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DESIGN, FORMULATION AND *IN VITRO* EVALUATION OF MICROSPONGES BASED GEL FOR TOPICAL DELIVERY OF KETOCONAZOLE

V. Pavani*, M. Vinod and P. Anantha

Department of Pharmaceutics, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad - 500090, Telangana, India.

Keywords:

Ketoconazole, Ethyl cellulose N22, Sustained release, Carbopol gel, *In vitro* diffusion studies

Correspondence to Author:
Dr. Pavani Vengala

Associate Professor, Department of Pharmaceutics, Gokaraju Rangaraju College of Pharmacy, Bachupally, Hyderabad - 500090, Telangana, India.

E-mail: pavani181@gmail.com

ABSTRACT: The aim of the present study was to formulate topical microsponge-based delivery system containing ketoconazole for controlled release of the drug for proficient treatment of fungal infections. Ketoconazole loaded microsponges were prepared by quasi emulsion solvent diffusion method using ethyl cellulose N22 polymer with varied drug polymer ratios. The prepared microsponges were characterized by SEM, FTIR, and evaluated for surface morphology, % drug loading, particle size, % entrapment efficiency and *in vitro* drug release. The effect of formulation variables such as drug to polymer ratio, stirring speed on the physical characteristics of microsponges was examined. Compatibility studies using UV and FTIR indicated that there is no chemical interaction between drug and polymers. SEM studies revealed that the prepared micro sponges were spherical and porous with a mean particle size of 82.25µm. The formulations were subjected to *in vitro* release studies for 8 hr which showed sustained release. Microsponges were further incorporated in to carbopol gel formulation for topical delivery. Prepared gel formulations were evaluated for physical parameters like pH, spreadability and *in vitro* drug diffusion. Hydrogel loaded with ketoconazole microsponges showed desirable physical properties and *in vitro* drug release, *i.e.* 54.66% in 6 h, which is more controlled than the gel prepared with the pure drug *i.e.* 82.64% in 6 h.

INTRODUCTION: Currently most of the developments in drug delivery systems are being integrated to optimize the efficacy and cost effectiveness of the therapy. Conventional products of topical drugs are anticipated to work on the outer layers of the skin. Generally, such formulations release their active ingredients upon application, producing a highly concentrated layer of drug that is rapidly absorbed though for a short period [1]. This may lead to a cycle of short term overmedication followed by long term under medication.

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Rashes or more serious side effects can occur when active ingredients penetrate the skin. Other drawbacks of topical formulations are uncontrolled evaporation of active ingredient, unpleasant odor and potential incompatibility of drugs with the vehicles. Thus there is a need to maximize amount of time that an active ingredient is present either on skin surface or within the epidermis, while minimizing its transdermal penetration into the body.

It could be overcome by using a unique, versatile and novel approach; microsponge drug delivery system. Microsponge technology allows an even and sustained rate of release, reducing irritation while maintaining efficacy [2]. It is a unique technology for the controlled release of topical agents and consists of microporous beads. Delivery system comprised of a polymeric bead having

network of pores with an active ingredient held within is developed to provide controlled release of the active ingredients whose final target is skin itself [3]. Microsponges are porous microspheres having myriad of interconnected voids of particle size range of 5-300µm. These microsponges have capacity to entrap wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infectives and are used as a topical carrier system. Further these porous microspheres with active ingredients can be incorporated into formulations such as creams, lotions, gels and powders [4]. Microsponges consist of non-collapsible structures with porous surface through which active ingredients are released in controlled manner [5]. 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 such as rubbing, temperature, and pH [1].

Ketoconazole is a broad spectrum antifungal, which belongs to imidazole class, acts by inhibiting the growth of fungal cell wall. It is of common use for treatment of various skin infections. Topical administration of ketoconazole may cause irritation, dermatitis and burning sensation [6-8]. Topical gels have been widely accepted in both cosmetics and pharmaceuticals. Gel formulation provides better application property and stability in comparison to cream and ointment [9]. Many researchers have worked on various formulations for the delivery of ketoconazole such as films [10], emulsomes [11], emulsion based gel [12], nano gel [13] *etc*. The present work has aimed at formulating microsponges for ketoconazole, which can encapsulate and release the drug in a controllable manner, thus reducing the side effects. The drug loaded microsponges are converted to gels for better applicability and patient compliance.

MATERIALS: Ketoconazole was a gift sample from Sarvotham care limited, Hyderabad. Ethylcellulose N 22 was obtained from SD Fine Chem. Limited, Mumbai. All other chemicals used were of analytical grade and purchased from authentic suppliers.

METHODS: Ketoconazole microsponges were prepared by quasi emulsion solvent diffusion method [14 - 15]. The internal phase consisted of dichloromethane, in which the polymer was dissolved. And then drug was added to the polymer solution. To this drug-polymer solution, 20% by weight glycerine was added to enhance the plasticity of the polymer. The internal phase was added slowly to 100 ml of 0.5% (w/v) PVA in water which served as the external phase. The external phase was placed in a vessel with mechanical stirrer rotating at fixed rpm.

The system was thermally controlled at 25 °C in a water bath. Agitations up to 30 min permit the formation of microsponges and stirring was continued for 3 h to get desired rigid microsponges due to the evaporation of organic solvent. The rigid microsponges were filtered through the filter paper (Whatmann filter paper 0.45µm), washed with distilled water and dried at 40 °C for 24 h. Process variables like drug: polymer ratio and stirring speed were optimized by 3^2 factorial design techniques. The design and composition of various microsponges is outlined in **Table 1** and **2**.

TABLE 1: INDEPENDENT VARIABLES CONSIDERED IN FORMULATION

Variables	Code	Level		
		-1	1	+1
Drug: polymer Ratio (mg)	X_1	100	200	400
Stirring speed (rpm)	X_2	1000	1500	2000

TABLE 2: EXPERIMENTAL PLAN FOR PREPARATION OF MICROSPONGES USING EC N 22 AND DCM

Formula	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug: polymer ratio	2:1	1:1	1:2	2:1	1:1	1:2	2:1	1:1	1:2
Ketoconazole (mg)	200	200	200	200	200	200	200	200	200
Ethylcellulose N 22 (mg)	100	200	400	100	200	400	100	200	400
Dichloromethane (ml)	5	5	5	5	5	5	5	5	5
Glycerin (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
PVA (mg)	50	50	50	50	50	50	50	50	50
Water (ml)	100	100	100	100	100	100	100	100	100
Stirring speed, rpm	1000	1500	2000	1500	2000	1000	2000	1000	1500

Fourier Transform Infrared Spectroscopy (FTIR): FTIR spectra of ketoconazole, ethyl cellulose (N22), physical mixture of ketoconazole and ethyl cellulose, and microsponge formulations were incorporated in potassium bromide discs and evaluated with a Perkin Elmer, U.S.A spectrophotometer 1600.

Drug Loading and Drug Entrapment: A sample of ketoconazole microsponges (100mg) was taken for evaluation. The drug loaded microsponges were powdered and dissolved in 100ml of phosphate buffer solution, pH 5.5. This solution was filtered after 24 h and absorbance was measured spectrophotometrically at 287nm against blank solution. The amount of drug loaded and entrapped in the microsponges was calculated by the following formulae.

$$\text{Drug Loading (\%)} = \frac{\text{Weight of drug}}{\text{Weight of microsponges}} \times 100$$

$$\text{Encapsulation efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Particle Size Evaluation: Average particle size of ketoconazole loaded microsponges was determined by an optical microscope using calibrated eye piece and stage micrometer under regular polarized light. A minute quantity of microsponges was spread on a clean glass slide and the average particle size was calculated by measuring 300 particles of each batch. The values were given for the formulations in the form of mean particle size.

Morphological Study Using SEM: The morphology and surface characterization of microsponges was carried out by Scanning Electron Microscope (SEM). Microsponges were scanned and examined under Electron Microscope HITACHI SU 1500, Japan connected with Fine coat, JEOL JFC-1100E Ion sputter. The sample was loaded on copper sample holder and sputter coated with carbon followed by Gold.

***In vitro* Dissolution Studies:** The release of ketoconazole from microsponge was investigated in phosphate buffer solution, pH 5.5 as a dissolution medium (500ml) using USP type II apparatus. A sample of microsponge equivalent to 50mg of ketoconazole in a capsule was taken in the basket. A speed of 50 rpm and temperature of 37 ± 0.5 °C was maintained throughout the experiment. At fixed intervals, aliquots (5ml) were withdrawn and replaced with fresh dissolution media. The concentration of drug released at different time intervals was then determined by measuring the absorbance using UV spectrophotometer at 287 nm against blank. The dissolution studies were performed in triplicate. The dissolution data was subjected to various release models namely, Zero, First, Higuchi and Peppas.

Preparation of Optimized Microsponge Gel: Accurately weighed quantity of carbopol 934 was dissolved in few ml of distilled water and set aside. In another beaker, microsponges equivalent to the required amount of drug in final formulation was taken and propylene glycol was added. Now the microsponge - solvent blend was added to the above swollen carbopol with constant stirring. To the whole mixture, triethanolamine was added dropwise until transparent gel was obtained. Water was added to make up the required volume. Stirring was stopped to escape entrapped air; formed gel was degassed by using ultrasonication and stored in an air tight container for further studies [16]. Similarly, plain gel was also prepared by taking pure drug in place of microsponges. The formulation of the gels was given in **Table 3**.

Evaluation of Microsponge Gel: Two gel formulations of microsponges containing ketoconazole were characterized for pH using pH meter, spreadability, extrudability and drug content.

TABLE 3: FORMULA FOR PREPARATION OF GEL[17]

Formula	Plain gel, G1	Microsponge gel, G2
Drug	2% w/w	Microsponges equivalent to 200mg of drug (2% w/w)
Carbopol 934	1% w/w	1% w/w
Propylene glycol	30% w/w	30% w/w
Triethanolamine	q.s	q.s
Water	up to 10 g	up to 10 g

pH: The pH of the various gel formulations was determined by using digital pH meter. 1% aqueous solution of gels was used for measuring the pH.

Spreadability: It was determined by wooden block and glass slide apparatus. Weight of about 50g was added to the pan and the time (seconds) was noted for upper slide (movable) to separate completely

from the fixed slide. Spreadability was then calculated by using the formula:

$$S = M.L / T$$

Where, S = Spreadability; M = Weight tied to upper slide; L = Length of glass slide; T = Time taken to separate the slide completely from each other.

Extrudability: Good extrudability is one of the ideal properties of a gel, the ease with which the gel can come out of tube upon application of slight pressure. Technique based upon percent quantity of gel extruded from tube on finger pressure application was adopted for examining extrudability. More the quantity extruded better the extrudability. Formulations were filled in clean, lacquered, collapsible aluminium tubes with 5mm nasal tip opening and pressure was applied on tubes by means of first finger and thumb. Afterwards, tube extrudability was estimated in percentage by measuring amount of gel extruded through tip and compared with plain gel considering its extrudability as 100% [18, 19].

Drug Content: Gel formulation (100mg) was dissolved in methanol, filtered and the volume was made to 100ml with pH 5.5 phosphate buffer. The drug content was determined by measuring the absorbance at 287nm using UV Visible spectrophotometer.

***In vitro* Diffusion Studies:** The release of ketoconazole from optimized microsponge gel and plain gel was determined using membrane diffusion technique. The gel equivalent to 40mg of ketoconazole was used for the diffusion study. The gel was taken in a glass tube having a diameter 2.5 cm with a length of 8cm that was covered with previously soaked cellophane diffusion membrane, which acts as a donor compartment. The glass tube was placed in a beaker containing 200ml of phosphate buffer solution, pH 5.5, which acts as receptor compartment. The whole assembly was fixed in such a way that the lower end of the tube containing gel was just touched (1-2mm deep) the surface of diffusion medium. The temperature of receptor medium maintained at 37 ± 0.5 °C and the medium was agitated at 50 ± 5 rpm speed using magnetic stirrer. Aliquots of 5ml sample were withdrawn periodically and after each withdrawal, same volume of medium was replaced. The collected samples were analyzed at 287 nm UV spectrophotometer using phosphate buffer solution, pH 5.5 as blank. The test was carried out in triplicates.

RESULTS AND DISCUSSION:

FTIR Spectroscopy: The FT-IR spectrum of the procured ketoconazole (**Fig. 1**) was recorded and spectral interpretation was done. The characteristic IR absorption peaks of ketoconazole (**Table 4**) were there in the drug sample spectrum; thus confirming its purity.

Drug Excipient Interaction Studies:

FTIR Analysis: To check out any interaction between ketoconazole and ethyl cellulose used, compatibility study using FTIR and UV spectroscopy was carried out. IR spectra of drug (ketoconazole), physical mixture of drug and polymer and final formulation were shown in **Fig. 1**. All the characteristic IR bands of drug were observed in the physical mixture as well as final formulation (**Table 4**). No new peak appearance or disappearance of existing peaks indicates that there is no interaction between ketoconazole and ethyl cellulose. And no chemical interactions or changes took place during the preparation of microsponges and the drug was stable in the final formulation.

TABLE 4: FTIR DATA FOR PURE DRUG AND MICROSPONGE FORMULATION

Characteristic bands	Observed values in pure drug, cm^{-1}	Literature value, cm^{-1}	Observed values in microsponge formulation, cm^{-1}
C=O, Amide	1645.28	1680-1630	1647.21
C-H, Stretching (alkane)	2829.57	3000-2850	2829.87
C-O, Stretch	1249.87	1300-1000	1242.56
C-Cl, bending	815.89	850-550	823.60

UV Spectral Interference of Ketoconazole with Ethyl Cellulose: Since the analysis of ketoconazole was done in the presence of ethyl cellulose, it was necessary to identify the interference of ethyl cellulose at analytical wavelength of ketoconazole. For this purpose,

solutions of 100µg/ml of ketoconazole and ethyl cellulose, and a combination of ketoconazole and ethyl cellulose were prepared. These solutions were scanned for UV absorption pattern between 200-400nm. The absorption spectra were shown in **Fig. 2**. Polymer did not show absorption at 287nm at working concentration because absorption was not significant.

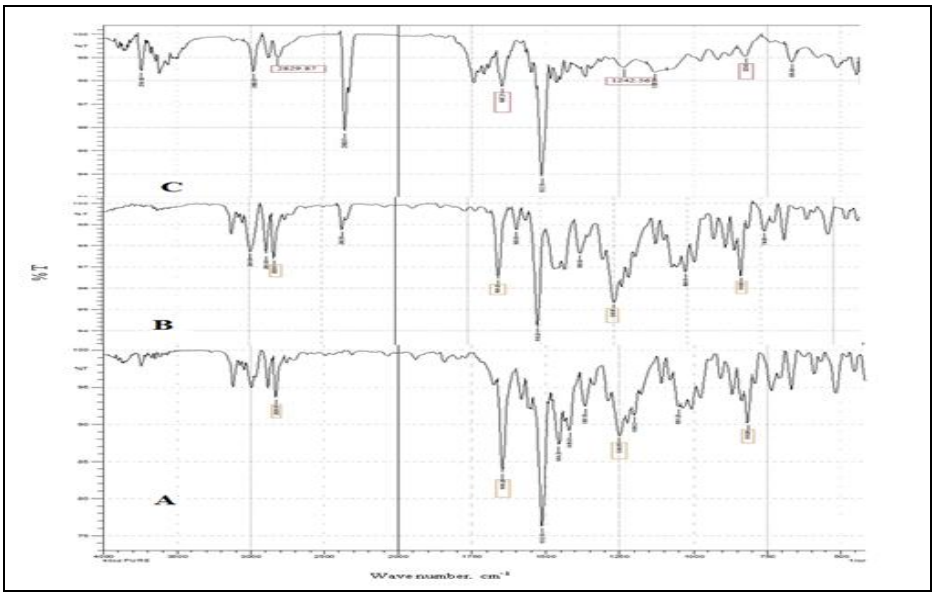


FIG. 1: FTIR SPECTRUM OF A) KETOCONAZOLE B) PHYSICAL MIXTURE (DRUG+ EC N22), AND C) MICROSPONGE FORMULATION

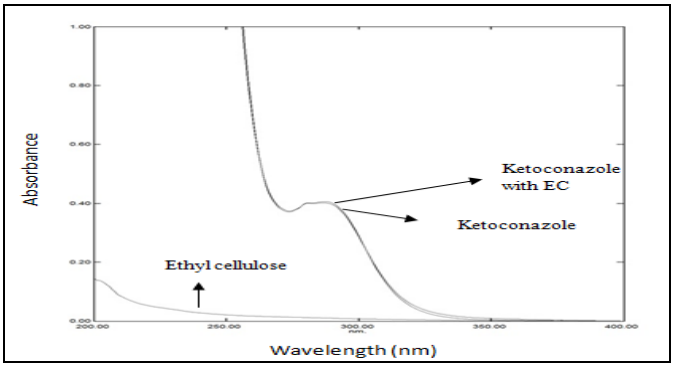


FIG. 2: UV ABSORPTION SPECTRA OF KETOCONAZOLE (100µg/ml), ETHYL CELLULOSE (100µg/ml) AND A MIXTURE OF THE ABOVE TWO SOLUTIONS, EACH 100µg/ml

Physical Characterization of Microsponges: Ketoconazole microsponges were prepared by quasi-emulsion solvent diffusion method. The method was simple, reproducible and rapid. The product observed to be of pale white colour with good flow properties than as compared with pure drug.

Percentage yield of different formulations was calculated and ranged between 66.58 to 79.07% (**Table 5**). Percentage drug loading, percentage entrapment efficiency were also determined for formulations and given in **Table 5**.

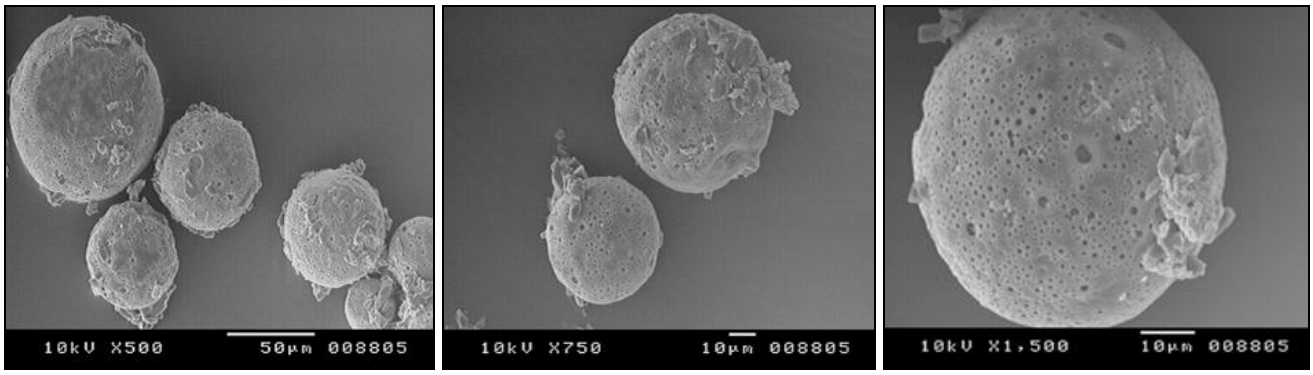
TABLE 5: PRODUCTION YIELD, DRUG LOADING, ENTRAPMENT EFFICIENCY, MEAN PARTICLE SIZE AND CUMULATIVE DRUG RELEASE OF FORMULATIONS (3^2 FULL FACTORIAL DESIGN) USING EC N 22 AS POLYMER

Formulation code	EC N 22 (mg)	Stirring Speed (RPM)	% Production yield, (AM±SD)*	% Drug loading, (AM±SD)*	%Entrapment efficiency, (AM±SD)*	Particle size, µm (AM±SD) **	% cumulative drug release (AM±SD)*
F_1	100	1000	66.65±1.9	70±0.54	72±0.41	87.39±5.21	86.54±0.21
F_2	200	1500	66.58±0.83	65±0.03	84±0.48	91.44±3.54	73.78±0.49
F_3	400	2000	79.07±1.14	63±0.59	89±0.07	104.5±4.76	68.22±0.21
F_4	100	1500	67.5 ±0.35	72±0.04	75±1.21	81.25±3.89	88.91±0.54
F_5	200	2000	75.6 ±0.48	67±0.23	85±0.78	89.87±2.99	72.65±0.55
F_6	400	1000	69.48±0.73	60±0.65	79±0.82	123.65±7.66	66.61±1.77
F_7	100	2000	73.5±1.63	74±0.52	76±1.33	75.81±6.78	84.99±0.72
F_8	200	1000	67.35±0.94	62±0.36	78±0.81	97.54±4.54	73.21±0.21
F_9	400	1500	76.66±0.68	61±0.44	87±0.21	116.92±5.42	68.94±0.21

*Average of three determinations; ** Average of 100 particles

Particle Size Analysis: Average particle size of microsponge formulations was determined by optical microscopy by using stage micrometer and eye piece micrometer and the values are shown in **Table 5**.

Scanning Electron Microscopy: The determination of shape and surface morphology was done by scanning electron microscope HITACHI SU 1500, Japan. The captured SEM image is shown in **Fig. 3**. SEM results indicated that the microsponges of ketoconazole with ethylcellulose were highly porous, spherical discrete particles. The surface topography reveals that the microsponges were porous and the pores may be induced by the rapid escape of the volatile solvents from the surface during formulation (**Fig. 3**).



A **B** **C**

FIG. 3: SEM OF KETOCONAZOLE LOADED MICROSPONGE FORMULATION CODED AS F13 UNDER A) 500X, B) 750X, C) 1500X

***In vitro* Release Studies of Ketoconazole Microsponges:** The dissolution of ketoconazole from microsponges was conducted in phosphate buffer pH 5.5 for 8 h. The release profiles obtained for ketoconazole microsponges formulations are presented in **Table 5** and **Fig. 4**. The profiles showed a gradual release of the drug from all the formulations. Cumulative release for the microsponges after 8 h ranged from 66-88%. Drug release from the formulations decreased with increase in the amount of polymer in the microsponges.

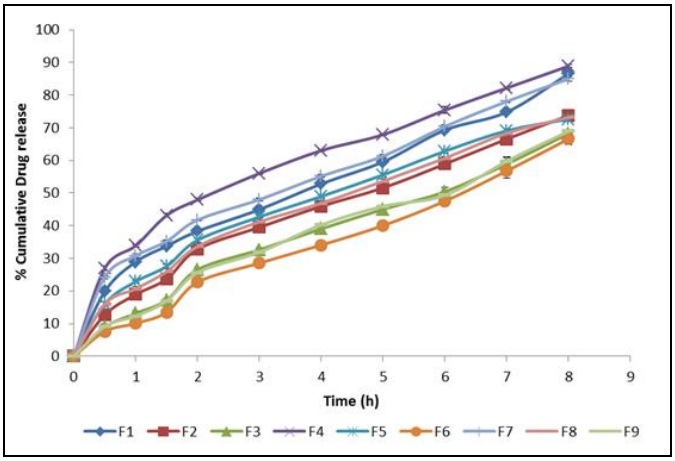


FIG. 4: DRUG RELEASE PROFILE OF F1-F9 FORMULATIONS

Effect of Stirring Speed on Microsponge Formation: The effect of stirring speed on particle size was studied. As the speed was increased, microsponges of smaller size were obtained, as shown in **Table 5**. This may be attributed to better dispersion at higher stirring speed. There was a slight increase in yield, drug loading and entrapment efficiency with increasing speed though the increase was not much significant.

Effect of Drug Polymer Ratio on Microsponge Formation: Drug-polymer ratio had an effect on the size of the microsponges, with an increase in drug polymer ratio from 2:1 to 1:2 the particle size has increased. It may be attributed to the availability of more amount of polymer to encapsulate the drug and increased viscosity of organic phase due to increased drug-polymer ratio leading to an increase in the size. The mean diameters for the drug-polymer ratios of 2:1 and 1:2 were 123.65 ± 7.66µm and 87.39 ± 5.21µm respectively at 1000 rpm speed (**Table 5**).

There was a decrease in percentage drug release with an increase in drug-polymer ratio (**Table 5**, **Fig. 4**). As the polymer concentration increased, more amount of polymer was surrounding the drug,

thus increasing the thickness of the wall of the polymer matrix which led to extended diffusion path and ultimately to lesser drug release or more sustained release.

Preparation of Microsponge Gel: Ketoconazole gels with plain drug and microsponges were prepared as per the formulations given in **Table 3**. Microsponges were inspected visually for their color, texture and appearance. Both the formulations were white, clear, and viscous in nature with smooth texture and of good homogeneity without any lumps and syneresis.

Physical Characterization of Gels: Physical parameters of gel formulations were shown in **Table 6**. Gels were evaluated for their pH, spreadability, viscosity and drug content. The pH value of both the gels was around 6.8 which is supposed to be suitable for skin without causing any irritation. The values of spreadability indicate that the gel is easily spreadable by small amount of shear. The extrudability of ketoconazole microsponge gel was found to be 97.34% by considering extrudability of plain gel as 100%, which indicates that the formulation exhibited better extrudability.

TABLE 6: PHYSICAL PARAMETERS OF PREPARED GELS

Formulation	pH	Spread-ability (gm-cm/sec)	Extrudability (%)	% Drug content
G1 (Plain gel)	6.81	13.85	100	95.1
G2 (Microsponge gel)	6.89	14.28	97.34	93.89

***In vitro* Diffusion Studies:** *In vitro* drug release of ketoconazole microsponges enriched gel has shown that the release profile was altered and controlled. The release profile was shown in **Fig. 5** which clearly shows that the release form microsponges loaded gel is more sustained than the plain gel, which may be beneficial in minimizing the side effects, skin irritation and hypersensitivity reactions.

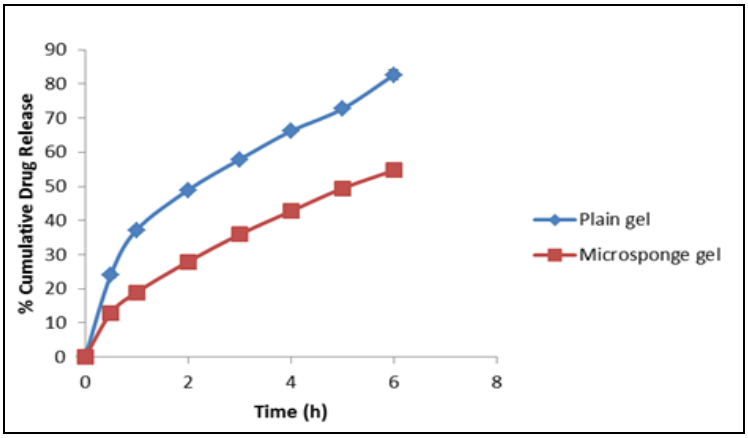


FIG. 5: *IN VITRO* CUMULATIVE RELEASE PROFILE OF KETOCONAZOLE FROM GELS (G1 AND G2) IN PHOSPHATE BUFFER pH 5.5

Mathematical Modelling: To compare drug release profiles of two formulations, model-dependent (curve fitting) method was studied. The *in vitro* release studies data was quantified to determine the release mechanism, to fit various mathematical models and to determine the best-fit model. The various parameters like the time exponent (n), the release rate constant (k) and the regression co-efficient (R^2) were also calculated. In a set of data, the model showing the highest value to R^2 was taken as the best-fit model. The data obtained from curve fitting analysis was tabulated in **Table 7**.

TABLE 7: DATA OF VARIOUS PARAMETERS OF MODEL FITTING FOR KETOCONAZOLE GEL FORMULATIONS (G1 AND G2)

Formulation	Zero Order		First Order		Korsmeyer Peppas		Higuchi	
	K_0	R^2	K_1	R^2	n	R^2	K_d	R^2
G1	11.716	0.8805	-0.007	0.9608	0.414	0.9682	29.516	0.9873
G2	9.687	0.9422	-0.006	0.9808	0.534	0.9757	23.698	0.9963

The results of mathematical model fitting of data obtained indicated that, the best fit model in both the cases is Higuchi model, which means that the mechanism of drug release from gel was diffusion.

CONCLUSION: The idea behind developing ketoconazole loaded microsponges was to deliver the drug in a continual manner for prolonged period of time to reduce frequency of application, hypersensitivity reactions. Microsponge loaded topical drug delivery system of ketoconazole was successfully developed using quasi emulsion solvent diffusion method, which was found to be simple and reproducible. Prepared microsponges were of spherical shape with high porosity. Varied drug polymer ratio and stirring speed reflected remarkable effect on particle size. Microsponge loaded gel showed more prolonged release than plain gel and followed diffusion kinetics. Thus, gel containing microsponges prepared in this study was found to be a promising delivery system offering prolonged release of ketoconazole in treating fungal infections like athlete's foot, jock itch, ringworm, and seborrhea (dry, flaking skin).

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CONFLICT OF INTEREST: The authors declare that there is no conflict of interests regarding the publication of this paper.

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