Brookfield viscometer using 1x model and cone number 01, with an angular velocity of 5 rpm at 25 ºC. A normal of five readings was utilized to compute consistency.15

5) In-Vitro release studies

The in- vitro release of formulations were done by using Franz diffusion cells. The cellophane layer (pore size 0.45 µm) was mounted onto diffusion cell with 37 ml receptor compartment volume. PBS (pH 6.8) was used as receptor medium and the system was thermo stated to 37 ± 1°C under stirring. All batches of drug microsponges gel and marketed formulation were subjected to the diffusion study. Aliquots of 1 ml volume were removed at explicit time spans by keeping up with sink condition all the while Withdrawn aliquots were then diluted using receptor medium and analyzed by UV spectrophotometer (Shimadzu UV – Visible spectrophotometer, model UV 1700) at 210 nm against PBS pH 6.8. To resolving drug release mechanism and to compare release profiles disparities amongst formulations, data obtained from drug release and time was used.16, 17

6) Skin irritation study –

All experiments and protocols described in present study were approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) (Reg. No: Spcop/2021-22/286), Ministry of Social Justice and Empowerment, Government of India. (College registration no: 1197/PO/C/08/CPCSEA)

Healthy adult male wistar rats weighing 250 – 300 g were used. Rats were housed in polypropylene cages, maintained under standardized condition (12 nil hour light/dark cycle, 24oC, 35to 60 % humidity) and provided free access to pelleted ‘Sabardan’ diet and purified drinking water.

Procedure –

Rats were anesthetized and shaved the back area 0.5 gm of gel was applied to the shaved area of rats. After that continuous visual inspection of the rats were done at 1 day, 2 day, 3 day, 4 day & up to 7 days. Rats were observed for the production of any irritant response such as erythema, edema & irritation after a single topical application.18

7) Antifungal activity

In vitro antifungal activity of FLZ microsponge optimized batch (F1) gel was carried out by Cup-plate method in comparison with FLZ marketed gel as standard. Growths societies utilized for organic assessment were Candida albicans.

Preparation of media

For 100 ml of media, 40 gm of agar is dissolved in 100 ml of distilled water in a 250 ml flask, prepared and autoclave at 1210C to 15 – 20 min at 15 lbs/inch2.

Preparation of Disk

The freshly prepared and sterilized fusion medium is poured into a petri dish inside the laminar and after pouring, the UV lamp is turned on to prevent contamination of the plate while the medium solidifies. It is left for half an hour to solidify wells. Once the medium has solidified the UV lamp is turned off and 10 µl of the bacterial suspension is pipette to the plate and gauze. A sterile disc is placed (using clamp) on top of a standard plate.19, 20

RESULT AND DISCUSSION

1) Physical appearance

White to practically white, microsponge particles were gotten by quasi-emulsion solvent diffusion technique.

2) Melting Point

The physical properties of compound such as melting point can provide useful information which can help in the identification of a sample or to establish its purity. The melting point of fluconazole was experiential in the range of 139°C (Literature standard 138–140°C). As exploratory qualities were in great concurrence with standard, acquired drug should be unadulterated.

3) FT – IR Spectrophotometric studies

The FTIR spectrum of the physical mixtures was compared with pure drug from FTIR the principle peaks of fluconazole were observed at wavelength 1505.74 cm C=N Stretching, 1611 cm N-H, 1743 cm C=C (Aromatic), 2794 cm C-H, 3596 cm O-H. In the FTIR spectra of the physical mixtures of the drug and polymer observed at wave numbers 1517 cm C=N, 3594 cm O-H, 2790 cm C-H, 1739 cm C=C, 1620 cm N-H, 1512 cm C=N, 3551 cm O-H, 2773 cm C-H, 1792 cm C=C, 1639 cm N-H. However some additional peaks which were in pure drug contains in physical mixtures this shows that there is no interaction

between fluconazole and polymer used.

Table no.2: FT-IR Spectra of Drug and Polymer

Sr. No	Formulations	Functional Group				
		C=N	O-H	C-H	C=C	N-H
1	Fluconazole	1505	3596	2794	1743	1611
2	Fluconazole + Ethyl Cellulose	1517	3594	2790	1739	1620
3	Fluconazole + Eudragit L-100	1512	3551	2773	1792	1639
4	Fluconazole + PVA	1507	3597	2766	1735	1618
5	Fluconazole + Carbapol 934	1517	3596	2781	1747	1645

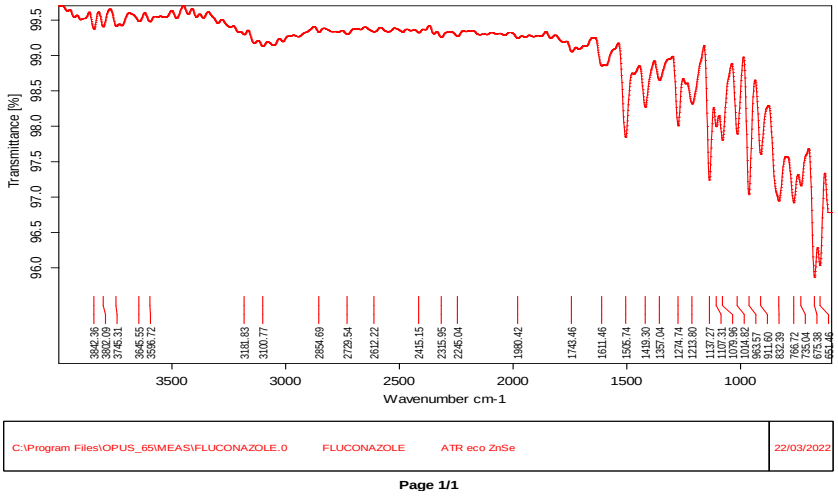

Fig no.1- IR Spectra of Fluconazole

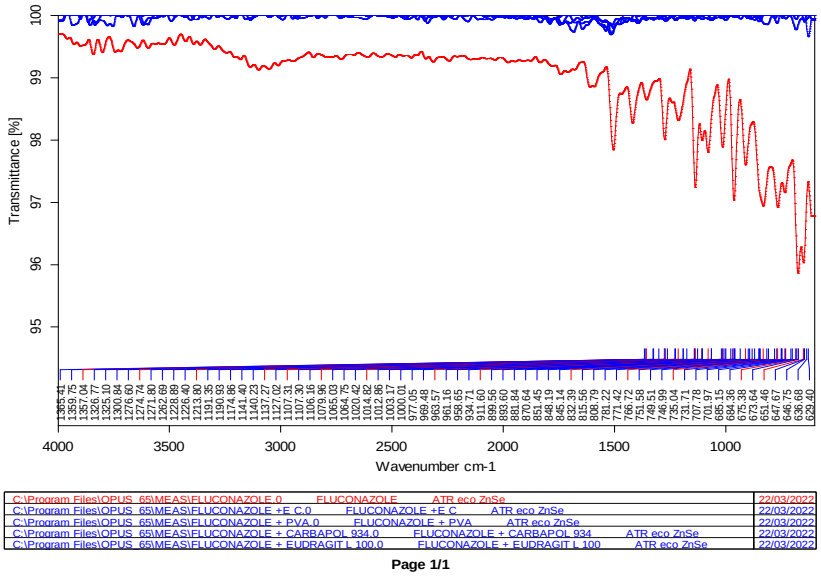

Fig no.2- IR Spectra of Fluconazole + All Excipient

- Evaluation of fluconazole microsponges formulations

1) Production Yield

The production yield of all batches of microsponges ranged from 34.60% to 47.22%, Drug: Polymer ratio and PVA

concentration were found to affect the production yield significantly. In the case of drug; polymer ratio 1:1 (F1), production yield was very low, i.e. 34.60% while for drug: polymer ratio 1:6 (F6), it was 47.22%.

Table no.3- Production yield of fluconazole microsponges

Formulation code	Production yield (%)
F1	34.60
F2	40.00
F3	45.24
F4	33.37
F5	43.31
F6	47.22

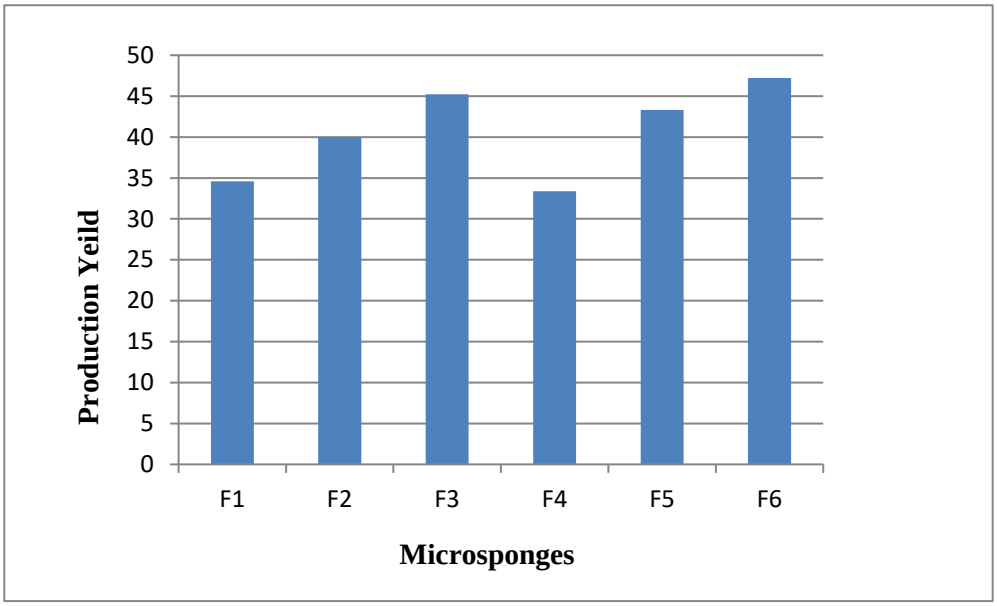

Fig no.3- Production yield of fluconazole microsponges formulations

2) Actual drug content

Table no.4- Actual Drug Content of fluconazole microsponges formulations

Formulation code	Actual drug content (%)
F1	88.99
F2	59.25
F3	44.68
F4	88.10
F5	59.22
F6	44.43

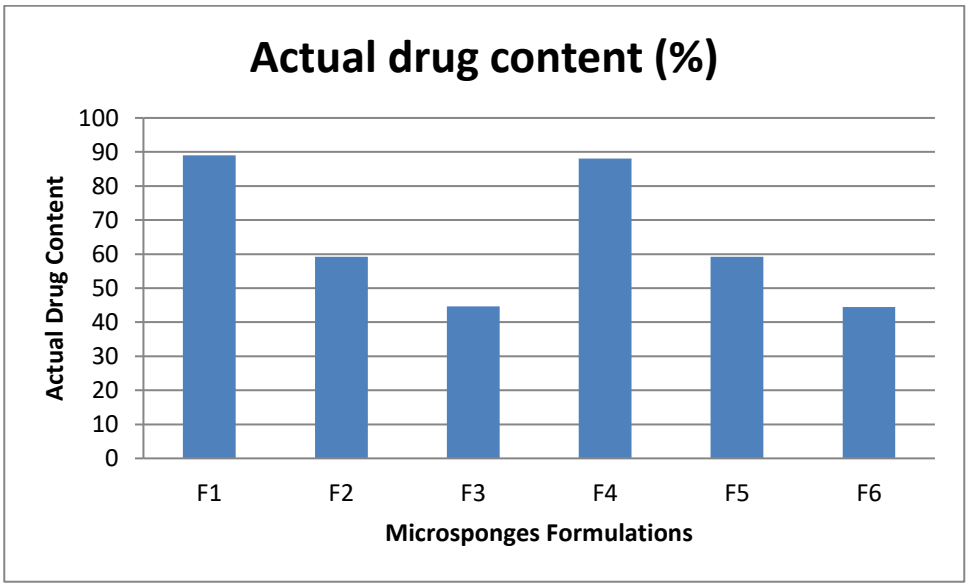

Fig no.4- Actual Drug Content of fluconazole microsponge formulations

3) Entrapment efficiency

Table no.5- Entrapment efficiency of fluconazole microsponge formulation

Formulation code	Entrapment efficiency (EE %)
F1	85.56
F2	83.42
F3	80.10
F4	83.42
F5	81.50
F6	79.20

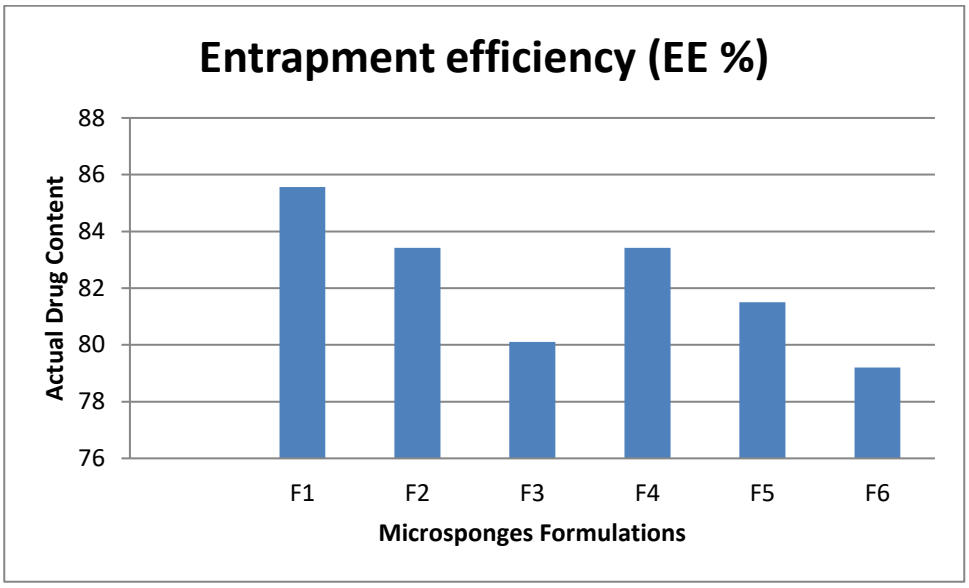

Fig no.5- Entrapment efficiency of fluconazole microsponge formulation

4) Particle size determination

Molecule size investigation of arranged microsponges was concentrated by utilizing zeta molecule size analyzer. Microsponges were scattered in twofold refined water prior to running the sample in the instrument to guarantee that light dissipating signal (as shown by particles count each second) was inside the delicate scope of the instrument. The examination was completed at room temperature. The standard particle size range of microsponges is 5µm - 300µm.

Table no.6- Particle size of formulation (F1 – F6)

Formulation	Particle Size
F1	6.8 µm (6803 nm)
F2	15.7 µm (15700 nm)
F3	25.5 µm (25500 nm)
F4	10.2 µm (10200 nm)
F5	17.1 µm (17100 nm)
F6	28.6 µm (28600 nm)

- Evaluation of fluconazole microsponge loaded Carbapol gel

1) Visual Inspection

The prepared fluconazole loaded microsponge gel formulations were inspected visually for their color, texture and appearance. All prepared formulations were White, viscous in nature with smooth texture and of good homogeneity without lumps.

2) pH measurement

The pH values of all prepared formulations were found in the range of 6.5–7, this is due to neutralization of formula by tri-ethanol amine.

Table no.7: pH Determination of fluconazole microsponges gel formulations

Formulation Code	pH
F1	6.8
F2	6.5
F3	7.0
F4	6.5
F5	6.8
F6	7.0

3) Spreadability test

Spreadability is one of the important characteristic of topical formulations and it helps to transfer correct dosage to the target site and make ease of application. Fluconazole microsponge loaded carbopol 934 forms a gel with Spreadability ranges between to 2.10- 4.38 gcm/s. There was a slight decrease in spreading diameters of formulations of F3 & F6 this variation was might be due to increased polymer concentration in microsponge.

Table no.8: Spreadability of fluconazole microsponges gel formulations

Formulation Code	Spreadability
F1	3.31
F2	3.10
F3	2.45
F4	3.30
F5	3.20
F6	2.50

4) Viscosity measurement

The viscosity of prepared fluconazole microsponge gel was measured in L4 Spindle Brookefield Viscometer, model. The results were depicted in Table.

Table no.9: Viscosity of fluconazole microsponges gel formulations

Formulation Code	Viscosity
F1	34,520
F2	38,630
F3	40,630
F4	33620
F5	33,500
F6	34,511

5) In-vitro drug release

The in vitro drug release was done for fluconazole microsponge formulas (F1-F6). From the in vitro release data it was noticed that the drug release was reduced from 89.318%- 80.633%, this is due to D/P ratio has increased i.e. the amount of polymer available was more in each formulation. It led to thickening of the polymer matrix wall, thus lesser drug release was occurring.

89.318% of drug release was found in the highest drug release (F1) within 8 Hrs, while the lowest 80.633% for F6 at the end of 8 Hrs. It has been reported that by increasing the amount of polymer in F3 and F6, there was no significant change in the drug release pattern as compared with F1 formulation. Drug release of all batches F1–F6 was shown in Figure. According to in vitro release data formulation code F1 was selected as optimized batch.

Table no.10- In-vitro drug release study of Fluconazole microsponges Formulation

Time (min)	**% Drug Release**					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
60	13.65	16.422	14.668	13.429	10.353	10.125
120	38.964	32.072	30.697	30.711	21.283	29.36
180	45.892	40.544	40.588	40.375	35.755	30.788
240	55.719	55.324	56.437	52.048	53.137	51.223
300	63.7	61.701	62.107	59.402	63.688	61.523
360	72.533	70.859	69.934	66.21	71.121	69.789
420	79.61	77.923	74.815	71.719	74.502	75.63
480	89.318	86.266	84.127	81.739	80.149	80.633

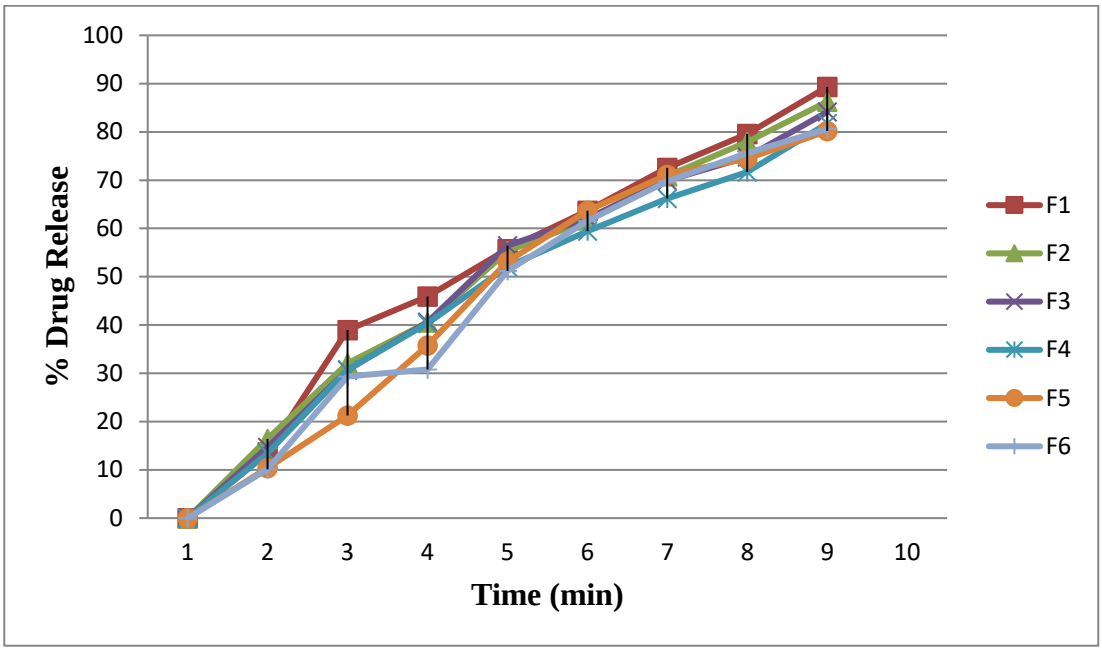

Fig no.6- In-vitro drug release profiles of Fluconazole Microsponges Formulation

6) Skin Irritation test

After applying topical dose of 0.5 g of the preparations the rats were visually observed up to 7 days and there was no sign of any untoward response.

Table no.11- Skin irritation test of fluconazole microsponge gel formulation

Formulation	**Signs of skin irritation**	Days						
		1 day	**2 Day**	**3 day**	**4 day**	**5 day**	**6 day**	**7 Day**
F1	Erythema	Nil	Nil	Nil	Nil	Nil	Nil	Nil
	Edema	Nil	Nil	Nil	Nil	Nil	Nil	Nil
	Irritation	Nil	Nil	Nil	Nil	Nil	Nil	Nil
Gel without fluconazole	Erythema	Nil	Nil	Nil	Nil	Nil	Nil	Nil
	Edema	Nil	Nil	Nil	Nil	Nil	Nil	Nil
	Irritation	Nil	Nil	Nil	Nil	Nil	Nil	Nil

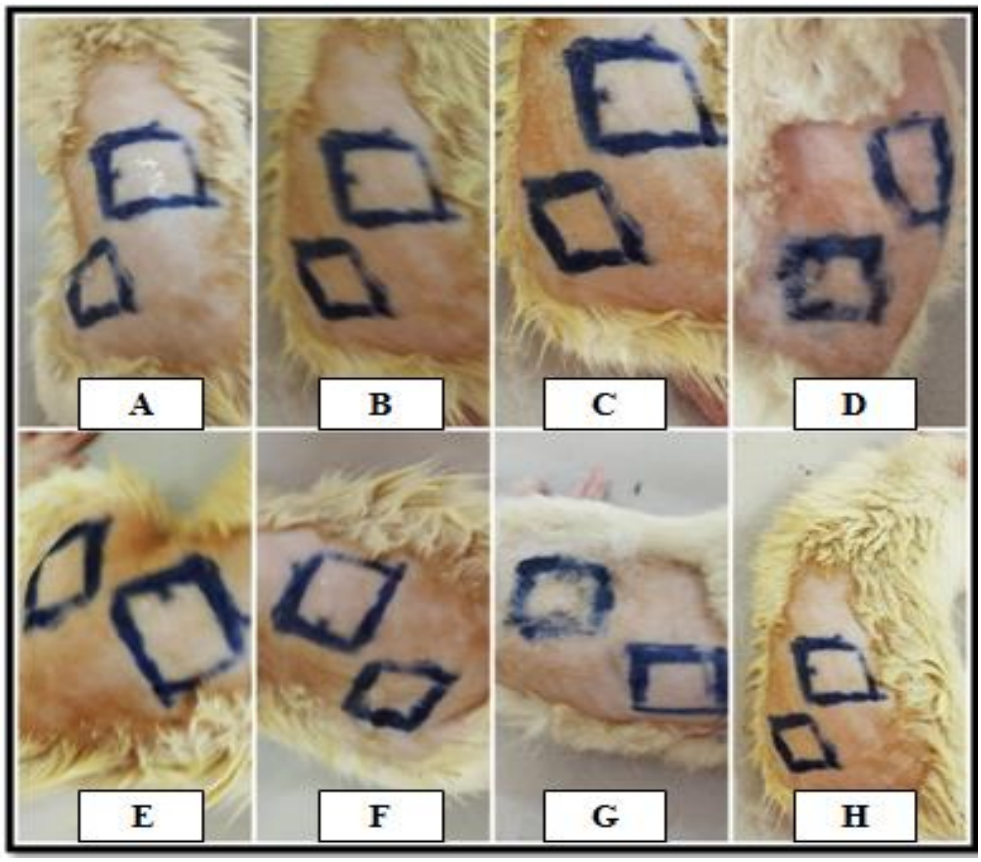

Fig no.7- Skin irritation study on rat

A – Gel apply to the rat, B – After 1 days, C – After 2 days, D – After 3 days, E – After 4 days, F – After 5 days, G – After 6 days, H – After 7 days.

7) Antifungal activity

Fig no.8- Antifungal activity of fluconazole microsponge gel against Candida albicans

Table no.12- Observations of Antifungal activity of fluconazole microsponge gel

Sample Code	Zone of Inhibition Diameter (mm)
MS	19
MSG	21
MG	24

MS – Fluconazole Microsponges

MSG – Fluconazole Microsponges Gel

MG – Marketed Gel

CONCLUSION

Microsponge-based novel delivery system has been developed to provide once a day sustained release medication for topical delivery of fluconazole. The method adopted was quasi-emulsion solvent diffusion; found to be simple, reproducible and rapid. Formed microsponges were circular shape, have high porosity.. Different drug–polymer ratio reflected good particle size, drug content and entrapment efficiency. Microsponge based gel showed viscous and homogenizes preparation and in vitro drug release. Microsponge formulated with 1:1 drug–polymer ratios were found more efficient to give an extended drug release 89.31% at the end of 8h. Gel containing microsponges prepared in this study was found to be promising as new-novel delivery system offering prolonged release of fluconazole in treatment of fungal infection.

Conflict of interest:

The authors declare that they have no conflict of interest.

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