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Research Article

Formulation And In-Vitro Evaluation of a Ketoconazole Microsponge Drug Delivery System for Enhanced Antifungal

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Abstract: This study focused on the synthesis and characterization of Ketoconazole microsponges using the quasi-emulsion solvent diffusion method, followed by a comprehensive evaluation of their properties and performance. The microsponges demonstrated high production yield, loading efficiency, and desirable particle size, with spectral analysis confirming characteristic drug peaks. Scanning Electron Microscopy (SEM) revealed distinct structural differences between styrene and Eudragit-based microsponges. Pore characterization indicated variation in pore types and porosity between the two formulations. Stability studies showed no significant morphological or drug release changes over six months of accelerated storage. Gel formulations incorporating microsponges exhibited enhanced viscosity and controlled drug release compared to gels containing the free drug alone. Antifungal assays indicated that microsponge-loaded gels maintained or improved efficacy relative to free drug gels and commercial formulations, along with reduced skin irritation. These findings highlight the potential of microsponge delivery systems for the topical administration of Ketoconazole, offering controlled release, reduced irritation, and potentially enhanced therapeutic outcomes.

Keywords: Microsponge drug delivery system, Ketoconazole, antifungal activity, quasi-emulsification technique.

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1. INTRODUCTION:

The release of drugs from microsponge-based gels was assessed in vitro using a Franz Diffusion cell. In this setup, gels containing either free or encapsulated drugs were placed in the donor compartment, allowing for precise monitoring of diffusion. Microsponge delivery systems represent a significant advancement in pharmaceutical and cosmetic sciences, providing a

controlled-release mechanism for active ingredients on the skin. These systems comprise finely engineered polymeric microspheres with uniform size, spherical shape, and porous structures, allowing effective entrapment and gradual release of therapeutic or cosmetic agents. Designed to address the limitations of traditional delivery methods, microsponge technology enables precise modulation of release kinetics, ensuring optimal therapeutic efficacy while minimizing side effects. Incorporating microsponges into various topical formulations—such as creams, lotions, and powders—enables targeted delivery to specific skin layers, enhancing drug penetration and prolonging activity. Capable of encapsulating a wide range of substances, including emollients, fragrances, sunscreens, and anti-infective agents, microsponge delivery systems offer versatility in formulating both pharmaceutical and cosmetic products. These microscopic polymeric beads, often smaller than a particle of talcum powder, hold promise for transforming skincare and dermatological treatments. By providing a platform for controlled and sustained release of active ingredients, microsponge technology not only enhances therapeutic outcomes but also improves patient comfort and compliance. This discussion explores the design principles, mechanisms of action, and potential applications of microsponge delivery systems in pharmaceutical and cosmetic formulations.

2. EXPERIMENTAL PREFORMULATION STUDIES:

Preformulation testing serves as the initial step in the systematic development of drug dosage forms, focusing on examining the physical and chemical characteristics of the drug substance alone and in combination with excipients. Its primary objective is to provide essential data that helps formulators design stable, bioavailable dosage forms suitable for large-scale production. Through a detailed analysis of the drug's physicochemical properties, preformulation testing informs formulation design, assists in identifying any necessary molecular adjustments, and assesses the feasibility of the drug's development by highlighting potential obstacles. This foundational stage supports the subsequent formulation process, paving the way for effective and market-ready pharmaceutical products.

A. CHARACTERIZATION OF KETOCONAZOLE PURE DRUG

1.1 UV Spectroscopy (Determination of λmax)

A stock solution of Ketoconazole was prepared at a concentration of 100 µg/mL in methanol. This solution was then diluted with appropriate solvents to achieve a concentration of 20 µg/mL. The UV spectra were recorded using a Shimadzu 1700 UV spectrophotometer within the wavelength range of 200-400 nm to identify the λmax.

1.2 IR Spectroscopy

The IR spectrum of Ketoconazole was recorded over a wavelength range of 4000 to 400 cm^{-1}. A homogeneous mixture of the drug and potassium bromide was prepared, loaded into the sample holder, and analyzed using a diffuse reflectance FTIR spectrophotometer.

IR Spectrum

- Wavenumber (cm^{-1})**:** The x-axis of an IR spectrum shows wavenumbers, which indicate the frequency of absorbed radiation. Wavenumbers range from approximately 4000 cm^{-1} to 400 cm^{-1}, where higher wavenumbers correspond to higher energy vibrations.
- Absorbance/Transmittance**:** The y-axis shows absorbance or transmittance. Peaks on the IR spectrum represent the frequencies at which the sample absorbs IR radiation.
- Fingerprint Region (600–1500 cm^{-1})**:** This is a unique region for each molecule, containing complex absorption patterns that can be used to identify substances.

B. CONSTRUCTION OF CALIBRATION CURVE FOR KETOCONAZOLE

A 100 µg/mL stock solution of Ketoconazole was prepared by dissolving 10 mg of the drug in methanol within a 100 mL volumetric flask. Various concentrations (2 to 20 µg/mL) were then prepared through serial dilutions. The absorbance of each solution was measured at 245 nm against the corresponding blank solvent.

Preparation of Standard Solutions

- Prepare a series of standard solutions of ketoconazole with known concentrations. Typically, this involves diluting a stock solution of ketoconazole with an appropriate solvent (e.g., methanol, acetonitrile, or a buffer) to obtain concentrations within a linear range suitable for detection.

Selection of Analytical Method

- Choose an appropriate analytical method, often UV-Visible spectrophotometry or HPLC, depending on the required sensitivity and specificity. For HPLC, select suitable conditions such as column type, mobile phase composition, flow rate, and detection wavelength.

Measurement of Absorbance/Peak Area

- For each standard solution, measure the absorbance if using UV spectrophotometry, or record the peak area if using HPLC. Ensure consistent measurement parameters to maintain accuracy.

Plotting the Calibration Curve

- Plot a graph with ketoconazole concentration on the x-axis and absorbance (or peak area) on the y-axis.
- For an accurate calibration curve, ensure at least 5-6 different concentrations, evenly spaced, to capture the linear relationship.

Linear Regression Analysis

- Perform a linear regression analysis on the data points to derive the best-fit line equation: y=mx+cy = mx + cy=mx+c, where:
  - y= absorbance or peak area
  - m = slope of the line

- x = concentration
- c= y-intercept

● Calculate the correlation coefficient (R^2) to confirm the linearity of the curve. An R^2 value close to 1.0 indicates good linearity.

Validation of the Calibration Curve

Validate the calibration curve by checking parameters such as linearity, precision, and accuracy according to the International Council for Harmonisation (ICH) guidelines or other relevant regulatory standards.

C. DRUG-EXCIPIENT COMPATIBILITY STUDIES

Compatibility studies between Ketoconazole and the excipients Eudragit RS 100 and PVA were conducted over one month. Samples of the drug-excipient mixtures were stored at both room temperature and at 45°C with 75% relative humidity in a stability chamber. Samples were retrieved on days 7, 14, 21, and 30 to assess compatibility through various parameters.

3. FORMULATION DEVELOPMENT OF MICROSPONGES

a. Free Radical Polymerization Reactions: Fundamentals

Addition polymers are synthesized from monomers with C=C double bonds, many of which spontaneously polymerize if not actively inhibited. A common approach to catalyze this reaction and form addition polymers is to introduce a source of free radicals to the monomer mixture. Free radicals are highly reactive and short-lived species that contain one or more unpaired electrons. In the presence of free radicals, the formation of addition polymers follows a chain reaction mechanism with three stages: initiation, propagation, and termination.

b. Quasi-emulsion Solvent Diffusion Method

To prepare Eudragit microsponges, the inner phase is created by dissolving Eudragit RS 100 in 3 mL of methanol, with triethylcitrate (TEC) added at 20% of the polymer to improve plasticity. The drug is then added to this solution and dissolved via ultrasonication at 35°C. This inner phase is combined with an outer phase, which consists of PVA (72,000) dissolved in 250 mL of water. The mixture is stirred for 60 minutes and then filtered to isolate the microsponges, which are washed and dried at 40°C for 24 hours. Seven different drug-to-Eudragit RS 100 ratios (from 1:1 to 13:1) are used to study the effect of drug-polymer ratios on the physical characteristics and dissolution properties of the microsponges, with agitation speed set at 500 rpm using a three-blade propeller stirrer.

Table no.1: Microsponge formulations using Eudragit RS100

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)	250	250	250	250	250	250	250
PVA 72000 (mg)	50	50	50	50	50	50	50

4. EVALUATION OF MICROSPONGES

The production yield of the microsponges was determined by comparing the initial weight of raw materials with the final weight of the obtained product, following the method described by Kilicarslan (2003). To calculate the loading efficiency (%) of the microsponges, various parameters were analyzed. Particle size was assessed using a Malvern Particle Size Analyzer Hydro 2000 MU (A), with the microsponges dispersed in double-distilled water to optimize signal clarity. Scanning Electron Microscopy (SEM) was employed to investigate the morphology and surface characteristics, following platinum coating of the microsponges at room temperature.

Fourier-Transform Infrared (FTIR) spectroscopy was performed on a Perkin Elmer Spectrum 100 FT-IR spectrometer, analyzing samples across a wavelength range of 4000 to 400 cm^{-1} with a sample dispersion ratio of 1:100 in potassium bromide. Differential Scanning Calorimetry (DSC) analysis was conducted using a TA4000 Mettler DSC instrument, where samples were heated at a constant rate of 5°C/min in an inert nitrogen atmosphere. Powder X-ray Diffraction (PXRD) was used to differentiate crystalline from amorphous forms by analyzing diffraction patterns. Pore structure characterization was conducted via gas adsorption and mercury intrusion porosimetry (MIP), with pore size distribution determined using the Washburn equation by plotting incremental intrusion volumes against pore diameters.

In vitro release studies were carried out by placing accurately weighed microsponges in solvent-containing glass bottles, followed by horizontal shaking at 37°C. Aliquot samples were withdrawn at set intervals and analyzed via UV spectrophotometry. Stability testing of the microsponge formulations followed ICH and WHO

guidelines, assessing stability under normal and accelerated temperature and humidity conditions over a six-month period. Physical changes and in vitro release profiles were monitored monthly.

5. FORMULATION OF GEL CONTAINING MICROSPONGE-LOADED AND FREE DRUG:

Table no 2: Composition of gels

Sr. No	Ingredients	Quantity (% w/w)
1.	Drug (free or entrapped, equivalent to)	Ketoconazole: 1
2.	Propylene glycol	40
3.	Methanol 8	8
4.	Menthol	0.04
5.	Methyl paraben	0.18
6.	Sodium metabisulphite	0.10
7.	Disodium edentate	0.10
8.	Carbopol 934	1.00
9.	Triethanolamine q. s.	q. s.
10.	Purified water	q. s. to make 100

A clear Carbopol dispersion was carefully prepared in water with moderate stirring, ensuring uniform sprinkling of Carbopol to prevent clumping and achieve a smooth, homogeneous mixture. Propylene glycol and methanol were used as solvents for the drug or drug-loaded microsponge formulation. Additional ingredients, including paraben, sodium metabisulfite, and disodium edetate, were dissolved in water and added to the solvent mixture. Triethanolamine was added for neutralization, and the final volume was adjusted with water. The formulated gels were then degassed by ultrasonication.

The gels containing microsponges and plain drug were subjected to various evaluations. Viscosity was measured using a Brookfield Viscometer with spindle type 93/TC. Samples were withdrawn at appropriate intervals from the receptor compartment for spectrophotometric analysis. Safety was assessed using Draize skin irritation testing, comparing the irritation potential of gels with free drug and those with drug-loaded microsponges to a marketed gel, following the Draize patch test on rabbits as per CPCSEA guidelines. Additionally, the antifungal efficacy of Ketoconazole, both in its free form and within the optimized microspongy-gel formulation, as well as in marketed products, was tested against *Candida albicans* using the cup plate method, with mean inhibition zones calculated as indicators of antifungal activity. Ethical clearance for animal studies was obtained from the Institutional Animal Ethical Committee, ensuring adherence to established protocols and standards.

6. RESULTS AND DISCUSSION:

a. Preformulation Study of Ketoconazole Characterization

Table No. 3 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

b. Spectroscopic Studies

UV Spectroscopy: (Determination of λmax)

The UV spectrum of Ketoconazole dissolved in methanol was analyzed, revealing a λmax of 245 nm.

IR Spectroscopy:

The IR spectra of pure Ketoconazole were recorded, and the results are presented in Table No. 4.

Table no. 4: IR spectrum interpretation of Ketoconazole

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

7. CONSTRUCTION OF CALIBRATION CURVE

Calibration curve of Ketoconazole

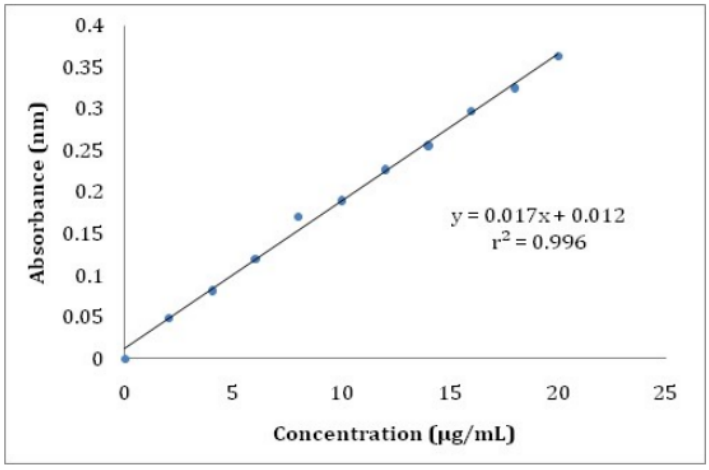

Figure no. 1: Calibration curve of Ketoconazole

8. DRUG-EXCIPIENT COMPATIBILITY STUDIES

a. Physical Changes

No significant physical changes, such as discoloration or alterations in texture, were observed during the compatibility study.

b. FTIR Analysis

The FTIR spectra of the three pure drugs and the drug-entrapped microsponges were compared to assess any incompatibility between the drugs and excipients under the reaction conditions. The principal peaks of the microsponge-entrapped drugs were evaluated against those of the pure drugs to determine their concordance. The overlay of the FTIR spectra for both the pure and entrapped drugs is illustrated in Figure 02.

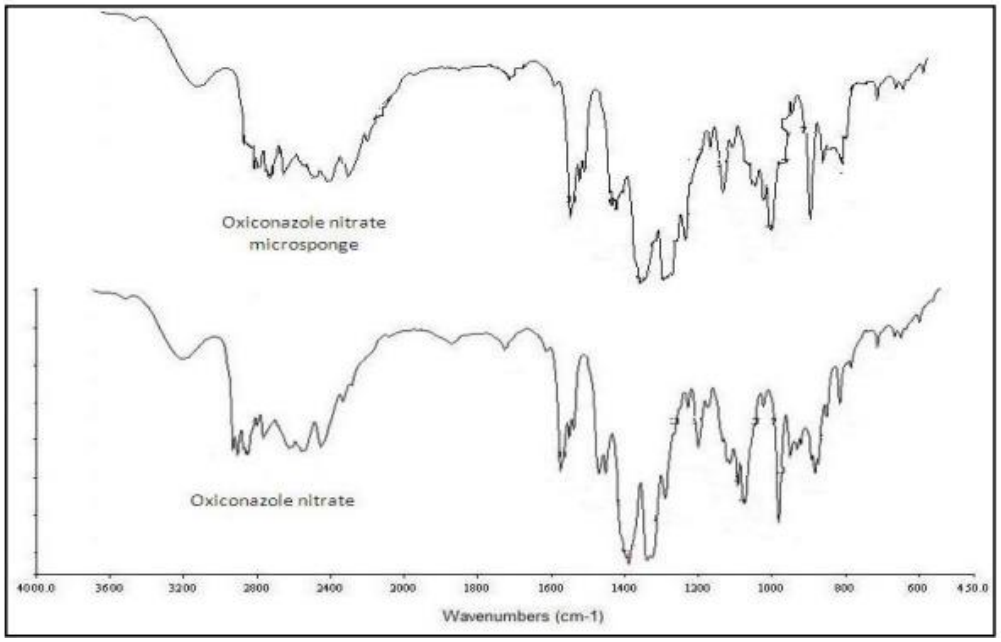

Figure no. 02: Compatibility study of Ketoconazole by IR

The main peaks of the drugs were retained, while the broadening of these peaks may result from the overlap between the peaks of the polymer system and the drug in the microsponge formulation.

9. EVALUATION OF MICROSPONGES

a. Production Yield

Table no. 5: Production yield of Ketoconazole microsponge

Formulation code	Production yield (%)
F17	70.60±1.07
F18	73.57±1.87
F19	77.88±2.54
F20	82.68±2.28
F21	83.79±1.07
F22	88.77±1.18
F23	90.86±2.08

Each value represents the average of three independent determinations ±SD. The production yield of ketoconazole microsponges ranged from 70.60% to 90.86% (Table 5). For Eudragit RS 100 microsponges, an increase in the drug-to-polymer ratio was associated with a higher production yield of the microsponges.

b. Drug Loading Efficiency:

Table no. 6: Drug loading efficiency of Ketoconazole microsponge formulations

Formulation code	Drug Loading efficiency (%)
F17	51.60±0.28
F18	63.85±2.84
F19	72.50±1.08
F20	70.55±1.84
F21	76.62±0.37
F22	80.64±1.86
F23	82.80 ±1.89

*Each value is average of three separate determinations ±SD

The loading efficiency in Ketoconazole microsponges was observed to be high, ranging from 51.60% to 82.80%. For Eudragit RS 100 microsponges, an increase in the drug-to-polymer ratio corresponded with a rise in drug loading efficiency. However, in the case of Salicylic acid microsponges, the concentration of divinylbenzene showed no significant impact on production yield or drug loading efficiency.

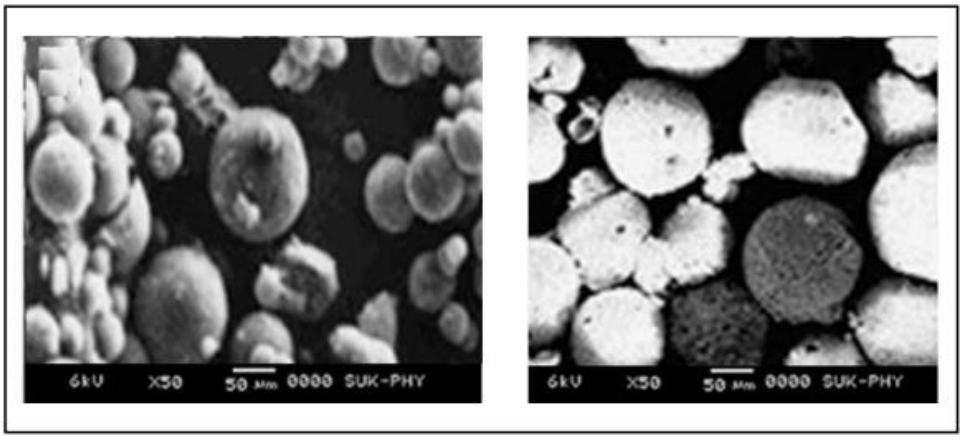

Figure no. 3 : SEM Photographs of Ketoconazole microsponges

c. Particle Size Analysis:

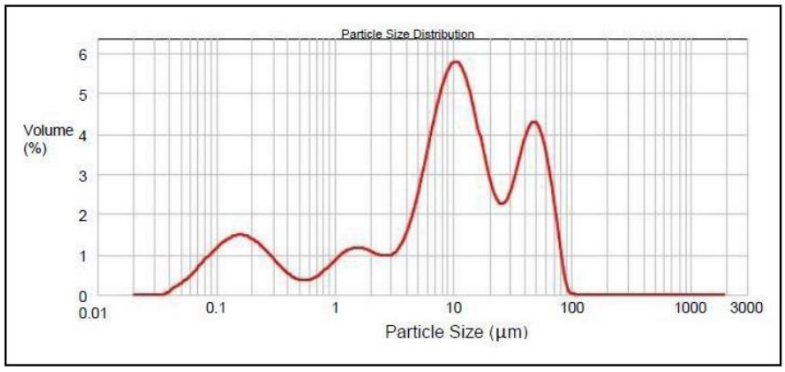

Figure no. 4: Particle size distribution of Ketoconazole microsponges (Mean particle size10.11µm)

Free-flowing powders with desirable aesthetic properties can be achieved by controlling particle size throughout the polymerization process. Figure 04 illustrates the particle size distribution of Ketoconazole microsponge. The average particle size of Ketoconazole was determined to be 10.11 µm.

d. Infrared Spectroscopy

The FTIR spectra of Ketoconazole, Eudragit RS 100, and the microsponges prepared using the Eudragit method (F23), along with the overlay spectra, are presented in Figure 5.

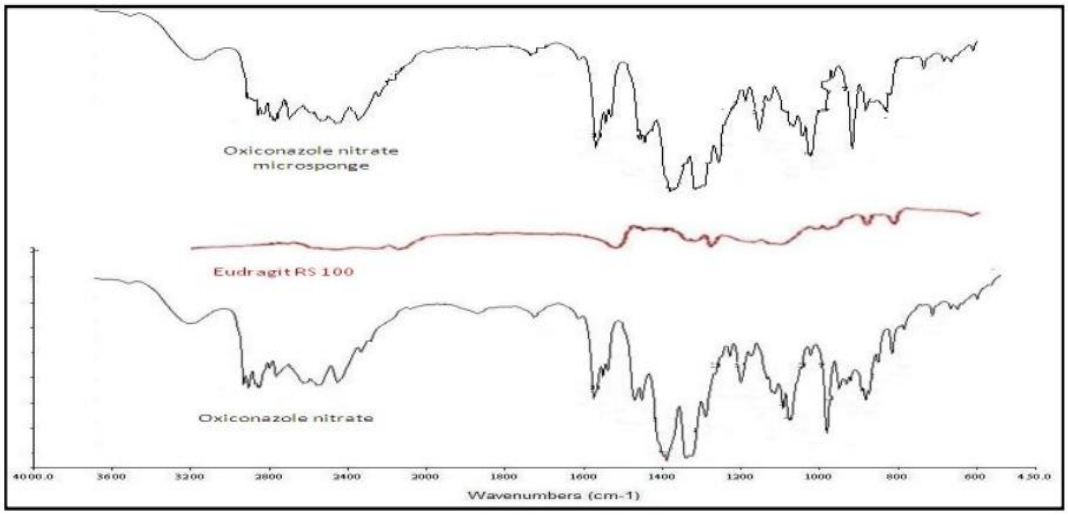

Figure no. 5: Overlay FTIR Spectra of: Ketoconazole, Eudragit RS 100 and Eudragit microsponges containing Ketoconazole

The IR spectra of the F23 formulations displayed all characteristic peaks of the drugs, aligning with those of the pure drugs. Additionally, Eudragit RS100 exhibited a distinct ester C=O stretching peak. These findings indicate that no chemical interactions or alterations occurred during the preparation of the microsponges.

e. Differential Scanning Calorimetry (DSC)

DSC analysis was conducted to assess the stability and integrity of the drug within the microsponge formulation created through the entrapment process.

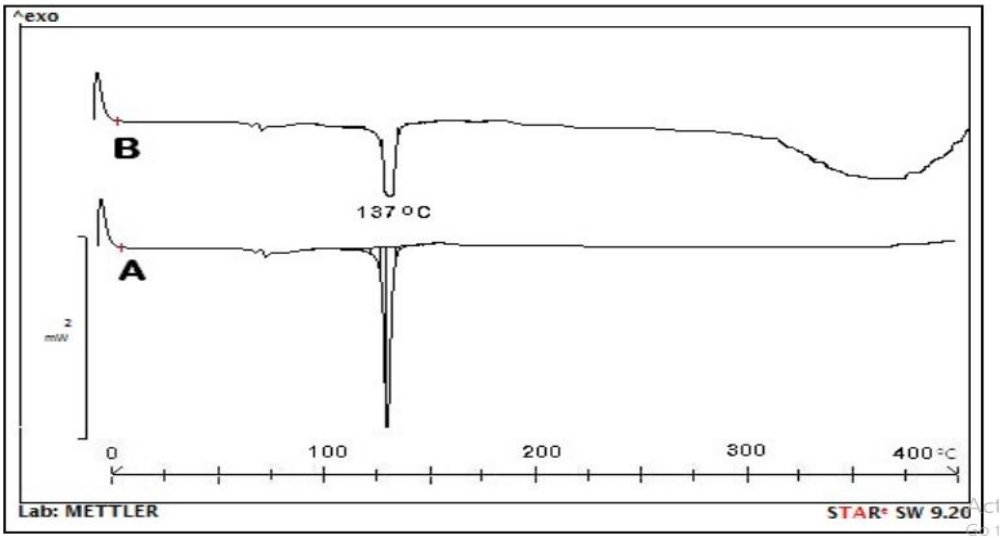

Figure no. 06 : Overlay DSC Thermograms of A: Pure Ketoconazole , B: Eudragit microsponges containing Ketoconazole

In the DSC curves for the F23 formulations, characteristic peaks corresponding to Ketoconazole and Eudragit RS 100 were observed. The thermograms for the F23 formulation indicated no interaction between the drug and the polymer.

f. Powder X-ray Diffraction Studies

A powder X-ray diffraction analysis was conducted to assess whether the process conditions induced any polymorphic modifications in the drug. The diffraction patterns for Ketoconazole microsponges (F23) and their overlay are presented in Figure 7.

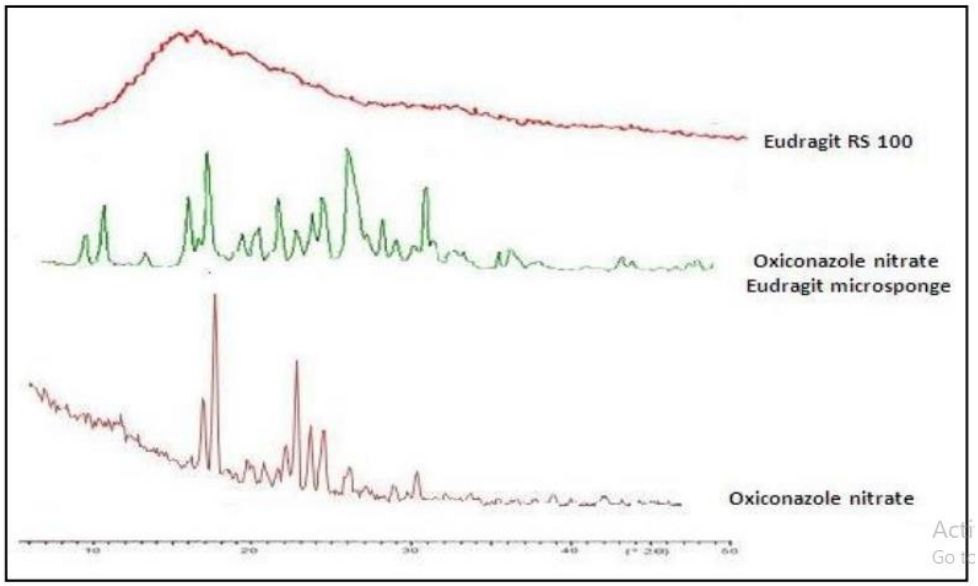

Figure 07: Overlay PXRD of Ketoconazole, Ketoconazole Microsponge, and Eudragit RS 100

The overlaid DSC thermograms and PXRD patterns of the microspongic drugs, pure drug, and polymer demonstrate retention of drug peaks, though with reduced intensity. This reduction in peak height likely results from the decreased drug content within the sample, distributed among the polymer matrix, and potentially from partial amorphization of the drug.

g. In-vitro Release Study of Microsponge

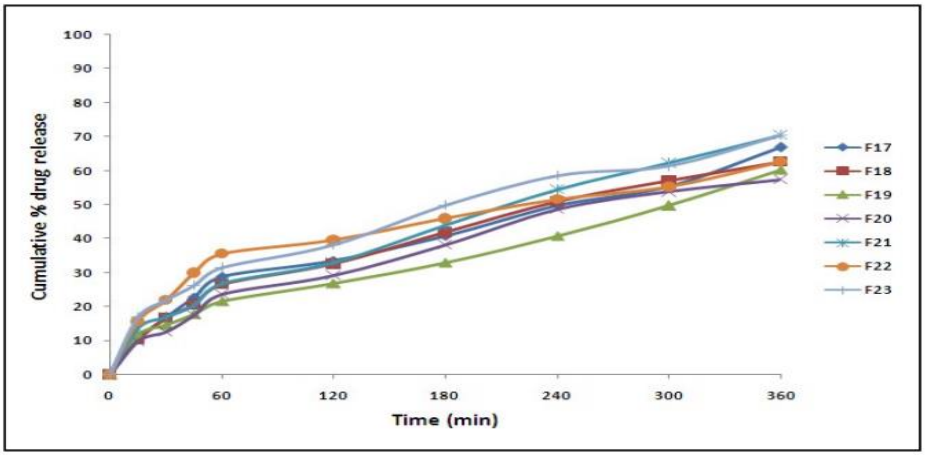

Figure no. 8: In-vitro drug release profiles of Ketoconazole microsponge formulations

The drug release profiles of the Ketoconazole microsponge formulations are shown in Figure 8, with drug release ranging from 57.42% to 70.55% across all formulations.

h. Stability Profile of Microsponge Formulation

The stability study of the MDS formulation demonstrated that there were no significant changes in physical parameters when stored under conditions of 40 ± 2°C temperature and 75 ± 5% relative humidity to evaluate long-term stability. Samples were withdrawn and analyzed for drug content at 30-day intervals over a period of six months.

Table no. 8: Drug release profile of formulation F23 before and after stability

Sampling Interval	Drug release (%) after 360 min*
	F23
0 month	70.41±0.81
1 month	69.26±1.69
2 month	70.40±0.27
3 month	70.33±1.81
4 month	69.15±1.38
5 month	70.18±0.57
6 month	70.25±0.29

*Each value represents the average of three separate determinations ± SD. The results showed no significant reduction in the percentage of drug release over a 6-month period, indicating no evidence of drug degradation.

11. EVALUATION OF GEL LOADED WITH MICROSPONGES AND PLAIN DRUG

a. Determination of Viscosity

Table no. 9: Viscosity of different gel formulations

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

Each value represents the average of three independent measurements ± SD. The viscosity analysis revealed that the gel containing microsponge exhibits greater viscosity compared to the gel containing the plain drug.

b. Drug Diffusion from Microspongic Gels

The percentage of drug released during diffusion studies over a 6-hour period from gels containing free drug and drug entrapped in microsponges (F23) is presented in Table 09 and illustrated in Figure 9.

Table no.10: Cumulative % drug released from gels loaded with pure drug and microsponge entrapped drug.

Time in minute	Cumulative % drug released	
	Free Ketoconazole	F23
0	0	0
30	2.13±1.28	3.42±1.01
60	4.28±1.94	5.28±1.32
90	6.28±1.05	11.48±0.93
120	9.85±1.32	13.44±1.71
150	12.77±0.74	15.48±1.37
180	14.68±0.39	15.98±1.28
210	17.92±0.26	16.90±1.03
240	19.25±1.85	17.88±1.35
270	22.44±1.06	19.40±1.28
300	25.32±1.71	21.65±0.94
330	27.88±1.06	23.55±0.34
360	31.62±1.02	25.98±0.63

*Each value is average of three separate determinations ±S

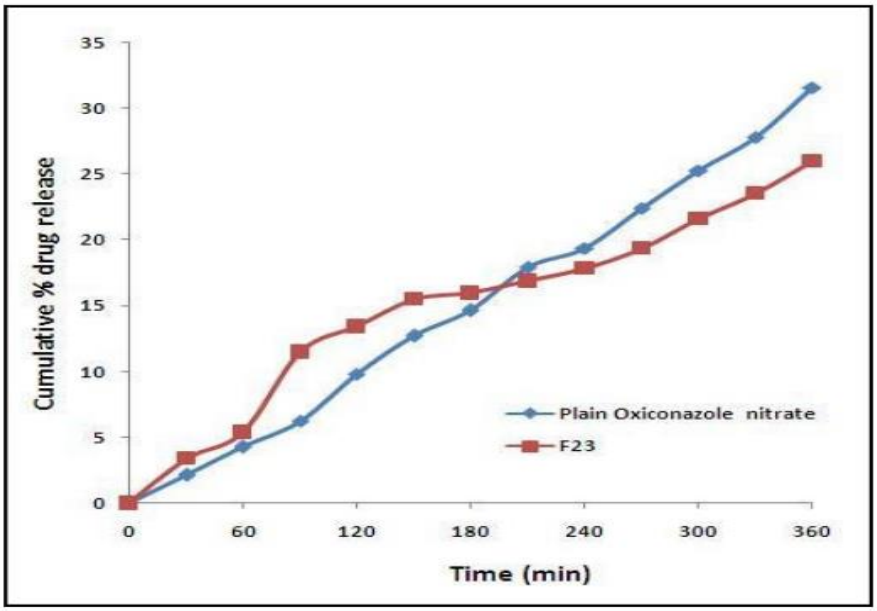

Figure no. 9: Drug release Vs Time plot of gels containing plain Ketoconazole and drug entrapped in F23 microsponges

Table no. 11: Kinetic study

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

c. Safety Considerations (Draize Skin Irritation Test)

Figure 10 presents photographs from primary skin irritation studies, where Site 1 represents the positive control, Site 2 represents the test drug encapsulated within microsponges, Site 3 represents the marketed product, and Site 4 represents the negative control.

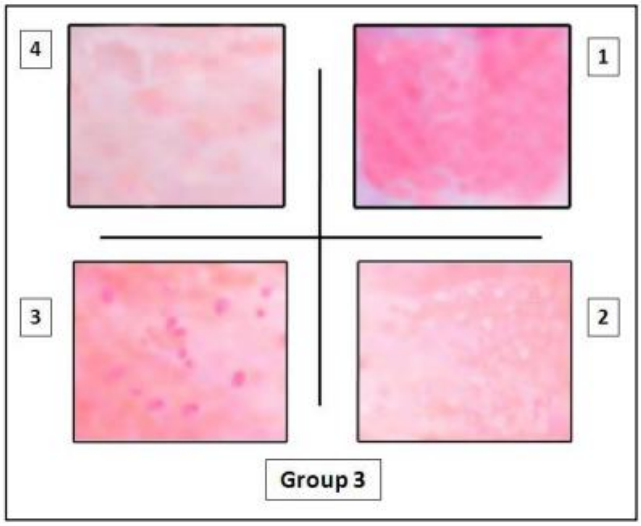

Figure no. 10: Photographs of skin irritation studies carried out on New Zealand rabbits: Group 3: Ketoconazole microsponge gel

d. Standard Calibration Curve of Ketoconazole using Cup Plate Method

Table no. 12: Zone of inhibitions for standard Ketoconazole for calibration curve

Concentration of Ketoconazole (µg/mL)	Zone of inhibition in mm					Mean ± SD
500	10.1	11.5	10.6	10.3	10.5	10.5±0.54
750	13.6	14.5	13.4	13.5	14.8	14.8±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	24.8±0.60
2000	27.8	26.8	27.5	27.5	26.9	26.9±0.43

CONCLUSION:

Quasi-emulsion solvent diffusion has proven to be an effective method for producing porous microparticles, successfully yielding Eudragit RS100 microsponges containing Ketoconazole. However, these microsponges were found to be less spherical than those made through other techniques. Analysis of intrusion and extrusion curves indicated that most pores in the Eudragit RS100 microsponges were spherical, setting them apart from conventional microspheres due to their highly porous surfaces. This unique structure promotes rapid drug release through the pores, although microsponges with smaller pore diameters demonstrated slower and reduced drug release compared to styrene microsponge formulations in in vitro studies, with all microsponges adhering to zero-order reaction kinetics.

Moreover, gel formulations containing microsponges exhibited higher viscosity than those with plain drug, supporting controlled drug release that aligns with the Higuchi model. Notably, gels containing microsponge-entrapped Ketoconazole showed enhanced antifungal activity compared to gels with free drug and marketed formulations. Importantly, no significant changes in surface morphology or drug release were detected during six months of accelerated storage, indicating the stability of the formulations. Additionally, gels with the free drug (marketed product) caused more irritation than those with drug entrapped in microsponge delivery systems, underscoring the potential of the latter to minimize irritation.

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