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Research Article

Formulation and Evaluation of Gel Containing Fluconazole Microsponges

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A B S T R A C T

The aim of current study was to develop gel containing Fluconazole microsponges; the microsponges were prepared by quasi emulsion solvent diffusion method using eudragit RL100 the gel was prepared and evaluated for various parameters and Invitro release studies. All the factors studied had an influence on the physical characteristics of the microsponges. In vitro dissolution results showed that the release rate of Fluconazole was modified in all formulations. The Fluconazole-loaded Eudragit RL 100 microspheres showed a good release characteristic and were stable under the condition studied.

Key Words: Fluconazole, Microsponges, Quasi-emulsion & Invitro release.

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1. INTRODUCTION

The microsponge technology was developed by Won in 1987, and the original patents were assigned to Advanced Polymer Systems, Inc[1]. Microsponges are porous microspheres having myriad of interconnected voids of particle size ranging between 5-300 µm. These microsponges have capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infectives etc. and are used as a topical carrier system. Further these porous microspheres with active ingredients can be incorporated into formulations such as creams, gel, lotions and powders[2].

Microsponges consist of non-collapsible structures with porous surface through which active ingredients are released in controlled manner[3]. Depending upon the size, the total pore length may range up to 10 ft and pore volume up to 1 ml/gm. When applied to the skin, the microsponge drug delivery system (MDS) releases its active ingredient on a time mode and also in response to other stimuli (rubbing, temperature, pH, etc) [4]. Microsponges have the capacity to absorb or load a high degree of active materials into the particle or onto its surface. Its large capacity for entrapment of actives up to 3 times its weight differentiates microsponges from other types of dermatological delivery systems[5].

The fundamental appeal of the microsponge technology stems from the difficulty experienced with conventional formulations in releasing active ingredients over an extended period of time. Conventional dermatological and personal care products typically provide active ingredients in relatively high concentrations but with a short duration of action. This may lead to a cycle of short-term overmedication followed by long-term under medication. Rashes or more serious side effects can occur when active ingredients penetrate the skin. In contrast, microsponge technology allows an even and sustained rate of release, reducing irritation while maintaining efficacy [6, 7].

2. MATERIALS AND EQUIPMENTS

2.1. Materials

Fluconazole, Eudragit RS 100,Dichloromethane, Sodium Alginate, Dibutyl Phthalate,Carbopol 940,Triethanolamine, Monobasic Potassium Dihydrogen Phosphate, Sodium Hydroxide

2.2. Equipments

Single Pan Electronic Balance ,Infrared Spectrophotometer ,Ultrasonicator Mechanical Stirrer ,Magnetic Stirrer ,UV Spectrophotometer ,Differential Scanning Calorimeter ,Scanning Electron Microscopy ,Particle Size Analyzer

2.3. Preparation of Fluconazole Microsponges

The microsponges containing fluconazole were prepared by quasi emulsion solvent diffusion method (9-11) using an internal phase that consisted of Eudragit RS-100 and dibutyl phthalate (1 % w/v) dissolved in 5 ml of dichloromethane. Dibutyl phthalate was added to enhance the plasticity of the polymer. This was, followed by the addition of fluconazole dissolved under ultrasonication at 350C.

The mixture was then poured into aqueous solution of sodium alginate which served as the external phase with 60 min. stirring at 400 rpm. The microsponges were formed due to the removal of dichloromethane from the system by evaporation. The microsponges were washed with water, filtered and dried at 40 °C for 12 h and weighed to determine production yield.

Table 1: Composition of Fluconazole Microsponges

Ingredients									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Fluconazole:Eudragit	1:1	2:1	3:1	4:1	5:1	3:1	3:1	3:1	3:1
Dichloromethane	5	5	5	5	5	5	5	5	5
Dibutyl Phthalate	1	1	1	1	1	1	1	1	1
Sodium Alginate	50	50	50	50	50	30	40	60	70
Water (ml)	100	100	100	100	100	100	100	100	100

2.4. Preparation of Fluconazole Microsponge Gel

0.5 gm of carbopol 940 was uniformly dispersed in beakers containing sufficient quantity of water and was allowed to hydrate overnight. It was then mixed with 5 g of glycerin containing preservative and a paste was made. Then 95 ml of water was added slowly to the paste under constant stirring. Finally, triethanolamine was added dropwise to adjust the pH to 6.5–7.5.[12]

Table 2: Composition of Gel Base

Sr. no.	Ingredients	Quantity (% w/w)	Use
1	Carbopol 940	0.5	Gelling agent
2	Glycerine	5	Co-solvent
3	Methyl paraben	0.18	Preservative
4	Propyl paraben	0.02	Preservative
5	Sodium metabisulphite	0.10	Antioxidant
6	Triethanolamine	q.s.	Neutralizer

The unentrapped drug-loaded gel was prepared by dissolving 58 mg of fluconazole in 5 g of gel base. In contrast, the microsponges of each batch having drug equivalent to 58 mg were incorporated in 5 g of gel base to get 1.16 %w/w microsponge-loaded gel.

Table 3: Parameters for microsponges formulation

Sr.	Parameters	Optimum Values
1	Drug: Polymer ratio	1:1, 2:1, 3:1, 4:1 and 5:1
2	Sodium alginate	30-70 mg
3	Inner phase solvent	Dichloromethane
4	Amount of Inner Phase Solvent	5 ml
5	Amount of Water in outer Phase	100 ml
6	Stirring rate	400 rpm
7	Stirring time	60 min.

4. RESULTS AND DISCUSSION

4.1. Determination of Production Yield

The production yield of the microparticles was determined by calculating accurately the initial weight of the raw materials and the last weight of the microsponges obtained[15].

Production Yield (PY) = Practical Mass of Micrsponges *100

Theorotical Mass (Polymer + Drug) ….Eqn (3)

The production yield of microsponge formulations obtained is shown in Table 4,

Table 4: Production yield of microsponge formulations

Batches	Drug: Polymer Ratio	Amount of Drug (mg)	Amount of sodium alginate (mg)	Therotical Yield (mg)	Practical Yield (mg)	Production Yield (%)
F1	1:1	200	50	400	98.2 ± 1.04	24.55 ± 0.26
F2	2:1	400	50	600	232.8 ± 1.38	38.8 ± 0.23
F3	3:1	600	50	800	340.8 ± 3.36	42.6 ± 0.42
F4	4:1	800	50	1000	592.2 ±1.10	59.2 ± 0.01
F5	5:1	1000	50	1200	853.6 ±1.02	71.13 ± 0.08
F6	3:1	600	30	800	167.3 ± 1.81	20.91 ± 0.23
F7	3:1	600	40	800	305.4± 0.98	38.17 ± 0.12
F8	3:1	600	60	800	368 ± 1.48	46 ± 0.18
F9	3:1	600	70	800	398.4 ± 1.32	49.8 ± 0.16

The production yield of all batches ranged from 20.91 % to 71.13%. It was found that production yield was greatly affected by drug: polymer ratio as well as by concentration of sodium alginate.

4.2. Scanning Electron Microscopy

The morphology of the microsponges prepared by quasi emulsion solvent diffusion method and entrapment method was investigated by SEM. The representative SEM images of the microsponges are shown in Fig.1. SEM images showed the microsponges to be porous and were having spherical shape and no entire fluconazole crystals were observed visually [16].

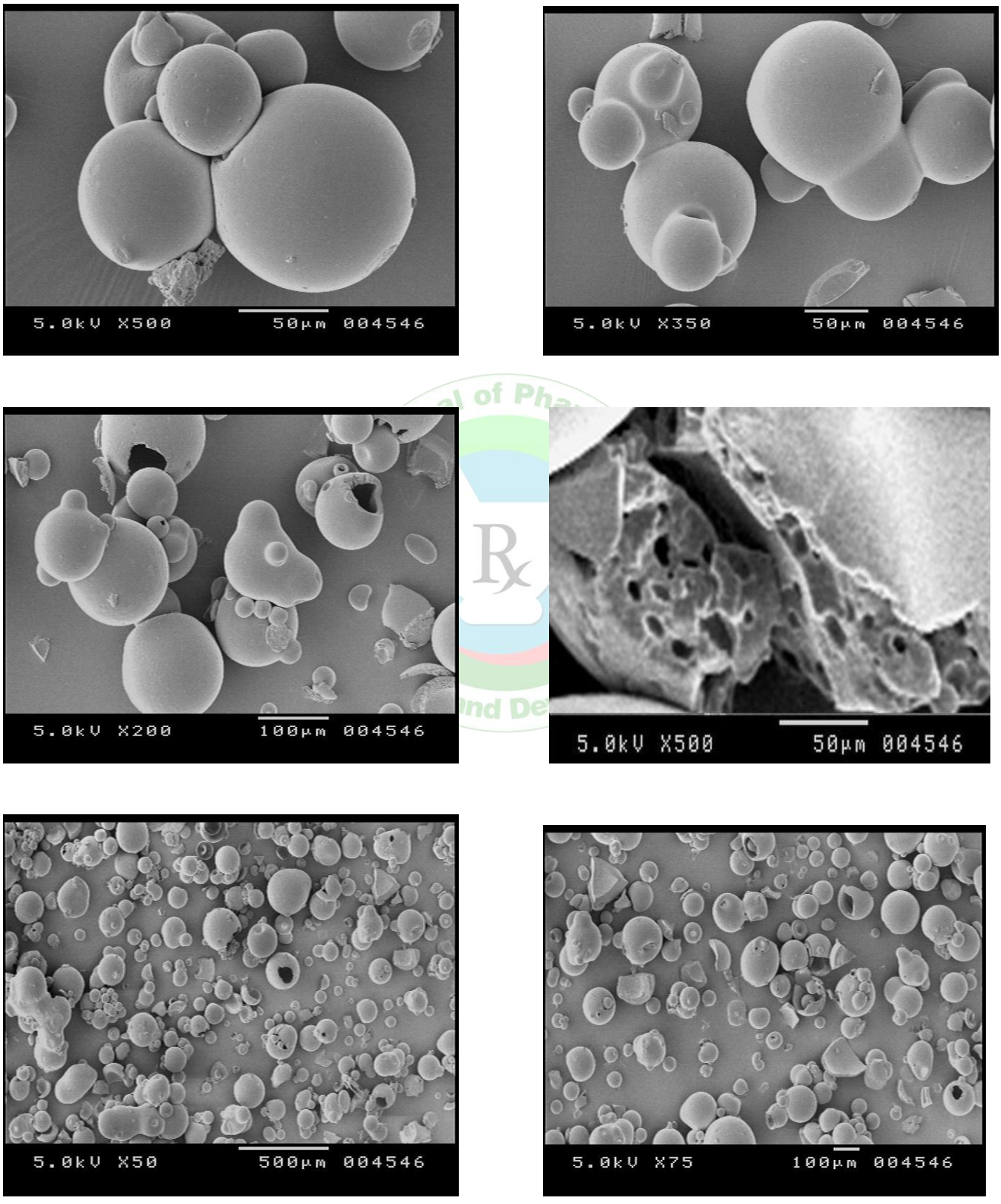

Figure 1: SEM images of fluconazole microsponges

From Fig. 8 it was revealed that the characteristic internal structure was a spherical cavity enclosed by a rigid shell constructed from drug and polymer. The inner structure consisted of void spaces.

4.3. Particle Size Analysis

Particle size analysis of prepared microsponges was carried by using Malvern particle size analyzer Hydro 2000 MU (A). Microsponges were dispersed in double distilled water before running sample in the instrument, to ensure that the light scattering signal, as indicated by particles count per second, was within instrument's sensitivity range.

The mean particle size of formulations F1–F5 was ranged from 10.07 to 7.21 µm and for F6-F9 from 8.07 to 8.49 µm. It was found that the mean particle size was increased with the decrease in the Eudragit RS 100 amount i.e on decrease of drug: polymer ratio. F5 possessed the lowest particle size corresponding to 7.21 µm. Also with increasing amount of sodium alginate, particle size was found to be increased. The particle size for all formulations was shown in table 5.

Table 5: Particle size analysis

Batches	Particle Size (µm)
F1	10.074
F2	9.562
F3	8.246
F4	7.869
F5	7.215
F6	8.079
F7	8.180
F8	8.331
F9	8.492

The particle size of formulations F1 to F5 was found to be decreased due to the fact that the polymer available at higher drug: polymer ratio was in less amount thereby decreasing polymer wall thickness which led to the smaller size of microsponges.

An increase in mean particle size of microsponges from F6 to F9 with an increase in the sodium alginate concentration can be attributed to an increase in apparent viscosity at increased stabilizer concentrations. Such increased viscosity would result in larger emulsion droplets and finally in greater microsponge size.

4.4. Evaluation fluconazole microsponge gel

4.4.1. Visual inspection

The organoleptic properties of the microsponge gel like color, turbidity, homogeneity and physical appearance were checked by visual observation.

The prepared gel formulations of fluconazole microsponges were white viscous preparations with a smooth and homogeneous appearance.

4.4.2. pH measurement

The pH of the gel formulations was determined by using digital pH meter. 2 gm of gel was stirred in distilled water until a uniform suspension was formed. The volume was made up to 50 ml and the pH of solution was measured.

The pH values of all prepared formulations were found to be in the range of 6.5 to 6.8, which are considered to be acceptable to avoid the risk of irritation upon application to the skin.

4.4.3. Spreadability studies

The values of spreadability indicate that the gel was easily spreadable by small amount of shear. One of the criteria for a gel to meet the ideal quantities is that it should possess good spreadability. It is the term expressed to denote the extent of area to which gel readily spreads on application to skin or affected part. The therapeutic efficacy of a formulation also depends upon its spreading value.

Spreadability is expressed in terms of time in seconds taken by two slides to slip off from gel and placed in between the slides under the direction of certain load. Lesser the time taken for separation of two slides, better the spreadability. It is calculated by using the formula[17].

$S = M. L / T$ ….Eqn (6)

Where, M = wt. tied to upper slide

L = length of glass slides

T = time taken to separate the slides

It was determined by wooden block and glass slide apparatus. Weights about 20g were added to the pan and the time were noted for upper slide (movable) to separate completely from the fixed slides.

Table 6: Spreadability Parameters

Spreadability Parameters	Pure drug Gel	Microsponge Gel
Weight tide to upper slide (M)	20 gm	20 gm
Length moved on the glass slide (L)	9 cm	9 cm
Time Taken to Separate Slides (T)	51 sec.	43 sec.

Spreadability of gel containing pure drug

S = 20*9/51 = 3.52 g.cm/sec

Spreadability of microsponge gel

S = 20*9/43 = 4.18 g.cm/sec

Spreadability of gel containing pure drug was found to be 3.52 g.cm/sec while that of microsponge formulation was found to be 4.18 g.cm/sec; indicating spreadability of drug loaded microsponge gel was good as compared to that of marketed one.

4.4.4. Rheological Study

Rheological measurement of gel formulation was performed using a controlled stress rheometer (Viscotech Rheometer, Rheologica Instruments AB, London, Sweden). Data analysis was done with Stress RheoLogic Basic software, version 5.0. A cone and plate geometry was used with 25 mm diameter and cone of 1.0 °. Fresh sample was used for every test and all measurements were carried out at 25°C. The sample was exposed to increasing stress (0.1-100 Pa) and relation between shear stress and shear rate was studied.

Oscillatory shear responses (G' or elastic modulus, and G" or loss/viscous modulus) were also determined at low strains over the frequency range 0.1- 10 Hz. The linearity of viscoelastic properties was verified.

Table. 7: Rheological parameters of optimized gel formulation

Time (s)	Stress (Pa)	Shear Rate (1/Pa)	Viscosity (mPa s)	Torque (Nm)	Frequency	G'	G"
0	0	0	0	0	0	0	0
5	1.10E+00	1.24E-03	4.23E+01	9.53E-07	1.00E-01	1.55E+01	1.78E+00
10	1.27E+00	-2.82E-02	4.20E+01	4.09E-07	3.09E-01	1.68E+01	1.54E+00
15	1.46E+00	-1.51E-02	3.95E+01	5.17E-06	5.43E-01	1.71E+01	1.68E+00
20	1.68E+00	-5.24E-03	3.93E+01	4.71E-07	7.20E-01	1.71E+01	1.71E+00
25	1.93E+00	2.00E-02	3.93E+01	6.24E-07	9.55E-01	1.71E+01	1.68E+00
30	2.22E+00	4.46E-02	3.92E+01	6.86E-06	1.10E+00	1.69E+01	1.92E+00
35	2.56E+00	9.37E-02	3.86E+01	7.90E-06	3.39E+00	1.78E+01	1.00E+00
40	2.95E+00	2.22E-01	3.82E+01	9.09E-06	5.18E+00	2.17E+01	2.42E+00
45	3.39E+00	5.05E-01	3.75E+01	1.05E-05	7.91E+00	1.82E+01	2.39E+00
50	3.91E+00	1.13E+00	3.65E+01	1.21E-05	9.10E+00	1.65E+01	9.65E+00
55	4.50E+00	2.11E+00	3.55E+01	1.39E-05	1.05E+01	1.15E+00	3.79E+00
60	5.18E+00	3.61E+00	3.43E+01	1.60E-05	2.12E+01	8.37E-01	8.95E+01
65	5.96E+00	5.81E+00	3.29E+01	1.84E-05	2.44E+01	9.17E+01	1.51E+02
70	6.87E+00	8.94E+00	3.17E+01	2.12E-05	3.24E+01	1.66E+02	1.83E+02
75	7.91E+00	1.38E+01	3.07E+01	2.44E-05	4.29E+01	4.54E+02	3.31E+02
80	9.10E+00	1.97E+01	2.83E+01	2.81E-05	5.69E+01	1.18E+03	2.14E+02
85	1.05E+01	2.75E+01	2.54E+01	3.23E-05	6.55E+01	4.27E+02	3.29E+03
90	1.21E+01	3.69E+01	2.16E+01	3.72E-05	7.54E+01	4.24E+03	2.52E+03
95	1.39E+01	4.80E+01	1.72E+01	4.29E-05	8.69E+01	8.48E+03	1.69E+03
100	1.60E+01	5.93E+01	1.31E+01	4.94E-05	1.00E+02	1.93E+04	5.67E+03

4.4.5. In vitro drug release study

The cumulative percent drug release (%CDR) for all formulations was carried out. The cumulative percent drug release of all formulations is shown in table 8a and 8b.

Table 8a: % Drug release profile of F1- F5

Time (min.)	Formulations (%CDR)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
60	8.77 ± 0.44	10.25 ± 0.04	13.03 ± 0.79	18.08 ± 1.16	24.03 ± 0.88
120	15.01 ± 0.36	17.22 ± 0.84	20.58 ± 0.37	25.68 ± 0.51	33.47 ± 0.07
180	21.93 ± 0.58	23.13 ± 0.33	25.40 ± 1.12	34.50 ± 0.39	44.88 ± 0.02
240	26.33 ± 1.05	28.60 ± 0.64	30.63 ± 0.25	44.78 ± 0.09	53.57 ± 0.47
300	30.57 ± 0.25	33.88 ± 0.14	35.08 ± 0.91	56.16 ± 0.24	61.23 ± 0.63
360	36.61 ± 0.74	41.14 ± 0.20	42.60 ± 0.25	60.79 ± 0.54	66.90 ± 0.68
420	38.98 ± 0.65	45.02 ± 0.67	50.22 ± 0.23	66.41 ± 0.21	75.99 ± 1.09
480	43.66 ± 0.19	50.27 ± 0.43	59.12 ± 0.53	75.88 ± 0.49	84.18 ± 0.27

Table 8b: % Drug release profile of F6- F9

Time (min.)	Formulations (% CDR)			
	F6	F7	F8	F9
0	0	0	0	0
60	14.02 ± 0.87	13.58 ± 0.37	12.83 ± 1.23	11.47 ± 0.41
120	25.03 ± 0.23	20.84 ± 0.74	17.85 ± 0.13	15.92 ± 0.09
180	32.42 ± 0.41	28.31 ± 0.83	22.64 ± 0.54	21.73 ± 0.42
240	35.83 ± 1.07	33.25 ± 1.14	29.79 ± 0.29	28.80 ± 0.97
300	43.59 ± 0.97	38.43 ± 0.08	33.28 ± 0.25	31.02 ± 0.84
360	49.34 ± 0.23	46.40 ± 0.44	38.64 ± 0.20	38.72 ± 1.21
420	54.59 ± 0.51	52.32 ± 0.13	47.96 ± 0.85	45.20 ± 0.47
480	62.51 ± 0.76	61.08 ± 0.59	58.81 ± 0.57	54.26 ± 0.62

The drug release was found to be increased in the range of 43.66 % to 84.18 % as the drug: polymer ratio was increased. This is because as drug: polymer ratio was increased, the amount of polymer available per microsponge to encapsulate the drug becomes less, thus reducing the thickness of the polymer wall. With the smaller drug: polymer ratios the drug release rates were found to be slower due to formation of thicker matrix wall which might lead to longer diffusion path.

The highest drug release i.e. 84.18 % was found for the formulation F5 while the lowest, 43.66 %, for F1. Initial burst release was observed for the formulations F4 and F5 i.e. 18.08 % and 24.03 % respectively. This could be due to

the presence of non encapsulated drug near or on the surface of the microsponges.

It was observed that for each formulation from F6 to F9, the drug release was found to be decreased with increase in the amount of sodium alginate. This may possibly be due to the fact that the release of drug from the polymer matrix takes place after complete swelling of the polymer and as the amount of polymer in the formulation increases the time required to swell also increases. The slight decrease in release rate was found from 62.51 % to 54.26 % from formulations F6-F9.

4.4.6. In Vitro Drug Release Kinetic Study

The release profile data was subjected to various release models, namely, zero order, first order, Higuchi and Korsmeyar-Peppas. The best fit model was decided by highest r2 value. To determine the drug release mechanism and to compare the release profile differences among microsponges and gel formulations, the data obtained from drug-released amount and time was used. The release data was analyzed with the following mathematical model:

1. Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be presented by the following equation:

$Q = K_0 t$ ….Eqn (11)

Where Q is the amount of drug released at time t,

K_0 is the zero-order rate constant expressed in units of concentration/time and

t is the time in hours.

The pharmaceutical dosage forms following this profile, release the same amount of drug by unit of time. This model represents an ideal release profile in order to achieve the prolonged pharmacological action [18].

2. First order kinetics

This model has also been used to describe absorption and/or elimination of some drugs, although it is difficult to conceptualize this mechanism in a theoretical basis.

$Q1 = Q_0$ e-K1t or

$\text{Log } Q1 = \text{Log } Q_0 + K1t$ ….Eqn (12)

2.303

Where Q1 is the amount of drug release in time t,

Q_0 is the initial amount of drug in the solution and

K1 is the first order release constant.

The pharmaceutical dosage form following this dissolution profile, such as water soluble drugs in porous matrices release the drug in such a way that is proportional to the amount of drug remaining in its interior, in such a way that the amount of drug released by unit of time diminishes [18].

3. Higuchi Model

This model is used to study the release of water soluble and low soluble drugs incorporated in semisolid and/or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media. It describes drug release as a diffusion process based on the Fick's law, square root time dependant [18].

$Q = KH\ t_{1/2}$ ….Eqn (13)

Where,

Q is the amount of drug release in time t,

KH is the Higuchi dissolution constant.

4. Korsmeyar-Peppas

Korsmeyer developed a simple, empirical model, relating exponentially the drug release to the elapsed time (t).

$ft = a.tn$ ….Eqn (14)

Where a is a constant incorporating structural and geometric characteristics of the drug dosage form, n is the release exponent, indicative of the drug release mechanism, and function of t is $Mt/M\infty$ (fractional release of drug) [18]

Table 9: Release kinetics data of microsponge formulations

Batch Code	Zero Order	First Order	Higuchi	Peppas	Korsemeyer Peppas Parameters		Best Fitting Model
					n	k	
F1	0.981	0.899	0.992	0.990	0.7723	0.3777	Higuchi
F2	0.989	0.934	0.988	0.992	0.7816	0.3993	Peppas
F3	0.983	0.967	0.953	0.982	0.6992	0.7078	Zero
F4	0.980	0.940	0.984	0.989	0.7108	0.9187	Peppas
F5	0.964	0.940	0.994	0.991	0.6095	1.9044	Higuchi
F6	0.971	0.905	0.992	0.992	0.6866	0.8781	Higuchi & Peppas
F7	0.986	0.953	0.967	0.990	0.7089	0.7147	Peppas
F8	0.987	0.983	0.927	0.965	0.7115	0.6222	Zero
F9	0.979	0.972	0.949	0.976	0.7432	0.4917	Zero

*k-Release Rate Constant, R-Coefficient of Correlation, n-Kinetic Constant

The in vitro drug release showed the highest regression value for the Higuchi model (0.994 for F5). Based on highest regression value, the best fit was observed as Higuchi matrix for formulation F5. The correlation coefficient values for Higuchi model confirmed that drug release followed matrix diffusion mechanism.

The mechanism of drug release of the all microsponge formulations was studied by fitting the release data to

korsemeyer equation. The n values for formulations F1- F9 was found to be between 0.6095 – 0.7816. As the n value for korsemeyer-peppas model was found to be in between 0.5-1, it is the indicative of non-fickian diffusion.

4.4.7. Drug Release Profile of Gel Containing Pure Drug

The drug release profile for gel containing unentrapped fluconazole was carried out as shown in table 10.

Table 10: Percent drug release profile for unentrapped (pure) drug

Time (min.)	% CDR	Flux (mg/cm2h)
0	0	0
60	25.42 ± 0.16	0.423
120	45.56 ± 0.24	0.379
180	58.89 ± 0.13	0.328
240	81.09 ± 0.08	0.326

The gel containing pure drug released 81.07% drug from gel formulation at the end of 4 h. As compared with gel containing pure drug formulation, the gel containing entrapped drug in microsponges released the drug slowly upto 8 h thereby minimizing the side effects caused due to accumulation of unentrapped drug. The F5 formulation exhibited 84.18 % release of drug at the end of 8 h. So, the fluconazole microsponges with Eudragit RS-100 co-polymer in the ratio of 5:1 were more efficient to give extended drug release.

4.4.8. In-vitro diffusion study

The *in vitro* release of gel formulations were studied using cellophane membrane using modified apparatus. The dissolution medium used was freshly prepared phosphate buffer, (pH 7.4). Cellophane membrane previously soaked overnight in the dissolution medium, was tied to one end of a specifically designed glass cylinder open at both ends. One gram of formulation was accurately placed into this assembly. The cylinder was attached to stand and suspended in 40 ml of dissolution medium maintained at 37 ± 1°C, the membrane just touching the receptor medium surface. The dissolution medium was stirred at 500 rpm speed using teflon coated magnetic bead. Aliquots, each of 5 ml volume were withdrawn periodically at predetermined time and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium and analyzed by UV-Viible spectrophotometer at 260 nm using phosphate buffer pH 7.4 as blank [19]. The graph of amount of drug diffused per unit area versus time was plotted and calculations were done by following formulae

1. Determination of concentration of diffused drug(µg/ml)

Slope and intercept were determined by using graph of absorbance versus concentration.

$Y = mX + c$ ….Eqn (7)

Where, Y = Absorbance, m = Slope, X = Concentration and c = Intercept.

2. Cumulative amount of drug diffused (CADD)

[Concentration (µg/ml)* Volume of diffusion medium* Dilution factor] / 1000

3. Surface area (A) of cellophane membrane (cm2)

$A = \pi r2$ ….Eqn (8)

4. Cumulative amount of drug diffused per unit area (CADD/cm2)

CADD/cm2 = CADD/ Area of membrane ….Eqn (9)

5. Flux (Jss) = slope of linear portion of amount of drug diffused per unit area versus time.

6. Permeability Coefficient (Kp) = Jss /Cv ….Eqn (10)

The in vitro diffusion studies were carried out for all formulations using PBS (pH 7.4). In vitro diffusion of formulation F1 to F5 is shown in table 11a and F6 to F9 in table 11b.

Table 11a: Amount of drug diffused per unit area of microsponge formulations

Time (h)	Formulations (CADD/cm2)				
	F1	F2	F3	F4	F5
0	**0**	**0**	**0**	**0**	**0**
1	0.28 ± 0.07	0.33 ± 0.18	0.42 ± 0.47	0.59 ± 0.05	0.82 ± 0.43
2	0.49 ± 0.09	0.52 ± 0.41	0.67 ± 0.04	0.84 ± 0.07	0.99 ± 0.28
3	0.72 ± 0.25	0.76 ± 0.62	0.86 ± 0.06	1.13 ± 0.21	1.41 ± 0.06
4	0.86 ± 0.28	0.94 ± 0.09	1.0 ± 0.35	1.47 ± 0.59	1.66 ± 0.24
5	1.00 ± 0.19	1.11 ± 0.23	1.15 ± 0.24	1.85 ± 0.13	1.90 ± 0.37
6	1.2 ± 0.69	1.35 ± 0.11	1.40 ± 0.16	2.00 ± 0.31	2.20 ± 0.13
7	1.28 ± 0.05	1.48 ± 0.14	1.65 ± 0.23	2.18 ± 0.58	2.50 ± 0.08
8	1.43 ± 0.08	1.65 ± 0.17	1.94 ± 0.08	2.5 ± 0.17	2.77 ± 0.59

Table 11b: Amount of drug diffused per unit area of microsponge formulations

Time (h)	Formulations (CADD/cm2)			
	F6	**F7**	**F8**	**F9**
0	**0**	**0**	**0**	**0**
1	0.46 ± 0.64	0.44 ± 0.08	0.42 ± 0.13	0.37 ± 0.21
2	0.82 ± 0.51	0.68 ± 0.18	0.58 ± 0.36	0.52 ± 0.06
3	1.06 ± 0.11	0.93 ± 0.05	0.74 ± 0.41	0.71 ± 0.13
4	1.18 ± 0.09	1.09 ± 0.08	0.98 ± 0.09	0.94 ± 0.05
5	1.43 ± 0.35	1.26 ± 0.19	1.09 ± 0.05	1.02 ± 0.18
6	1.62 ± 0.26	1.52 ± 0.21	1.27 ± 0.17	1.27 ± 0.23
7	1.79 ± 0.31	1.72 ± 0.47	1.58 ± 0.11	1.48 ± 0.07
8	2.06 ± 0.04	2.01 ± 0.12	1.93 ± 0.25	1.78 ± 0.65

It was observed that the formulation F5 showed higher amount of drug diffused at the end of 8 h while that of F1 showed the less amount of drug diffused at the end of 8 h. Similarly in case of formulations F6 to F9, there was a slight decrease in amount of drug diffused from F6 to F9 respectively. This indicated that the Q value (cumulative amount of drug permeated per unit skin surface area) was increased at higher ratios due to an increase in the amount of DDEA concentration while it was decreased at high concentrations of sodium alginate.

The cumulative amount of drug permeated per unit skin surface area (Q) from the microsponge-loaded gel formulations was plotted against time.

It was observed that for each formulation from F6 to F9, the drug release was found to be decreased with increase in the amount of sodium alginate. This may possibly be due to the fact that the release of drug from the polymer matrix takes place after complete swelling of the polymer and as the amount of polymer in the formulation increases the time required to swell also increases. The slight decrease in release rate was found from 62.51 % to 54.26 % from formulations F6-F9.

The slopes of the linear portion of the permeation profiles were estimated as a steady state flux (J) of the drug from the gel formulations. The flux of the drug was found to be comparatively slower for microsponges having drug/polymer ratio 1:1, 2:1, and 3:1 as compared to 4:1, 5:1. This slower flux indicated the slow release of entrapped drug from the microsponges. The amount of drug permeated through unit area after 8 h was also found to be lower for F1, F2 and F3.

Table 12: Flux of all formulations

Time (h)	Flux (mg/cm2h)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
1	0.289	0.3379	0.4297	0.5961	0.5793	0.4623	0.4476	0.4228	0.3782
2	0.2474	0.2839	0.3392	0.4232	0.5519	0.4125	0.3435	0.2942	0.2624
3	0.2375	0.2517	0.276	0.3663	0.4746	0.3569	0.3039	0.2404	0.2295
4	0.217	0.231	0.2426	0.3493	0.4207	0.2968	0.2678	0.2287	0.2237
5	0.2007	0.2169	0.2194	0.3481	0.3819	0.2738	0.2436	0.2091	0.2005
6	0.1939	0.2143	0.2141	0.3268	0.3532	0.2565	0.237	0.1987	0.1979
7	0.1817	0.206	0.215	0.3061	0.332	0.2424	0.2307	0.2033	0.1981
8	0.1742	0.1999	0.2207	0.2968	0.3181	0.237	0.2317	0.2158	0.2049

The rate of drug released over the first hour was found to be higher compared to the rate of drug released over the next 7 hours. This may possibly be attributable to the release of free DDEA and effect the flux that gets slowly decreased for the next 7 hrs and this slower flux indicates the release of entrapped drug from microsponges.

CONCLUSION

The controlled release formulation of fluconazole was prepared using microsponge drug delivery system. These microsponges were then incorporated in gel dosage form.

The quasi-emulsion solvent diffusion method used for the preparation of the microsponges was simple, reproducible, and rapid. The obtained microsponges exhibited spherical shape, high porosity, and good flowability. The advantage is that microsponges were found to be self sterilizing. The drug: polymer ratio showed significant effect on drug content, encapsulation efficiency and particle size. The effect of sodium alginate concentration on drug release showed the slight decrease in drug release on increasing the sodium alginate amount.

The gel containing microsponges showed the viscous modulus along with pseudo plastic behavior. The in-vitro drug release showed the highest regression value for the Higuchi model indicating diffusion to be the predominant mechanism of drug release. This study concluded that a microsponge with Eudragit RS-100 co-polymer in the ratio of 5:1 was more efficient to give extended drug release.

CONFLICT OF INTEREST:

None

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