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Research Article

Design, Formulation and *In-Vitro* Evaluation of Ketoconazole Microsponges by Quasi-Emulsion Solvent Diffusion Method

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Abstract



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Ketoconazole-loaded micro sponges were successfully formulated employing the quasi-emulsion solvent diffusion technique, aiming to optimize drug entrapment efficiency and enhance sustain release of the drug. Ethyl cellulose served as the release-retarding polymer, while polyvinyl alcohol (PVA) functioned as the emulsifying agent. Formulations were prepared in varying ratios of drug: PVA: ethyl cellulose to assess the impact of composition on micro sponge properties. The effect of variables including the drug: polymer ratio, emulsifier (PVA) concentration in organic solvent (dichloro methane) was examined. FTIR studies confirmed that there was no significant changes in the characteristic peaks suggesting the absence of interactions between the ketoconazole and the polymer. The encapsulation efficiency for selected (F₄) formulation was found to be 94.78%. SEM analysis determined the surface morphology of microsponges and particle size of the microsponges were within the limits. The maximum *in-vitro* percentage drug release for F₄ formulation was found to be 92.87% over 12h. These results indicate that ketoconazole-loaded microsponges, formulated with ethyl cellulose and PVA, are a promising system for sustained antifungal drug delivery.

Keywords: Ethyl cellulose, poly vinyl alcohol, FTIR, SEM, micro sponges, drug release studies.

1. INTRODUCTION

Controlled drug delivery systems (CDDS) are designed to release therapeutic agents at a predetermined rate for a specified duration either locally or systematically. The primary objective of the CDDS is to maintain ideal concentrations in the bloodstream over extended periods, thereby enhancing therapeutic efficacy and reducing dosing frequency.

Microsponges are one of the controlled drug delivery system which are inert, biocompatible, porous, polymeric microspheres consisting of myriad of interconnecting vacuum within a non-collapsible structure with a large porous surface through which active ingredient is released in a controlled manner². Its size ranges from 5-300µm³. The main aim of designing microsponges was to deliver pharmaceutical active ingredient effectively at a minimal dosage, while minimizing side effects and enhancing stability⁴. They can be formulated into conventional dosage forms such as ointments, creams, lotions, gels, tablets and powders⁵. The properties of microsponges include their stability over a pH range of 1-11 and a temperature of up to 1300°C. The mechanism of drug release from microsponges involves the incorporation of active

ingredient to a vehicle in its entrapped form⁶. Due to porous structure of the micro sponge particles, the drug can diffuse in and out of the particles and into the surrounding vehicle until equilibrium is achieved⁷.

Ketoconazole belongs to category of imidazole antifungal agent, which plays a crucial role in prevention and treatment of fungal infections⁸. It blocks the synthesis of ergosterol, a vital component of fungal cell membranes that serves a similar function to cholesterol in human cells. By blocking ergosterol production, ketoconazole enhances the membrane fluidity of fungal cells. This interference finally impairs fungal growth and leads to cell death.

Topical administration is the best route of administration for treating the majority of fungal infections. Topical application of many formulations is often associated with side effects like burning sensation, dermatitis and itching. To enhance patient acceptability of the side effects, gels are widely accepted dosage forms due to their better stability and ease of application compared to creams and ointments. In the present work, microsponges were designed to encapsulate the drug to achieve controlled drug release, thereby minimizing side effects.

2. MATERIALS AND METHODS

Ketoconazole was purchased from Yarrow chem. Ltd., Mumbai, Poly vinyl alcohol from Yarrow chem. Ltd., Mumbai, Ethyl cellulose from Yarrow chem. Ltd., Mumbai, Dichloro methane from S.d.fine chem. Ltd., Mumbai.

2.1. Preparation method of ketoconazole microsponges

Method: Quasi emulsion solvent diffusion method

Four batches of microsponges F₁- F₄, were formulated using varying ratios of ethyl cellulose and polyvinyl alcohol as detailed in **table 1**. The quasi-emulsion solvent diffusion method was employed for the preparation of ketoconazole microsponges. Dispersed phase consisting of ketoconazole (100mg) and ethyl cellulose dissolved in 20ml dichloromethane¹⁰ was gradually introduced to a weighed amount of polyvinyl alcohol in aqueous continuous phase (150ml). The mixture was at 600rpm for two hours on magnetic stirrer. The microsponges formed were strained and dried in hot air oven at 40°C for 24 h¹¹. The microsponges were then stored in desiccator to preserve dryness and prevent moisture absorption.

Table 1: Formulation code of different ketoconazole microsphere formulation

Ratio of components Drug: PVA: EC	Formulation code
1:1:1	F ₁
1:2:1	F ₂
1:1:2	F ₃
1:2:2	F ₄

2.2. Evaluation of microsponges

2.2.1. Particle size analysis:

Particle size of the microsponges can be analyzed by using dynamic light scattering using 90 plus particle sizer equipped with MAS OPTION software¹².

2.2.2. IR studies

FTIR Spectroscopy was performed on each sample to determine the structure and specific functional groups of organic compounds. Drug polymer compatibility was examined using the resulting IR spectra. FTIR analysis were conducted using a thermo nicolet nexus 470 FTIR ESP. Little amount of sample to be examined was added to 100mg of KBr. Using motor and pestle the mixture was ground to fine powder and then compressed to transparent disc using a pellet press. The above formed discs were placed in FTIR spectrophotometer and spectra were collected. The range of the spectra should range from 4000-400cm⁻¹.

2.2.3. Surface Morphology

Scanning electron microscopy (SEM) was utilized to investigate the morphological characteristics of microsponges, including particle shape, surface texture and structural topography¹³. Scanning electron microscopy (JEOL JSM-IT 500, Japan) was used to visualize external and surface morphology of plain drug and optimized formulation.

2.2.4. Drug content

Micro sponges equivalent to 40mg were accurately weighed and transferred into a standard volumetric flask. To extract the drug, 100 ml of methanol was added, and the mixture was stirred for 24h to ensure complete lysis. After extraction, 1ml of resulting solution was further diluted with 10ml of phosphate buffer (6.8 pH). The absorbance of the final solution was measured at 210 nm using UV-Visible spectrophotometer. The drug content was calculated by using the below formula

$$\% \text{drug content} = \frac{\text{practical drug content}}{\text{Theoretical drug content}} \times 100$$

2.2.5. Encapsulation Efficiency

Micro sponges equivalent to 10 mg were accurately weighed and transferred in to 100 ml volumetric flask. The volume was made upto 100 ml with buffer (pH 6.8) and to facilitate drug extraction the mixture was allowed to stand for 24h. The solution was then filtered through Whatmann's filter paper to remove particulate matter. From the stock solution, 1 ml was pipetted in to 100 ml volumetric flask and diluted to 100 ml with pH 6.8 phosphate buffer¹⁴. Entrapment efficiency was analyzed by UV spectrophotometer at 210 nm. The entrapment was determined using the below formula

$$\% \text{Entrapment efficiency} = \frac{\text{Amount of drug entrapped}}{\text{Total amount of drug}} \times 100$$

2.2.6. Drug release studies

Drug release from microsphere formulations can be evaluated by Franz diffusion cell. Drug loaded microsponges complex were placed in donor phase while the receptor phase consists of pH 6.8 phosphate buffer¹⁵. Aliquots were withdrawn from receptor phase after fixed time intervals, suitably diluted and then analyzed by UV spectrophotometer¹⁶.

2.2.7. Drug release kinetics

The drug release data were analyzed to investigate the kinetics and mechanism of drug release by fitting them to different kinetic models like zero order rate kinetics, first order rate kinetics and Higuchi's classical diffusion equation.

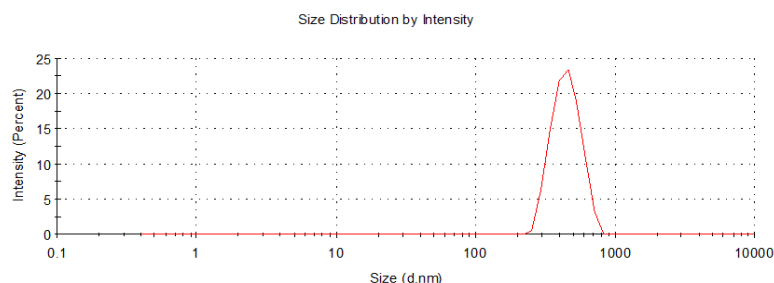
3. RESULTS AND DISCUSSION

3.1. Particle size

The average particle size of ketoconazole formulations were in the range of 100 to 476 nm as shown in **table 2**. The average particle size of the microsponges is influenced by the rotation speed of the magnetic stirrer.

Table 2: Particle size analysis of ketoconazole microsp sponge formulations

Formulation code	Particle size (nm)
F ₁	125 ± 2.516
F ₂	166 ± 3.055
F ₃	227 ± 3
F ₄	476 ± 3.055

**Figure 1: Particle size distribution graph of F₄ microsp sponge**

3.2. FTIR studies

Spectral graphs of ketoconazole showed distinctive peaks at 1647, 1510, 1244, 1029 cm⁻¹. From Figures 2

and 3, all the characteristic peaks of ketoconazole were observed in the physical mixture of all the microsp sponge formulations, indicating compatibility of the drug with the other formulation ingredients.

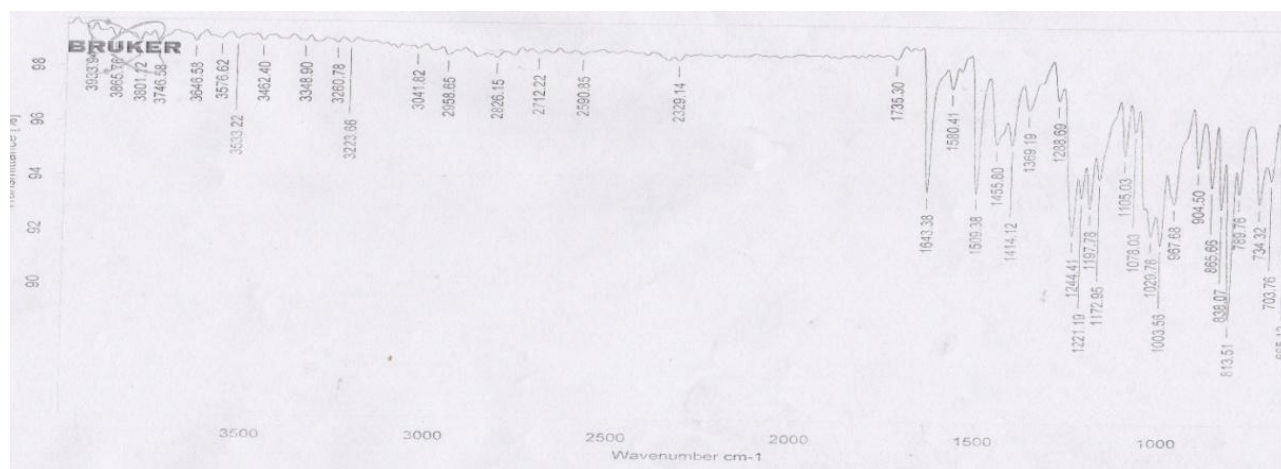
**Figure 2: IR spectral graph of Ketoconazole pure drug****Figure 3: IR spectral graph of optimized formulation (F₄)**

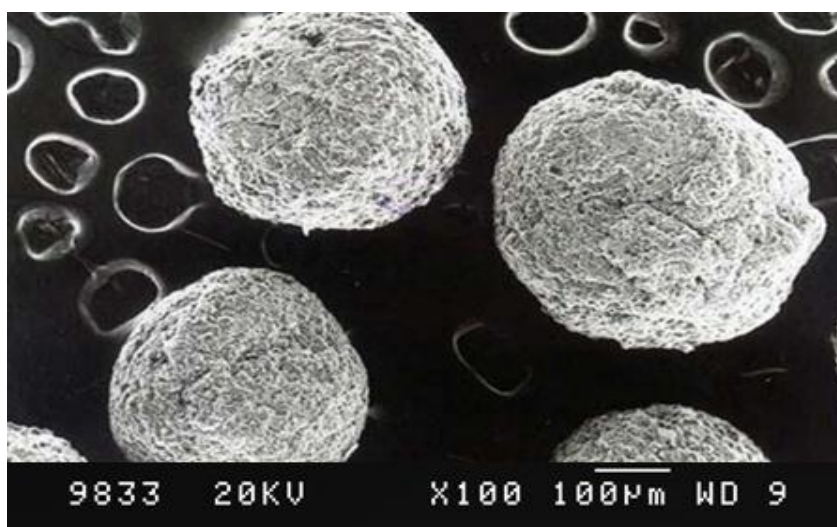
Table 3: IR spectra indicating functional groups of ketoconazole

Functional group	Wave number obtained for pure drug (Ketoconazole) in cm^{-1}	Wave number obtained for formulation (F ₄) in cm^{-1}
C=O stretching	1643.38	1642.74
C=N bond	1509.38	1508.76
C-O aliphatic ether	1029.76	1032.37
C-O cyclic ether	1244.41	1243.64
C-Cl bond	605.12	606.42

3.3. SEM analysis

From the scanning electron microphotographs of optimized formulation (F₄) it was found that the surface

of microsponges were round, soft, porous and spongy. The porous nature of the microsponges was likely attributed to the rapid evaporation of volatile solvents from the formulation as shown in **fig 4**.

**Figure 4: SEM image of F₄ formulation**

3.4. Drug content

The drug content of different ketoconazole microsponges (F₁-F₄) were found to be 81.33 to 87.58% respectively. With the increase in the concentration of polymer, the drug was surrounded by more amount of polymer which led to enhanced thickness of the polymer matrix wall. The diffusion of the drug from the polymer matrix was sustained due to the thickness of the wall.

Table 4: %Drug content of ketoconazole microsponges

Formulation code	Drug content (%)
F ₁	87.58 ± 0.799
F ₂	85.6 ± 0.4
F ₃	83.4 ± 0.4509
F ₄	81.33 ± 0.3464

3.5. Drug entrapment efficiency

The entrapment efficiency of different Ketoconazole microsponges (F₁-F₄) were found to be 82.46% to 89.8

% respectively. Higher ratios of drug: polymer led to enhanced loading of drug in polymer matrix.

Table 5: % entrapment efficiency of different formulations of ketoconazole microsponges

Formulation code	% Entrapment efficiency
F ₁	82.46 ± 0.403
F ₂	89.8 ± 0.901
F ₃	84.78 ± 0.606
F ₄	87.25 ± 0.525

3.6. Drug release studies

From **fig. 5** it was observed that the formulation F₄ was found to be optimized with controlled drug release of 92.87% for 12h. With the increase in the concentration of polymer, the drug was surrounded by the thick polymer matrix retarding the diffusion of drug.

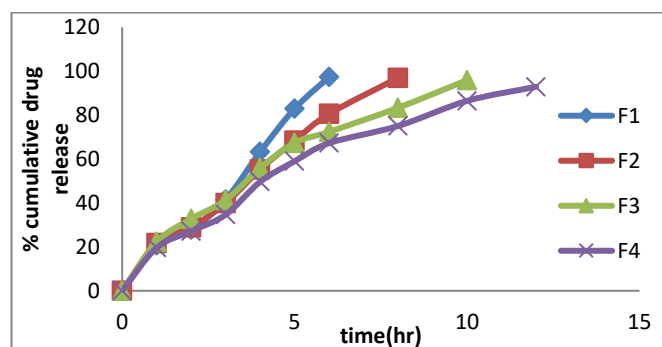


Figure 5: *In-vitro* diffusion studies of ketoconazole microsponges

Table 6: Curve fitting data of different formulations of microsponges

Formulation	Zero order		First order		Higuchi's	
	K ₀	R ²	K ₁	R ²	K _d	R ²
F1	15.952	0.9873	0.2679	0.7275	32.516	0.8474
F2	13.067	0.976	0.1904	0.6338	29.913	0.9167
F3	11.104	0.8873	0.1377	0.594	28.73	0.9704
F4	9.1562	0.8742	0.112	0.556	25.95	0.9649

4. CONCLUSION:

Ketoconazole loaded microsponges were formulated using quasi emulsion solvent diffusion method to achieve sustained drug release over a prolonged period of time, thereby minimizing the frequency of application. The average particle size of ketoconazole formulations were within the range of microsponges. Compatibility of the drug with other ingredients of the formulation was observed in FTIR studies. With the increase in the concentration of polymer, the drug was surrounded by the thick polymer matrix retarding the diffusion of drug. Thus, ketoconazole loaded microsponges formulated in the study prolonged drug release of ketoconazole in treating various fungal infections. Therefore, Ketoconazole loaded microsponges can be further improved as topical formulations like gels, creams, lotions and ointments for effective treatment of fungal infections.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

3.7. Release kinetics:

Drug release profile of all the formulations were evaluated through curve fitting analysis. In-vitro release data were applied to Zero order, first order and Higuchi's release studies. Regression coefficient (R²) and rate constant (k) were calculated for different microsphere formulations. From the data it was observed that the microsponges follow diffusion mechanism for drug release.

Ethical approval: This study does not involve experiments on animals or human subjects.

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