FORMULATION DEVELOPMENT AND IN-VITRO EVALUTION OF KETOCONAZOLE MICROSPONGE DRUG DELIVERY SYSTEM OF ANTIFUNGAL DRUG

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Abstract: *This study investigated the synthesis and characterization of Ketoconazole microsponges through the quasi-emulsion solvent diffusion method, followed by comprehensive evaluation of their properties and performance. The microsponges exhibited satisfactory production yield, loading efficiency, and particle size, with spectral analyses confirming the presence of characteristic drug peaks. Morphological assessments via SEM revealed the distinct structural differences between styrene and Eudragit microsponges. Pore characterization indicated variations in pore types and porosity between the two types of microsponges. Stability studies demonstrated no significant changes in morphology or drug release over six months of storage under accelerated conditions. Gel formulations incorporating microsponges exhibited higher viscosity and controlled drug release compared to plain drug gels. Antifungal activity assays revealed retained efficacy and potentially enhanced activity of microsponge-loaded gels compared to free drug gels and commercial formulations, along with reduced skin irritation. Overall, the findings suggest the promising potential of microsponge delivery systems for topical administration of Ketoconazole , offering controlled release, reduced irritation, and potentially improved therapeutic outcomes.*

Key words*: Micro sponge Drug delivery system, Ketoconazole, anti-fungal activity, quasi emulsification technique.*

INTRODUCTION

Drug diffusion from the microsponge gels was measured in vitro using a Franz Diffusion cell, where gels containing free or entrapped drug were placed in the donor compartment, and aliquots microsponge delivery systems represent a groundbreaking advancement in pharmaceutical and cosmetic sciences, offering a novel approach to controlled release of active ingredients onto the skin. [1-2] These systems consist of highly engineered polymeric microspheres with uniform size, spherical shape, and porous structures, enabling efficient entrapment and gradual release of therapeutic or cosmetic agents. Developed to overcome the limitations of traditional delivery methods, microsponge technology allows for precise modulation of release kinetics, ensuring optimal therapeutic efficacy while minimizing adverse effects. By incorporating microsponges into various topical formulations such as creams, lotions, and powders, targeted delivery to specific skin layers is achieved, facilitating enhanced drug penetration and sustained activity.[3-5]

With their ability to encapsulate a diverse range of substances, including emollients, fragrances, sunscreens, and anti-infective agents, microsponge delivery systems offer versatility in formulating pharmaceutical and cosmetic products. These microscopic polymeric beads,

often smaller than a particle of talcum powder, hold the promise of revolutionizing skincare and dermatological treatments. [6-8] By providing a platform for controlled and sustained release of active ingredients, microsponge technology not only improves therapeutic outcomes but also enhances patient comfort and compliance. In the following discussion, we delve deeper into the design principles, mechanisms of action, and potential applications of microsponge delivery systems in pharmaceutical and cosmetic formulations.[9]

EXPERIMENTAL PREFORMULATION STUDIES :

Preformulation testing represents the initial stage in the systematic development of drug dosage forms, encompassing an exploration of the physical and chemical properties of the drug substance both independently and when combined with excipients. Its overarching aim is to furnish the formulator with pertinent data for crafting stable and bioavailable dosage forms that can be produced on a large scale. [10] Through comprehensive examination of physicochemical attributes, preformulation testing aids in informing formulation design decisions, guiding molecular modifications if necessary, and validating the feasibility of the compound's development by identifying potential barriers. This phase lays the foundation for subsequent formulation processes, facilitating the creation of effective and commercially viable pharmaceutical products.[11]

1 Characterization of Ketoconazole Pure Drug:

1.1 UV spectroscopy: (Determination of λ max)

Stock solutions of the drugs, each at a concentration of 100µg/mL in methanol for Ketoconazole, were prepared. These stock solutions were then diluted with the appropriate solvents to achieve a concentration of 20µg/mL. Subsequently, UV spectra were recorded using a Schimadzu 1700 UV spectrophotometer within the wavelength range of 200-400 nm to determine the λmax.

1.2 IR Spectroscopy

The spectrum was captured within the wavelength range of 4000 to 400 cm-1. A homogeneous mixture of the drug and potassium bromide was prepared and loaded evenly into the die cavity of the sample holder. Subsequently, an IR spectrum was obtained using a diffuse reflectance FTIR spectrophotometer.

2 Construction of Calibration Curve for Drugs

To prepare the stock solution (100 µg/mL), 10 mg of the Ketoconazole drug was dissolved in methanol within a 100 mL volumetric flask. From this stock solution, various concentrations ranging from 2 to 20 µg/mL were prepared through proper dilution. The absorbance of these solutions against the respective blank solvents was measured specifically at 245 nm for Ketoconazole.

3 DRUG-EXCIPIENT COMPATIBILITY STUDIES

Drug-excipient compatibility studies were conducted over a period of one month. The drug, in combination with excipients Eudragit RS 100 and PVA, underwent storage under two conditions: at room temperature and at an elevated temperature of 45°C with 75% relative humidity in a stability chamber. At intervals of 7, 14, 21, and 30 days, samples were retrieved to assess various parameters.

4 FORMULATION DEVELOPMENT OF MICROSPONGES [12-13]

4.1 Free Radical Polymerization Reactions: Fundamentals

Addition polymers can be formed from monomers containing C=C double bonds, and many of these compounds undergo spontaneous polymerization unless actively inhibited. One common method to catalyze the polymerization reaction leading to an addition polymer involves introducing a source of free radicals to the monomer. Free radicals are highly reactive, short-lived species within a reaction, possessing one or more unpaired electrons. In the presence of free radicals, addition polymers form via a chain reaction mechanism involving initiation, propagation, and termination steps.

4.2 Quasi-emulsion solvent diffusion method

Employed to create Eudragit microsponges, the inner phase is prepared by dissolving Eudragit RS 100 in 3 mL of methanol, with the addition of triethylcitrate (TEC) at 20% of the polymer to enhance plasticity. The drug is then incorporated into the solution and dissolved with ultrasonication at 35°C. This inner phase is combined with a solution of PVA (72000) in 200 mL of water (outer phase). The resulting mixture is stirred for 60 minutes and then filtered to isolate the microsponges, which are subsequently washed and dried at 40°C for 24 hours. Seven different ratios of drug to Eudragit RS 100 (ranging from 1:1 to 13:1) are utilized to investigate the impact of drug-polymer ratio on the physical characteristics and dissolution properties of the microsponges, with agitation speed maintained at 500 rpm using three-blade propeller stirrers.

Constituents	**Ketoconazole Microsponges**						
	F17	F18	F19	F20	F21	F22	F23
Inner phase							
Ketoconazole	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Eudragit RS 100 (g)	2.5	0.83	0.50	0.36	0.28	0.23	0.19
Methanol (mL)	3	3	3	3	3	3	3
Outer phase							
Distilled water (mL)	200	200	200	200	200	200	200
PVA 72000 (mg)	50	50	50	50	50	50	50

Table no.01: Microsponge formulations using Eudragit RS100

5 EVALUATION OFMICROSPONGES [14-15]

The production yield of the microparticles was determined by accurately measuring the initial weight of the raw materials and the final weight of the microsponge obtained, as described by Kilicarslan (2003). To calculate the loading efficiency (%) of the microsponges, various parameters were assessed. Particle size analysis was conducted using a Malvern Particle Size Analyzer Hydro 2000 MU (A), where the microsponges were dispersed in double-distilled water before analysis to ensure optimal signal detection. Scanning Electron Microscopy (SEM) was employed to examine the morphology and surface topography of the prepared microsponges, after coating them with platinum at room temperature. FTIR spectroscopy was performed using a Perkin Elmer Spectrum 100 FT-IR spectrometer to analyze the samples in the wavelength range of 4000 to 400 cm-1, with a sample dispersion ratio of 1:100 in potassium bromide. Differential Scanning Calorimetry (DSC) was carried out using a TA4000 Mettler DSC instrument, with samples heated at a constant rate of 5°C/min in an inert nitrogen atmosphere. Powder X-ray Diffraction (PXRD) studies were conducted to characterize the crystalline forms of the samples, distinguishing between crystalline and amorphous structures based on diffraction patterns. Characterization of pore structure was achieved through physical and chemical gas adsorption and mercury intrusion porosimetery (MIP), with pore size distributions determined by plotting incremental intrusion volumes against pore diameters using the Washburn equation. In-vitro release studies of microsponges involved placing accurately weighed loaded microsponges in solvent-containing glass bottles and horizontally shaking them at 37°C, with aliquot samples withdrawn at predetermined intervals and analyzed UV spectrophotometrically. Stability profiles of the microsponge formulations were evaluated according to ICH and WHO guidelines, involving exposure to normal and accelerated conditions of temperature and humidity over a 6-month period, with samples analyzed for physical changes and in-vitro release profiles at monthly intervals.

6 FORMULATION OF GEL LOADED WITH MICROSPONGES AND PLAIN DRUG

Ingredients	Quantity (% w/w)
Drug (free or entrapped, equivalent to)	Ketoconazole: 1
Propylene glycol	40
Methanol	8
Menthol	0.04
Methyl paraben	0.18
Sodium metabisulphite	0.10
Disodium edentate	0.10
Carbopol 934	1.00
Triethanolamine	q. s.
Purified water q. s. to make	100

Table no 02: Composition of gels

A clear dispersion of Carbopol was meticulously prepared in water using moderate agitation, with intermittent sprinkling of Carbopol to prevent lump formation and ensure a clear homogeneous dispersion. For the drug or drug-containing microsponge formulation, Propylene glycol and methanol were used as solvents. Additional ingredients such as paraben, sodium metabisulfite, and disodium edetate were dissolved in water and added to the drug solvent system. Triethanolamine was employed for neutralization, and the final weight was adjusted with water. The formulated gels underwent degassing via ultrasonication.

Evaluation of the gel loaded with microsponges and plain drug involved several assessments. Viscosity was determined using a Brookfield Viscometer with Spindle type 93/T-Cwere withdrawn at suitable intervals from the receptor compartment for spectrophotometric analysis. Safety considerations were addressed through Draize skin irritation testing, comparing the irritation potential of gels containing free drug and drugs entrapped in microsponges with a marketed gel, using a Draize patch test on rabbits in accordance with CPCSEA guidelines. Additionally, the antifungal activity of Ketoconazole and Ketoconazole from the optimized microspongy-gels, free forms, and marketed formulations was assessed using Candida albicans via the cup plate method, with mean inhibition zones calculated as indicators of antifungal activity. Ethical approval for animal experimentation was obtained from the Institutional Animal Ethical Committee, ensuring compliance with established protocols and standards.

RESULT AND DISUSSION

PREFORMULATIONSTUDY

Characterization of Ketoconazole Pure Drug Ketoconazole

Sr. No.	Characters	Specification	Result
1.	Description	Nearly white crystalline powder	Nearly white crystalline powder
2.	Melting point	137-138°C	137-138°C
3.	Solubility	Soluble in methanol; sparingly soluble in ethanol, chloroform, and acetone; and very slightly soluble in water	Soluble in methanol; sparingly soluble in ethanol, chloroform, and acetone; and very slightly soluble in water

SPECTROSCOPIC STUDIES

UV Spectroscopy: (Determination of λ_{max})

The UV spectrum of Ketoconazole in methanol were scanned and λmax. Was 245 nm.

IR Spectroscopy: IR Spectra of Ketoconazole in their pure form was recorded. Results are depicted in Table no. 03

Functional group	Wave number observed (cm^{-1})
C-H (methylene, CH2)	2959
C=N	1474, 1455
N-O (of cis isomer)	1330 – 1384
C-H (aromatic)	3139 – 3059

Table no. 03: IR spectrum interpretation of Ketoconazole

7 CONSTRUCTION OF CALIBRATION CURVE

Calibration curve of Ketoconazole

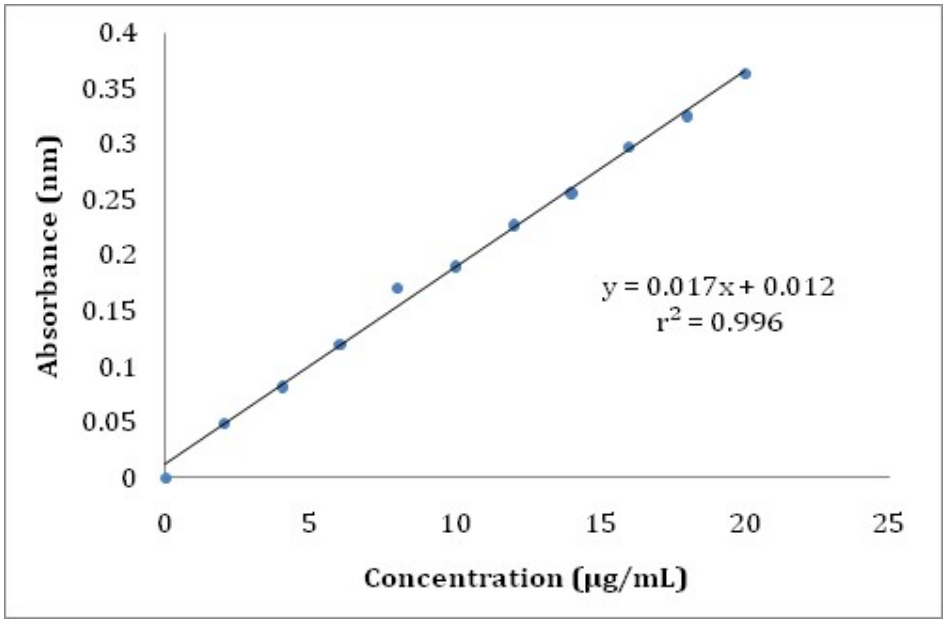

Figure no. 01: Calibration curve of Ketoconazole

8 DRUG-EXCIPIENT COMPATIBILITYSTUDIES

8.1Physical Change

No physical changes such as discoloration; change in texture etc. were observed during compatibility study.

8.2 FTIR Study

FTIR spectra of all the three 'pure drugs' and 'drug entrapped microsponges' were compared to study incompatibility of drugs with excipients and reaction conditions. Principal peaks of microsponge-entrapped drugs were compared with peaks of pure drugs to know about whether they are concordant with each other. Overlay FTIR spectra of pure and entrapped drugs are shown in Figure no. 02 .

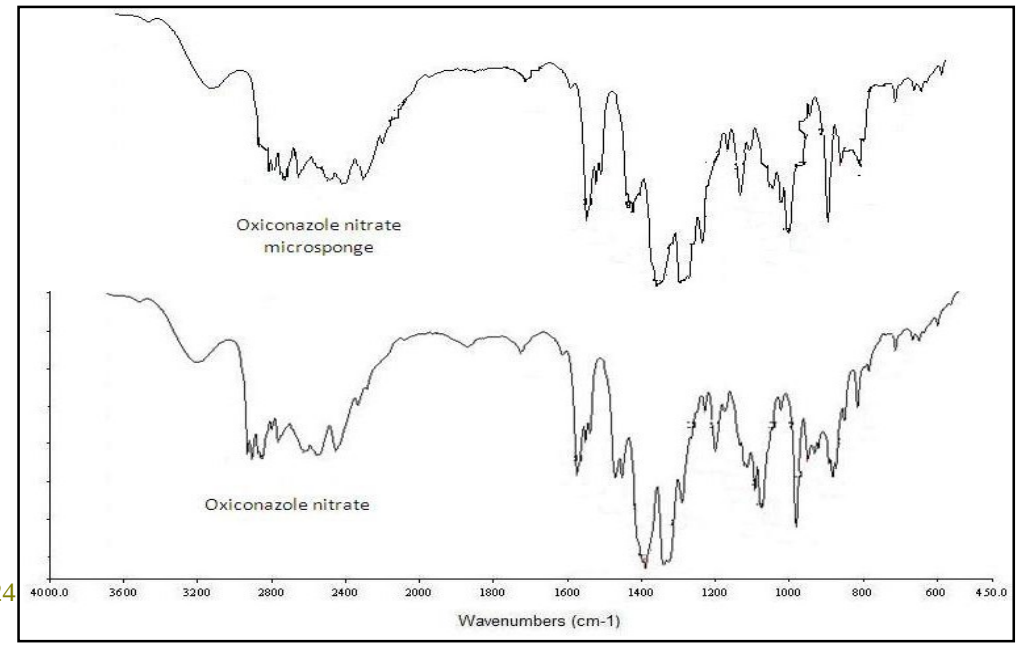

Figure no. 02: Compatibility study of Ketoconazole by IR

Principle peaks of drugs were observed retained; broadening of peaks may be due to overlapping of peaks of polymer system and drug in microsponge formulation.

10 EVALUATION OF MICROSPONGES

10.1 Production Yield

Formulation code	Production yield (%)
F17	70.76±1.07
F18	73.67±1.87
F19	77.98±2.54
F20	82.98±2.28
F21	83.78±1.07
F22	88.76±1.18
F23	90.87±2.08

Table no. 04: Production yield of Ketoconazole microsponge

*Each value is average of three separate determinations ±SD

production yield of Ketoconazole microsponges were between 70.76 to 90.87 % (Table no.04). In case of Eudragit RS 100 microsponges, it was revealed that, by increasing drug: polymer ratio there is increase in the production yield of the microsponges.

10.2 Drug Loading Efficiency

Formulation code	Drug Loading efficiency (%)
F1	84.90±1.13
F2	83.28±0.18
F3	83.98±1.24
F4	85.8±2.03
F5	86.54±1.28
F6	84.32±0.68
F7	86.56±0.47
F8	88.07±2.17
F9	84.97±0.19

Table no. 05: Drug loading efficiency of Ketoconazole microsponge

formulations

*Each value is average of three separate determinations ±SD

Formulation code	Drug Loading efficiency (%)
F17	51.97±0.28
F18	63.87±2.84
F19	72.54±1.08
F20	70.56±1.84
F21	76.65±0.37
F22	80.65±1.86
F23	82.86 ±1.89

Table no. 06: Drug loading efficiency of Ketoconazole microsponge formulations

*Each value is average of three separate determinations ±SD

The loading efficiency was found to be high 51.97 to 86.56 % in Ketoconazole microsponges. In case of Eudragit RS 100 microsponges, it was found that as drug: polymer ratio increases, drug loading efficiency also increases, whereas in case of Salicylic acid microsponges, it was found that, there was no significant effect of concentration of divinylbenzene on production yield and drug loading efficiency.

10.3 Scanning Electron Microscopy

SEM images showed that Eudragit RS 100 microsponges prepared by quasi-emulsion solvent diffusion method (Ketoconazole) were comparatively less spherical. .

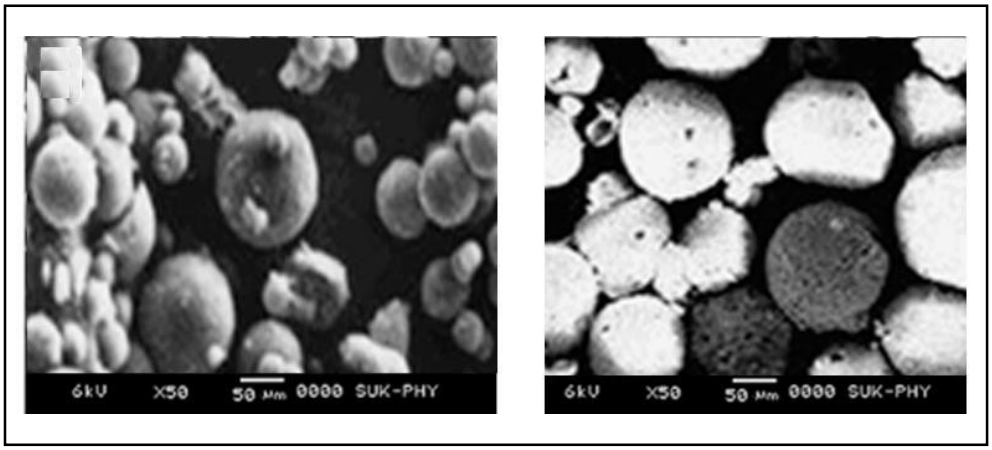

Figure no. 02 : SEM Photographs of Ketoconazole microsponges

10.4 Particle Size Analysis

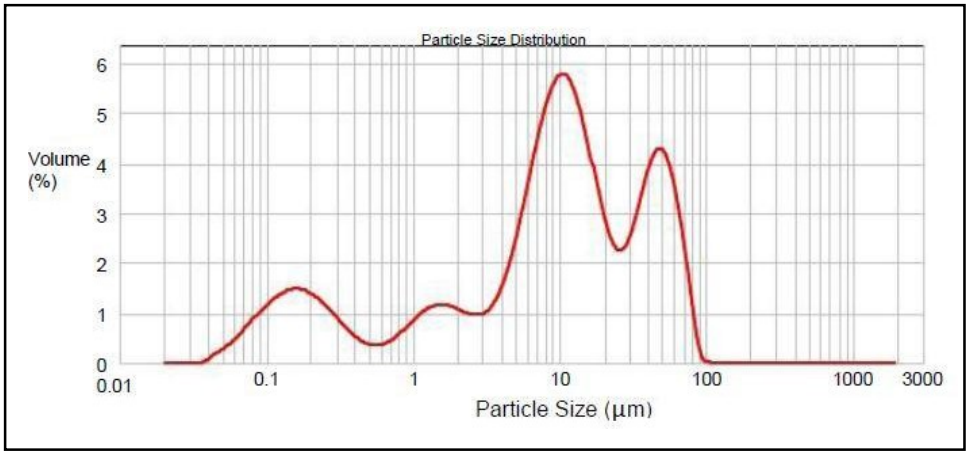

Figure no. 03 :Particle size distribution of Ketoconazole microsponges (Mean particle size10.11µm)

Free-flowing powders with fine aesthetic attributes are possible to obtain by controlling the size of particles during both the polymerization methods. Representative of the particle size distribution of Ketoconazole microsponge) is shown in Figure no. 03 The mean particle size of Ketoconazole was found to be 10.11 µm

10.5 Infrared Spectroscopy

FTIR spectra of Ketoconazole, Eudragit RS 100 and microsponges prepared by Eudragit method (F23) and overlay spectra are, as shown in Figure no. 04

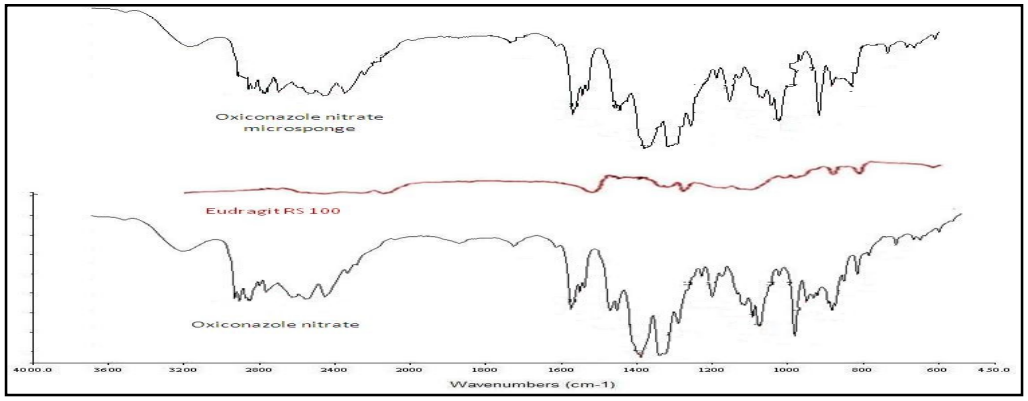

Figure no. 04: Overlay FTIR Spectra of: Ketoconazole, Eudragit RS 100 and Eudragit microsponges containing Ketoconazole

All characteristic peaks of drugs in the IR spectra of F23 formulations were observed to be concordant with respective pure drugs. Eudragit RS100 also showed an ester C=O stretching peak. These results showed that there was no chemical interaction or changes during microsponge preparation.

10.6 Differential Scanning Calorimetry (DSC)

The results of DSC were observed for the integrity of the drug in microsponge

formulation prepared by the entrapment process.

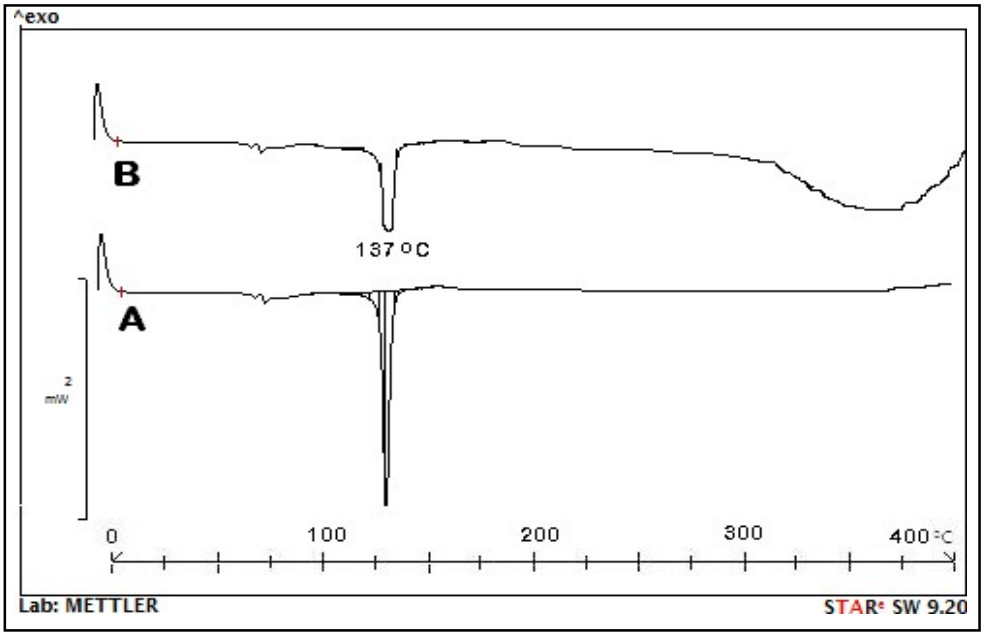

Figure no. 05 : Overlay DSC Thermograms of A: Pure Ketoconazole , B: Eudragit microsponges containing Ketoconazole

In the DSC curves of F23 formulations, characteristic peaks of, Ketoconazole and Eudragit RS 100 were seen. The thermograms of F23 formulation showed that there was no interaction between the drugs and the polymer.

10.7 Powder X-ray Diffraction Studies

X-ray powder diffraction study was done in order to get information on whether process conditions have triggered polymorphic modifications in the drug. Ketoconazole microsponges (F23) and overlay patterns are as shown in Figure no. 06.

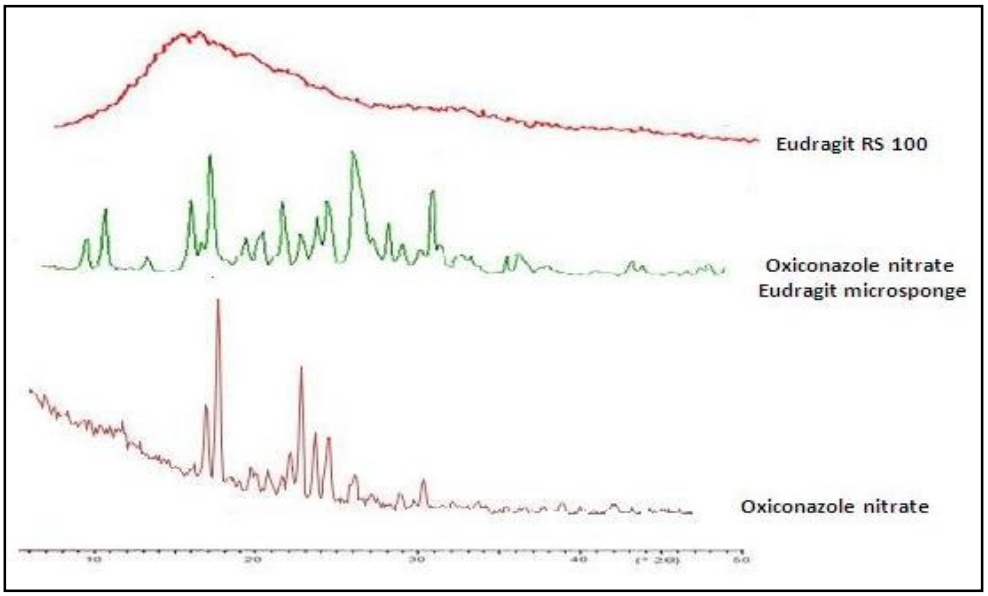

Figure no. 06: Overlay PXRD of: Ketoconazole, Ketoconazole microsponge and Eudragit RS 100

Overlain DSC thermograms, PXRDs of microspongic drugs, pure drugs and polymers revealed that drug peaks are retained but with decrease height, this is due to decreased quantity of drug in sample shared by polymers and may be due to partial amorphization of drugs.

***In-vitro* Release Study of Microsponge**

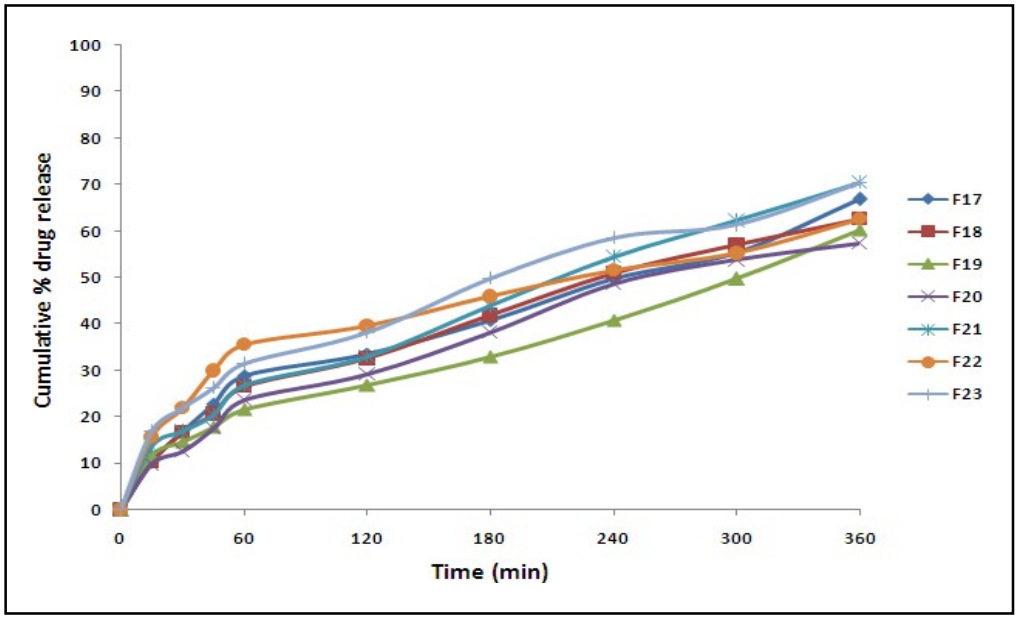

Figure no. 07: In-vitro drug release profiles of Ketoconazole microsponge formulations

The drug release profiles of the Ketoconazole microsponge formulations are illustrated in Figure no. 07. Drug release from Ketoconazole microsponge was found to range from 57.42 % to 70.55 % for all the formulations.

10.8 Stability Profile of Microsponge Formulation

The stability studies of MDS formulation revealed that no significant changes were observed in the physical parameters, when stored at temperature and humidity conditions of 40 ± 2°C and 75 ± 5% RH to access their long-term stability. The samples were withdrawn and retested for drug content at an interval of 30 days up to 6 months.

Sampling Interval	**Drug release (%) after 360 min***
	F23
0 month	70.42±0.81
1 month	69.26±1.69
2 month	70.39±0.27

3 month	70.31±1.81
4 month	69.14±1.38
5 month	70.17±0.57
6 month	70.21±0.29

Table no. 07: Drug release profile of formulation F23 before and after stability

*Each value is average of three separate determinations ±SD

The results indicated that no significant reduction in percentage drug release was observed over a period of 6 months; there fore no evidence of degradation of drug was observed.

11 EVALUATION OF GEL LOADED WITH MICROSPONGES AND PLAIN DRUG

11.1 Determination of Viscosity

Gel formulation	**Viscosity (cps)**
Gel containing F23 microsponge	351650±1.80
Gel containing free Ketoconazole	211584±1.30

Table no. 08: Viscosity of different gel formulations

*Each value is average of three separate determinations ±SD

Results of viscosity determination of gel showed that gel loaded with microsponge is more viscous than gel loaded with plain drug.

11.2 Drug Diffusion from Microspongic Gels

Percentage of drug released from diffusion studies during 6 hrs. from gels containing free drug, drug entrapped in microsponges (F23) are shown in Table no. 09 and in Figure no. 08

Time in minute		**Cumulative % drug released**
	Free Ketoconazole	**F23**
0	0	0

30	2.12±1.28	3.41±1.01
60	4.27±1.94	5.38±1.32
90	6.27±1.05	11.47±0.93
120	9.84±1.32	13.41±1.71
150	12.71±0.74	15.48±1.37
180	14.64±0.39	15.97±1.28
210	17.96±0.26	16.89±1.03
240	19.38±1.85	17.85±1.35
270	22.41±1.06	19.38±1.28
300	25.31±1.71	21.61±0.94
330	27.84±1.06	23.54±0.34
360	31.59±1.02	25.96±0.63

Table no.09 : Cumulative % drug released from gels loaded with pure drug and microsponge entrapped drug.

*Each value is average of three separate determinations ±S

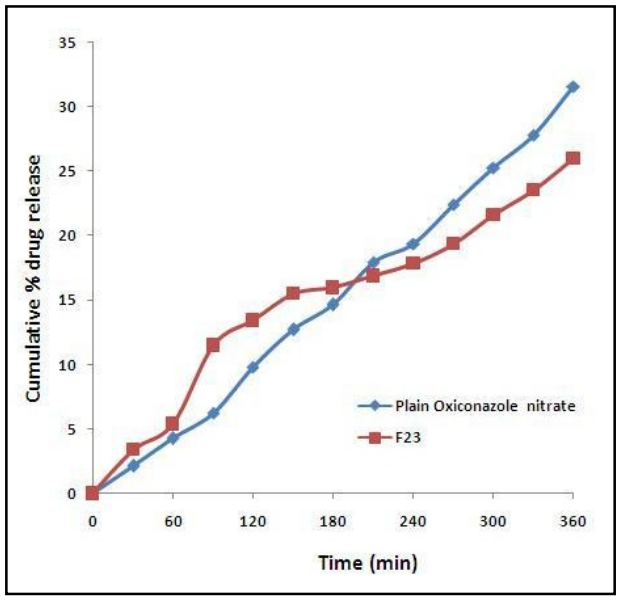

Figure no. 08: Drug release Vs Time plot of gels containing plain Ketoconazole and drug entrapped in F23 microsponges

Sr. No.	Kinetic model	F23
1.	First order	0.893
2.	**Higuchi**	**0.969**
3.	Korsemayer Peppas	0.959
4.	Hixon Crowell	0.969
5.	Zero order	0.962

Table no. 10: Kinetic study

11.3 Safety Considerations (Draize Skin Irritation Test)

Figure no. 09 shows photographs of primary skin irritation studies where Site 1 indicates positive control; Site 2 indicates test drug entrapped in the microsponges; Site 3 indicates marketed product and Site 4 indicates negative control

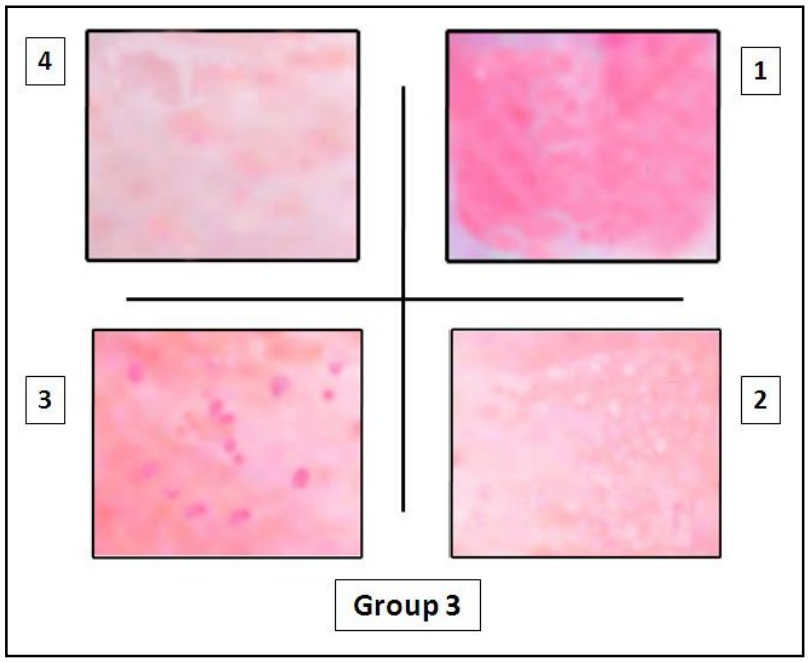

Figure no. 0: Photographs of skin irritation studies carried out on New Zealand rabbits: Group 3: Ketoconazole microsponge gel

Standard Calibration Curve of Ketoconazole using Cup Plate Method

Concentration of Ketoconazole (µg/mL)	Zone of inhibition in mm					Mean ± SD
500	10.1	11.5	10.6	10.3	10.5	10.1±0.54
750	13.5	14.6	13.4	13.5	14.8	13.4±0.68
1000	16.4	16.9	16.5	16.4	16.7	16.4±0.22
1250	19.2	18.7	18.7	19.6	18.6	18.6±0.43
1500	21.4	21.4	21.3	21.7	21.5	21.3±0.15
1750	24.6	24.5	24.6	23.3	24.8	23.3±0.60
2000	27.8	26.8	27.5	27.5	26.9	26.8±0.43

Table no. 11: Zone of inhibitions for standard Ketoconazole for calibration curve

CONCLUSION

Quasi-emulsion solvent diffusion has emerged as the preferred method for fabricating porous microparticles, with successful preparation demonstrated for Eudragit RS100 microsponges containing Ketoconazole. However, microsponges produced by this method were observed to be comparatively less spherical compared to those prepared by other means. Analysis of intrusion and extrusion curves revealed that the majority of pores present in Eudragit RS100 microsponges were of the spherical type, distinguishing them from regular microspheres due to their highly porous surface. This porous structure facilitates faster drug release through the pores, although Eudragit RS100 microsponges with smaller pore diameters exhibited slower and less drug release compared to styrene microsponge formulations in in-vitro studies, with all microsponges following zero-order reaction kinetics. Furthermore, gel formulations loaded with microsponges displayed higher viscosity than those loaded with plain drug, facilitating controlled drug release, which was best fitted to the Higuchi model. Importantly, gels containing microsponge-entrapped Ketoconazole and Ketoconazole retained higher antifungal activity compared to gels containing free drug and marketed formulations. Notably, during storage under accelerated conditions for 6 months, no significant changes in surface morphology or drug release were observed, indicating stability of the formulations. Additionally, gels containing free drug (marketed product) exhibited greater irritation compared to gels containing drug entrapped in microsponge delivery systems, highlighting the potential of the latter for minimizing irritation.

Acknowledgement

I would like to acknowledge and give my warmest thank to my guide Dr. Suresh Kumar Dev who made this work possible. His guidance and advice carried me through all the satges of writing my project.

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