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FORMULATION AND EVALUATION OF KETOCONAZOLE LOADED MICROSPONGE GEL FOR TOPICAL DRUG DELIVERY

Neha Sodiyal*

Department of Pharmaceutical Sciences H.N.B. Garhwal University (Central University), Srinagar (Garhwal).

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***Corresponding Author**
Ms. Neha Sodiyal
Department of Pharmaceutical Sciences
H.N.B. Garhwal University (Central University),
Srinagar (Garhwal).

ABSTRACT

Ketoconazole is broad spectrum antifungal which shows fungi static activity and have biological half-life of 2 hours but it shows many gastrointestinal side effects when administered orally. To overcome these side effects, the aim of the present study was to formulate and evaluate ketoconazole loaded microsponge gel for topical delivery. Ketoconazole loaded microsponges were prepared by quasi emulsion solvent diffusion method using ethyl cellulose with varied drug polymer ratio. The prepared microsponges were characterized by SEM, FTIR, XRD, and evaluated for % drug content, particle size, % entrapment efficiency and *in-vitro* drug release. By all the results it was observed that the formulation F1 show excellent flow property and the formulation F5 shows better shape and morphology.

KEYWORDS: Ketoconazole, Ethyl Cellulose, Carbopol gel, *In – vitro* drug release.

INTRODUCTION

Topical application has been used for centuries, the treatment of localized skin diseases. In topical formulation skin is most partially accessible organs on human body. Topical preparations prevent the gastro-intestinal irritation and metabolism of drug.[1] Topical delivery includes: External topical that are spread, sprayed, or dispersed on to cutaneous tissues to cover the affected area and Internal topical that are applied to the mucous membrane orally, vaginally or on anorectal tissues for local activity.[2] A microsponge delivery system (MDS) is highly cross-linked, porous, polymeric microspheres, polymeric system consisting of porous microspheres that can trap wide range of actives ingredients and then release them on to the skin over a time and in response to trigger. These days more developments in

delivery systems are being desegregated to optimize the drug efficacy and cost-effectiveness of the therapy, microsponge delivery system(MDS)has been successively addressed for the controlled release of drug onto the outer layer of skin (epidermis). Drug loaded microsponge consist of microporous beads, typically 10-25µm in diameter that possess a versatility to entrap wide range of active agents (drug or therapeutic agents). Microsponge systems are based on microscopic, polymer-based microsphere that can suspend or entrap a wide variety of substance. Microsponge technology offers entrapment of substances and to contribute towards reduced side effects, improved stability, increased smoothness, and enhanced formulation flexibility.

Microsponges has ability to retain in skin cell and prevent the dose dumping in blood circulation, which may cause side effects. Microsponge system offers entrapment of ingredients improved stability, reduced side effects, enhanced formulation flexibility. According to various studies microsponges systems are non-allergic, non-irritating, non-mutagenic and non-toxic. This method is currently used in cosmetics, skin care, sunscreens and prescription products.[3]

Gel is a semi solid formulation that has a pair of components which is rich in liquid phase. After the application of gel, the liquids are drying by the evaporation and, gels of drug are covering the skin. Gels are defined as significant extent dilute cross linked system, that is in the steady state and shows no flow. Gel formulation provides better application property and stability in comparison to cream and ointment.[4]

MATERIALS

Ketoconazole was a gift sample from Life Bio Sciences and Medicine Paunta sahib. Ethyl Cellulose, Carbopol was purchased from Central Drug House Pvt. Ltd.

METHODS

The microsponges containing ketoconazole were prepared by quasi-emulsion solvent diffusion method. Using an inner phase comprising ethyl cellulose dissolved in 20 ml of dicholoromethane. Further ketoconazole was put in and dissolved through ultrasonication at 3℃. This mixture was then poured into an aqueous solution of polyvinyl alcohol (outer phase) with stirring rate 1000 rpm for 3 hours. Next on, microsponges were formed due to the removal of dichloromethane from the system by evaporation. Prepared microsponges were filtered and then washed with distilled water and subjected to dried at room temperature for

24 hours.

Table 1: Composition of microsponges.

Formula	F1	F2	F3	F4	F5
Drug (mg)	200	200	200	200	200
Ethyl Cellulose (mg)	400	800	1200	1600	2000
Dichloromethane (ml)	10	10	10	10	10
Glycerin(ml)	0.1	0.1	0.1	0.1	0.1
PVA(mg)	100	100	100	100	100
Distill water(ml)	100	100	100	100	100
Stirring speed	1000	1500	1000	1500	1500

Evaluation parameters[5]

Morphology of microsponge

The morphology of the microsponges can be studied by scanning electron microscopy (SEM).

Theoretical drug content

The production yield of micro particles can be determined by calculating accurately the initial weight of the raw materials and last weight of the microsponge obtained.

Production yield = practical mass of microsponge ×100

Particle size evaluation

Average particle size of ketoconazole loaded microsponges was determined by an optical microscope using calibrated eye piece. A minimum quantity of microsponge was spread on a clean slide and 300 particles of each batch was calculated.

In vitro dissolution studies

In vitro dissolution studies carried out using dissolution assembly (basket type) in 500 ml of pH 7.4 saline phosphate buffer solution at 37±°C and rotated at 50 rpm. Specified amount of aliquots withdrawn at hourly intervals up to 8h.

Drug- polymer compatibility

Analyzed by FTIR.

Preparation of microsponge gel[6]

Gel forming polymer (carbopol 934) was dissolved in few ml of distilled water and set aside for 2 hours. In another beaker, microsponge equivalent to the required amount of the drug in

final formulation was taken and propylene glycol was added. Now the microsponge-solvent blend was added to the above swollen carbopol with a constant stirring at 600 rpm. The whole mixture, triethanolamine was added dropwise until transparent gel was obtained. Water was added to the require volume. Stirring was stopped to escape entrapped air; formed gel stored in an air tight container for further studies.

Table 2: Composition of microsponge gel.

Component	F1	F2
ketoconazole	1	-
ketoconazole micropsonge	-	1
Carbopol(%w/v)	1	1
Triethanolamine(ml)	0.25	0.25
Propylene glycol (ml)	-	5
Distilled water (ml)	100	100

Characterization of ketoconazole microsponge gel

In vitro diffusion studies

In – vitro permeation studies were performed by using egg shell membrane with a receptor compartment capacity of 60mL. The egg shell membrane was fixed at the end of hollow tube was thread represent as a donor and receptor present in beaker. The whole assembly was placed on a magnetic stirrer, and the solution in the receptor beaker was continuously stirring using magnetic beads. The temperature was maintained at 37±0.5℃. 1 mL samples were withdrawn at suitable time interval and were analyzed for drug content spectrophotometrically at 287 nm.

RESULT AND DISCUSSION

- **Micromeretics evaluation[6]**

The microsponge formulation were subjected to various micromeretics parameters such as particle size, bulk density, tapped density, carr's compressibility index, huasner's ratio and angle of repose.

Table 3: Micromeretics evaluation data of Ketoconazole microsponge.

Code	Particle size (µm)	Bulk density	Tapped density	Carr's index(%)	Hausner's ratio	Angle of repose	Flow character
F1	24.27	240	302.12	20.521	1.258	25.60	Excellent
F2	27.06	301.12	332.32	9.388	1.103	29.12	Excellent
F3	35.25	318.03	345.22	7.876	1.085	31.50	Good
F4	45.32	325..65	354.16	8.050	1.087	33.41	Good
F5	52.05	224.32	324.48	30.867	1.446	35.25	Fair

Drug content analysis[7]

Drug content was determined for all microsponge formulations of using phosphate buffer (7.4 pH) as the medium.

Entrapment efficiency

The entrapment efficiency calculated for the prepared micropsonge formulation is shown in table:

Table 4: Drug content and Entrapment efficiency.

Formulation	Drug content(%)	Entrapment efficiency(%)
F1	46	42
F2	51	57
F3	58	62
F4	67	68
F5	74	75

FTIR

In FTIR analysis drug in alone and in combination with other excipients subjected for checking compatibility of drug other excipients.

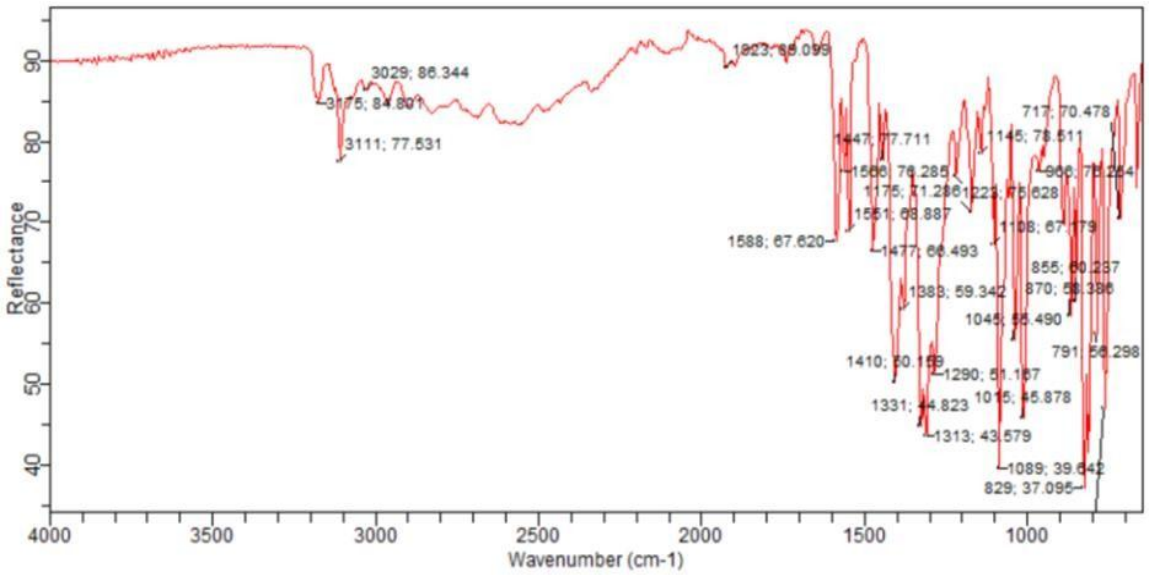

Figure 1: FTIR spectrum of procured sample of ketoconazole.

IR spectrum of ketoconazole showed absorption peak at 3175cm-1 and 3111cm-1 denoting -C-H stretching. The absorption peak at 1477cm-1 and 1313 cm-1 due to stretching of C-H aromatic stretching and C-N stretching respectively. The absorption peak at 855cm-1 were due to -C-Cl groups.

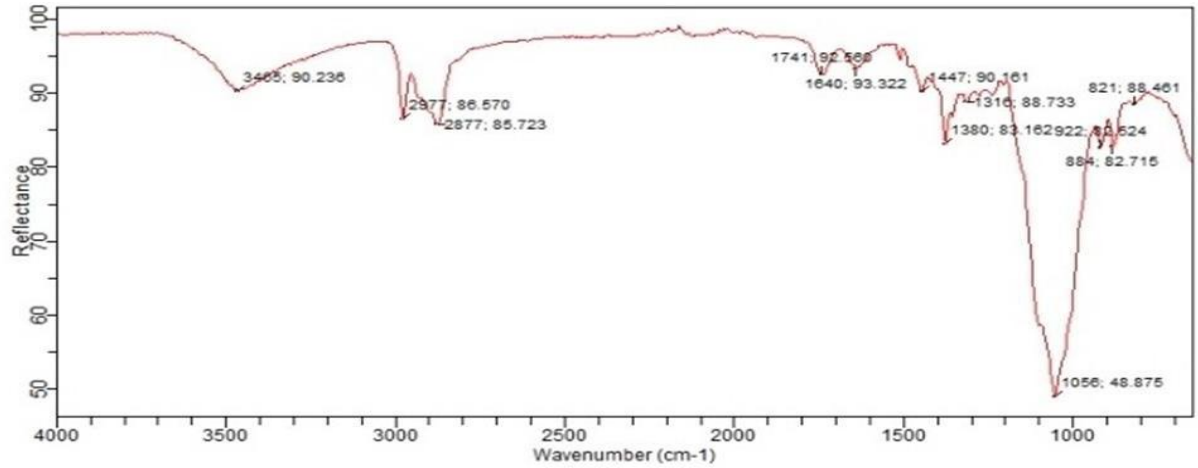

Figure 2: FTIR spectrum of formulation.

As per the observations from FTIR spectra no major changes or shifting in the peaks of drugs were observed which indicates that there happens no chemical interaction between the drug and polymers physical mixtures. It was concluded that the drug is present in free form in all the formulation irrespective of the variation in the composition.

- **Scanning Electron Microscopy (SEM)**

The Scanning electron microscopy of all prepared microsponge formulations were carried out to study the particle size, shape, surface, morphology and appearance.

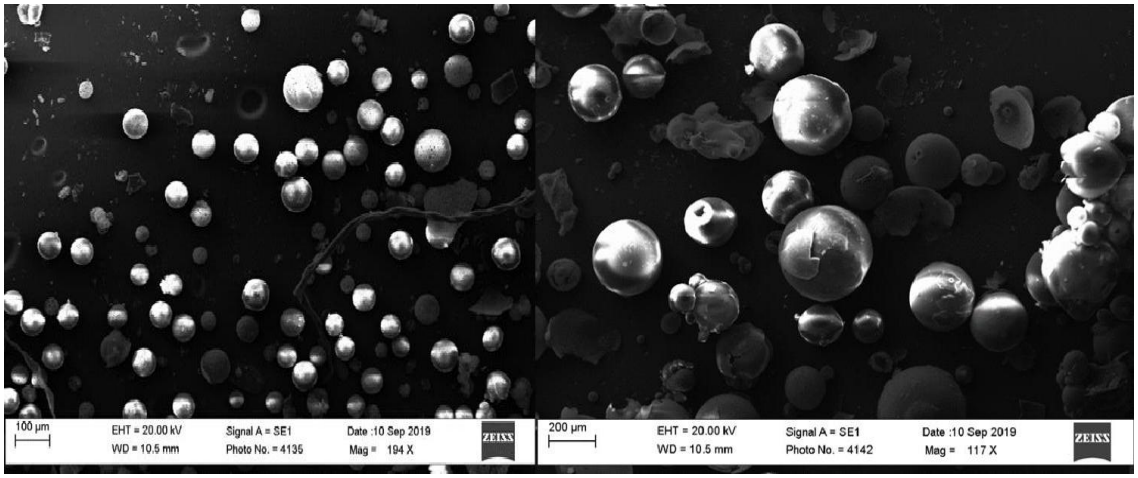

Figure 3: SEM of ketoconazole loaded microsponge formulation.

X-RAY POWDER DIFFRACTROMETRY (XRPD)[8]

X-RD analysis revealed that drug loaded microsponge are amorphous in nature. X-RD patterns recorded for drug loading microsponge are presented in fig.4. here for microsponge, the major peaks were observed at 163.8639, suggesting that the crystalline nature of drug

loading microsponge might have been reduced as the major peaks are decreased in all the formulation. Hence crystalline nature is absent.

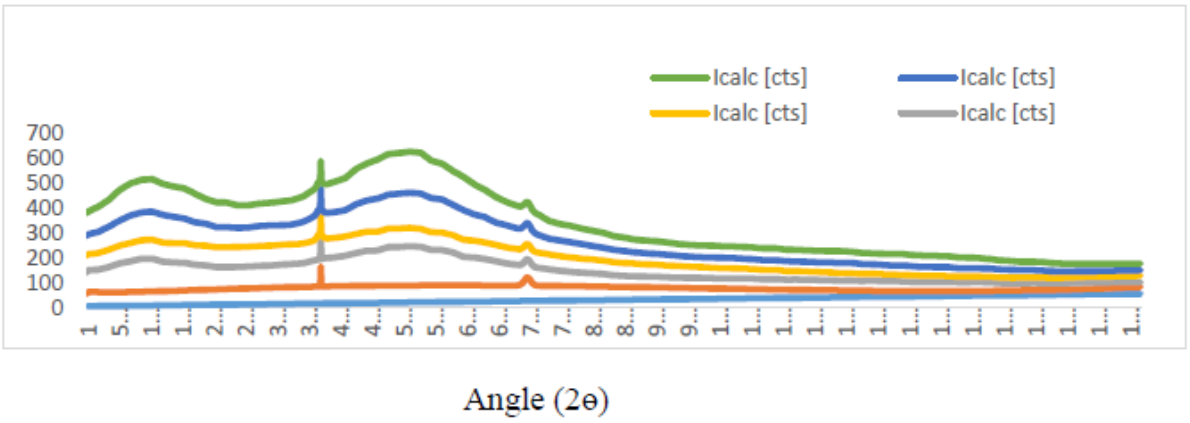

Figure 4: X-Ray powder Diffracotrometry (XRPD)

***In-vitro* release studies of ketoconazole microsponge**

In- vitro dissolution studies were carried out in 500mL of phosphate buffer pH 7.4, maintained at 37±℃ using USP type-II eight station dissolution test apparatus (ESICO International) at a rotation speed of 150rpm. The sampling was done by withdrawing 1mL of sample from the basket at pre-set time intervals up to 8hrs. the media in the dissolution flask was replenished by the pre- warmed medium to maintain the constant volume. Each sample was diluted suitably and analyzed spectrophometrically at 287nm.

Table 5: Comparative *in- vitro* dissolution study data table of formulation F1-F5 for zero order release kinetics.

Time (min)	% Cumulative Drug Release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
15	3.24	3.57	5.55	2.59	4.78
30	7.22	7.32	11.35	5.54	9.73
60	11.94	11.15	17.40	10.84	14.84
120	17.22	39.39	23.78	16.17	20.10
180	23.05	43.47	30.41	21.53	25.47
240	29.44	47.72	37.36	28.23	31.11
300	36.57	52.06	44.73	35.18	36.95
360	44.07	56.56	52.34	42.38	42.91
420	52.12	61.23	60.12	49.69	49.07
480	60.74	62.54	68.06	57.02	55.34

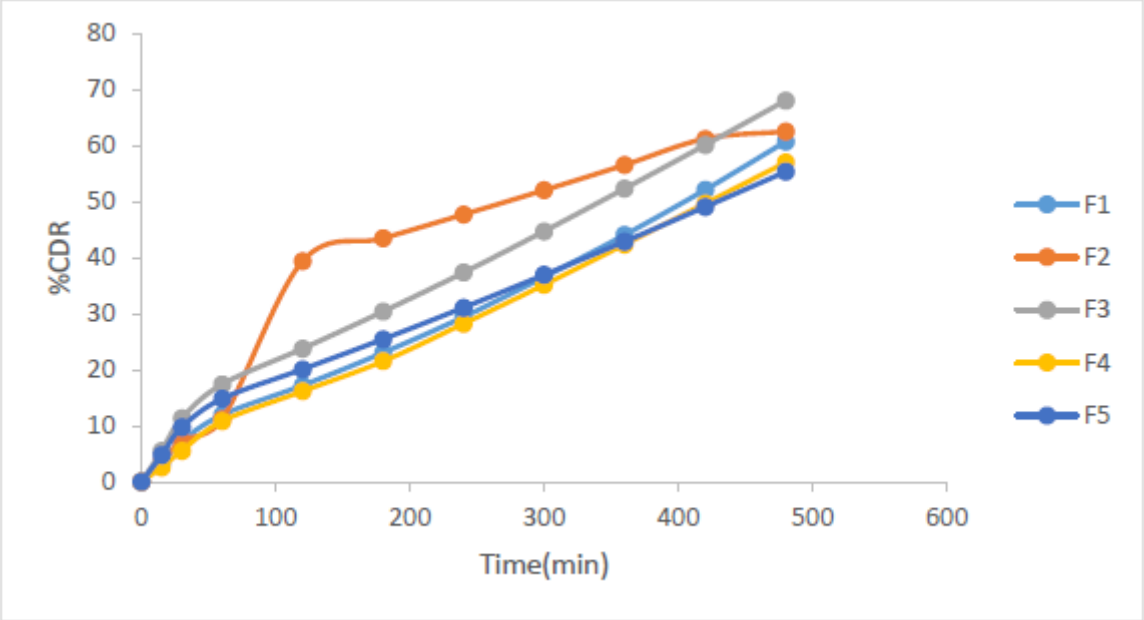

Figure 5: Comparative *in-vitro* dissolution study graph of all formulation F1-F5 of zero order release kinetics.

Preparation of ketoconazole microsponge Gel

Gel forming polymer (carbopol 934) was dissolved in few ml of distilled water and set aside for 2 hours. In another beaker, microsponge equivalent to the required amount of the drug in final formulation was taken and propylene glycol was added. Now the microsponge-solvent blend was added to the above swollen carbopol with a constant stirring at 600 rpm. The whole mixture, triethanolamine was added dropwise until transparent gel was obtained. Water was added to the require volume. Stirring was stopped to escape entrapped air, formed gel stored in an air tight container for further studies.

Table 6: Physical parameter of prepared gel.

Formulation	pH	Spreadability(gm-cm/sec)	% drug content
F1	6.4	8	94.2
F2	6.2	10	91.32

- ***In – vitro* drug diffusion**

In – vitro permeation studies were performed by using egg shell membrane with a receptor compartment capacity of 60mL. The egg shell membrane was fixed at the end of hollow tube was thread represent as a donor and receptor present in beaker. The whole assembly was placed on a magnetic stirrer, and the solution in the receptor beaker was continuously stirring using magnetic beads. The temperature was maintained at 37 ± 0.5^{0}C. 1 mL samples were

withdrawn at suitable time interval and were analyzed for drug content spectrophotometrically at 287nm.

Table 7: Comparative *in- vitro* permeation study data table of formulation G1-G2 for zero order release kinetics.

Time	%Cumulative Drug Release	
	G1	G2
0	0	0
15	21.34	19.38
30	22.87	22.57
60	28.49	31.21
120	29.96	34.81
180	30.81	43.28
240	51.25	52.95
300	55.72	57.77
360	60.80	63.46
420	68.86	69.84
480	71.43	72.32
540	78.71	80.89
600	79.97	85.65

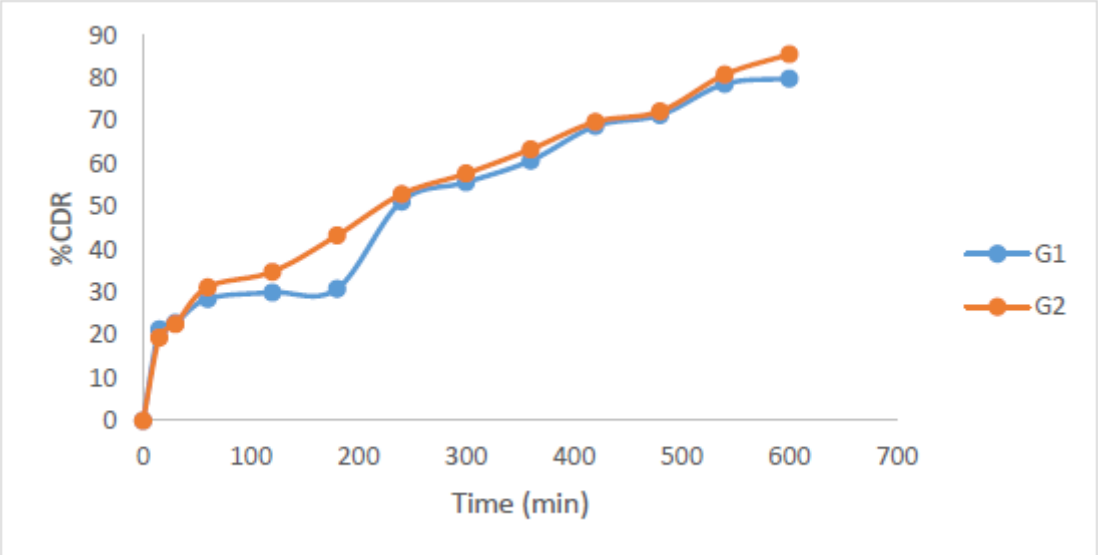

Figure 6: Comparative *in – vitro* permeation study graph of all formulation G1-G2 of zero order release kinetics.

CONCLUSION

Microsponge loaded topical drug delivery of ketoconazole was successfully developed using quasi emulsion solvent diffusion method. Drug content decreased and entrapment efficiency increased with the increase in polymer concentration. FTIR analysis of all the formulations showed no interaction between the dug and polymer thus confirming their compatibility. The

SEM analysis showed that the SEM images of all the formulations were observed to be slightly round and spherical shape. The microsponges were then subjected to micromeretics evaluation for the particle size, bulk density, tapped density, carr's compressibility index, hausner's ratio. The particle size of microsponges ranged from 24µm to 52µm. It was found that with the increase in polymer concentration, percentage yield and particle size also increased. Thus, gel containing microsponges prepared in this study was to found to be a promising delivery system offering prolonged released of ketoconazole in treating fungal infections.

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