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# Formulation of microsponges of anti-fungal drugs and their pharmacokinetic and in vitro analysis

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## Abstract

Microsponges are uniform, spherical, porous polymeric microspheres having myriad interconnected voids of particle size range 5-300 µm. These microsponges have the capacity to entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens and anti-infective, etc. and then release them onto the skin over a time in response to a trigger. Microsponge Delivery System (MDS) can be used to resolve the problem associated with these conventional approaches. The drug entrapped microsponges can be incorporated into a formulated product, such as a gel, cream, liquid or powder. Microsponge is as tiny as a particle of talcum powder. Although they are microscopic in size, these systems are too large to pass through the stratum corneum thus preventing excessive accumulation of drugs within the epidermis and dermis, and hence systemic entry of the drugs. They increase the rate of solubilization of poorly water soluble drugs by entrapping such drugs in pores of the microsponges.

In this study, Flutrimazole and Oxiconazole nitrate microsponge were prepared by quasi-emulsion solvent diffusion method. The microsponges thus prepared, were evaluated for production yield, loading efficiency, particle size analysis, SEM, IR, DSC, PXRD, characterization of pore structure, *in-vitro* release study of microsponges, and stability. Then, gels loaded with microsponge and plain drug were formulated and evaluated for rheology, diffusion, skin irritation and antifungal activity. Antifungal activity of Flutrimazole and Oxiconazole nitrate containing microspongic gels were compared with marketed formulations. The microsponges showed good production yield, loading efficiency and particle size. All characteristic peaks of the drugs were concordant with IR spectra of pure drugs. PXRD and DSC studies revealed amorphization of drugs. SEM images showed that styrene microsponges prepared by suspension polymerization were finely spherical and uniform, while Eudragit microsponges prepared by quasi-emulsion solvent diffusion method were comparatively less spherical. According to intrusion and extrusion curves, majority of the pores present in Eudragit microsponges were spherical type, whereas the pores of styrene microsponges were mainly cylindrical-hole type. BET multipoint adsorption isotherm studies revealed that the percent of porosity of styrene microsponges is comparatively higher than Eudragit based microsponges. During the storage of drug-

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entrapped microsponges at 40±2°C and 75±5% RH for 6 months, surface morphology and release of drug showed no notable changes. Viscosity determination of gel showed that gels loaded with microsponge are more viscous than gel loaded with plain drug. The controlled drug release was observed with all the microspongic gels. Antifungal activity of gels containing microsponge entrapped Flutrimazole and Oxiconazole nitrate showed that antifungal activity of drugs was retained even after entrapment in microsponges and it was higher as compared with the gel containing free drug and marketed formulation. Gels containing drugs entrapped in microsponges.

**Keywords:** Flutrimazole, Oxiconazole nitrate, Microsponge, Antifungal drug, Microsponge gel, Topical delivery.

## Introduction

The investigation of new drug delivery systems has increased to achieve targeted and controlled drug release, as many conventional systems require high concentrations of active agents due to their low efficiency as delivery systems. Microsponges, which are highly cross-linked and patented porous polymeric microspheres, have the ability to entrap a wide variety of active ingredients, such as emollients, fragrances, essential oils, sunscreens, and anti-infective, anti-fungal, and anti-inflammatory agents. These microsponges are designed to deliver pharmaceutically active ingredients at minimal doses, enhance stability and elegance, provide flexibility in formulation, reduce side effects, and modify drug release profiles. Microsponges also prevent excessive accumulation of ingredients within the epidermis and dermis, and are typically presented to consumers in conventional forms such as creams, gels, or lotions that contain relatively high concentrations of active ingredients.[1-3]

There have been concerns about traditional topical dosage forms, such as lotions, creams, ointments, and powders, with regard to drug diffusion or release from the vehicle and delivery through the skin. Creams and lotions often have poor bioavailability of the drug because they are rapidly cleared from the skin and do not effectively release the drug from the base. Non-hydrophilic ointments are oleaginous, greasy, and inconvenient for patients. Medicated powders for topical application have a short residence time on the skin. Gels are semisolid systems in which the movement of the dispersion medium is restricted by an interlacing three-dimensional network of particles or solvated macromolecules of the dispersed phase.[4] The increased viscosity caused by interlacing and consequently internal friction is responsible for the semisolid state. Additionally, a gel may consist of twisted, matted strands often tied together by stronger types of Van der Waals forces to form crystalline and amorphous regions throughout the system. The use of gels as a delivery system can increase the residence time of drugs on the skin and consequently enhance bioavailability. Gel delivery systems offer several advantages, such as ease of administration, non-greasy application, patient compliance, high residence time on the skin, and better drug release [5]. Oxiconazole inhibits ergosterol biosynthesis, which is necessary for cytoplasmic membrane integrity in fungi. It acts to destabilize the fungal cytochrome P450 51 enzyme (also known as Lanosterol 14-alpha demethylase)[6], which is vital in the cell membrane structure of the fungus. Its inhibition leads to cell lysis. Oxiconazole has also shown inhibition of DNA synthesis and suppresses intracellular concentrations of ATP. Like other imidazole antifungals, Oxiconazole can increase membrane permeability to zinc, enhancing its cytotoxicity.

Oxiconazole nitrate is a powerful anti-fungal medication that is prescribed for the treatment of fungal infections. This medication is available as a cream or lotion that is applied topically to the affected area. Oxiconazole nitrate is classified as a BCS-II drug, and its adverse effects may include skin irritation, blistering, dryness, redness, and swelling. Additionally, it may cause itching, soreness, and pain in hairy areas. Other potential side effects include allergic reactions, such as rash and nodules.

In order to minimize the side effects associated with oxiconazole nitrate, researchers are currently investigating alternative routes of administration and novel drug delivery systems. One such example is the

oxiconazole nitrate microsponge gel, which has shown promising results in delivering the drug to deep tissues such as fascia, muscle, and synovium after topical application. This feature may help to provide relief from local symptoms with a low dose, thereby reducing the potential for side effects.

In this study, oxiconazole microsponges were prepared using polymers such as eudragit S-100 and eudragit L-100 at different proportions. These microsponges were prepared using an individual polymer with the help of a quasi-emulsion solvent diffusion method. The microsponge gel formulations were then prepared from the optimized oxiconazole nitrate microsponges using carbapol 934 with the help of a simple dispersion method.[6]

## Materials And Methods

### Materials

Flutrimazole & Oxiconazole nitrate was procured from Yarrow Chem Products, Mumbai. Eudragit S-100, Eudragit L-100 was obtained from Research-Lab Fine Chem Industries Mumbai. Carbapol-934 and polyvinyl Alcohol was purchased from Loba Chemie Pvt. Ltd., Mumbai and Cosmo chem respectively. All other reagents used were of analytical grade. The microsponges were prepared by the *quasi- emulsion solvent diffusion* method.

**Table No 1 : List of instruments**

| Sr no | Instruments /glassware | Supplier / Make |
|---|---|---|
| 1. | 3 Necked Reaction Vessel | Blown |
| 2. | AUTOSORB-1C BET analyzer | Quantachrome, USA |
| 3. | Mercury Intrusion Porosimetry | Quantachrome Equipments |
| 4. | Differential Scanning Calorimetry (SDT-2960) | TA4000, Mettler, USA |
| 5. | Franz diffusion cell | Blown |
| 6. | FTIR | Perkin Elmer, Spectrum100 FTIR |
| 7. | Malvern Particle Size Analyzer (Mastersizer2000, Version 2.0,) | Malvern Instruments Ltd, UK |
| 8. | Viscotech Rheometer with Stress Rheologica Basic software, version5.0 | Rheologica instruments AB, Lund, Sweden |
| 9. | Scanning Electron Microscopy | JEOL-JSM, 6360, Japan |
| 10. | X- ray Diffractometry | D8 Advanced, Bruker AXS. |
| 11. | 3 Necked Reaction Vessel | Blown |
| 12. | AUTOSORB-1C BET analyzer | Quantachrome, USA |
| 13. | Mercury Intrusion Porosimetry | Quantachrome Equipments |

### Methods

To prepare the inner phase, Eudragit RS 100 was dissolved in 3 mL of methanol and triethylcitrate (TEC) was added at an amount of 20% of the polymer in order to facilitate the plasticity. The drug was then added to the

solution and dissolved under ultrasonication at 35°C. The inner phase was poured into the PVA (72000) solution in 200 mL of water (outer phase). The resultant mixture was stirred for60 min, and filtered to separate the microsponges. The microsponges were washed and dried at 40°C for 24h [8]. Seven different ratios of drug to Eudragit RS 100 (1:1, 3:1, 5:1, 7:1, 9:1, 11:1 and 13:1) were employed to determine the effects of drug : polymer ratio on physical characteristics and dissolution properties of microsponges. Agitation speed employed was 500 rpm using three blade propeller stirrers.[9]

**Table 2: Composition of microsponges**

| **Constituents** | Flutrimazole Microsponges | | | | | | |
|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
| | Oxiconazole nitrate Microsponges | | | | | | |
| | F8 | F9 | F10 | F11 | F12 | F13 | F14 |
| **Inner phase** | | | | | | | |
| **Flutrimazole / Oxiconazole nitrate** | 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 |

**Evaluation of Microsponges**

**Determination of production yield and loading efficiency**

The production yield of the microparticles was determined by calculating accurately the initial weight of the raw materials and the last weight of themicrosponge obtained (Kilicarslan M., 2003).

$$\text{Production Yield} = \frac{\text{Practical Mass of Microsponges}}{\text{Therotical Mass (polymer + drug)}} \times 100$$

The loading efficiency (%) of the microsponges can be calculated according to the following equation:

$$\text{Loading Efficiency} = \frac{\text{Actual Drug Content in Microsponges}}{\text{Therotical drug Content}} \times 100$$

**Particle size analysis**

Particle size analysis of prepared microsponges was carried by using Malvern Particle Size Analyzer Hydro 2000 MU (A). Microsponges were dispersed in double distilled water before running sample in the instrument, to ensure that the light scattering signal, as indicated by particles count per second, was within instrument's sensitivity range. It is a flexible, modular and fully integrated, particle sizing system with assured measurement performance from submicron to millimeter. It can measure particle size of wet or dry particles from milligram quantities of precious pharmaceuticals. During the measurement, particles are passed through a focused laser beam. These particles scatter light at an angle that is inversely proportional to their size. The angular intensity of the scattered light is then measured by a series of photosensitive detectors. The map of scattering intensity versus angle is the primary source of information used to calculate the particle size. The scattering of particles is accurately predicted by the Mie scattering model. The Mastersizer 2000 software, allows accurate sizing across the widest possible dynamic range.

*Infrared spectroscopy*

FTIR spectroscopy was conducted using Perkin Elmer, Spectrum 100 FT-IR spectrometer. Spectrum was recorded in the wavelength region of 4000 to 400 cm-1. The procedure consisted of dispersing a sample in excess of potassium bromide nearly at the ratio 1:100, mixed well, after which the mixture was kept into the sample holder for analysis.[11].

*Differential scanning calorimetry (DSC)*

Thermal analysis is an important evaluation technique to find any possible interaction between the drug and used polymers. Any of such interaction may reduce the drug entrapment efficiency of the polymer and may also alter the efficacy of the drug. Such interaction can be identified by any change in thermogram. Thermograms of pure Salicylic acid, blank styrene microsponge, Salicylic acid entrapped microsponge, pure Eudragit RS 100, pure ketaconazole, oxiconazole nitrate and drug entrapped microsponges were obtained using DSC instrument, Differential Scanning Calorimetry (SDT-2960); TA4000, Mettler, Japan. Indium standard was used to calibrate the DSC temperature and enthalpy scale. The powder sample of microsponges was hermetically kept in the aluminum pan and heated at constant rate 5°C/min, over temperature range of 100 C to 250°C. An inert atmosphere was maintained by purging nitrogen at the flow rate of 100 mL/min. [11].

***In vitro* drug release study**

Accurately weighed loaded microsponges (5 mg) were placed in 50 ml of ethanol/methanol in 100 ml glass bottles. The later were horizontally shaken at 37°C at predetermined time intervals. Aliquot samples were withdrawn (replaced with fresh medium) and analysed UV spectrophotometrically at 238 nm for Flutrimazole and 211 nm for Oxiconazole nitrate. The contents of drugs were calculated at different time intervals up to 6hrs. [12].

**Formulation of Gel Loaded with Microsponges and Plain Drug**

A clear dispersion of carbopol was prepared in water using moderate agitation. Intermittent sprinkling of carbopol prevents lump formation resulting in clear homogenous dispersion. Drug or drug containing microsponge formulation was dispersed in propylene glycol and methanol. Various ingredients viz. paraben, sodium metabisulphite and disodium edetate were dissolved in water and added to the drug solvent system. Triethanolamine was used to neutralize and adjusted to final weight with water. Gels prepared were degassed by ultrasonication. [13]

**Table 3: Composition of Gels**

| Ingredients | Quantity (% w/w) |
|---|---|
| Drug (free or entrapped, equivalent to) | Flutrimazole : 2 Oxiconazole nitrate : 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 |

**Evaluation of Gel Loaded with Microsponges and Plain Drug**

**Determination of viscosity**

Viscosity of the formulated gels was determined by Brookfield Viscometer using Spindle type 93/T-C.

**Drug Diffusion from Microspongic Gels**

The *in-vitro* measurement of drug permeation through cellophane membrane was performed in Franz Diffusion cell [14]. 1 g of gels containing free or entrapped drug were placed in the donor compartment, while the receptor compartment contained 12 mL of the receptor phase. Aliquots of 0.5 mL samples were withdrawn at suitable intervals from the receptor compartment and the drug was assayed spectrophotometrically.

**Safety Considerations (Draize Skin Irritation Testing)**

The irritation potential of the gels containing free drug and drugs entrapped in microsponges were evaluated in comparison to marketed gel by carrying out the Draize patch test on rabbits [15]. Animal care and handling throughout the experimental procedure was performed in accordance to the CPCSEA guidelines. The experimental protocol was approved by the Institutional Animal Ethical Committee. White New Zealand rabbits weighing 2.5-3 kg were obtained and acclimatized before the beginning of the study.

**Antifungal Activity of Flutrimazole and Oxiconazole nitrate Gels**

The antifungal activity of Flutrimazole and Oxiconazole nitrate from the optimum formula (microspongic-gels) as well as the free Flutrimazole and Oxiconazole nitrate and marketed formulations of the same were determined using Candida albicans as a representative fungus, adopting the cup plate method. The mean inhibition zone was calculated for each plate, and this value was taken as an indicator for the antifungal activity.

## Results and Discussion

**Table No 4 Characterization of Flutrimazole and Oxiconazole nitrate Pure Drug Flutrimazole**

| Sr. No. | Characters | Specification | Result |
|---|---|---|---|
| 1. | Description | White or almost white powder., crystalline powder | White or almost white powder., crystalline powder |
| 2. | Melting point | 161-166°C | 161-166°C |

| | | | |
|---|---|---|---|
| 3. | Solubility | insoluble in water, freely soluble in tetrahydrofuran, soluble in methanol.. | insoluble in water, freely soluble in tetrahydrofuran, soluble in methanol.. |

**Oxiconazole nitrate**

| 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 |

**IR Spectroscopy:** IR Spectra of Flutrimazole and Oxiconazole nitrate in their pure form were recorded. Results are depicted in 1,2 and Table No. 5 and 6 respectively.

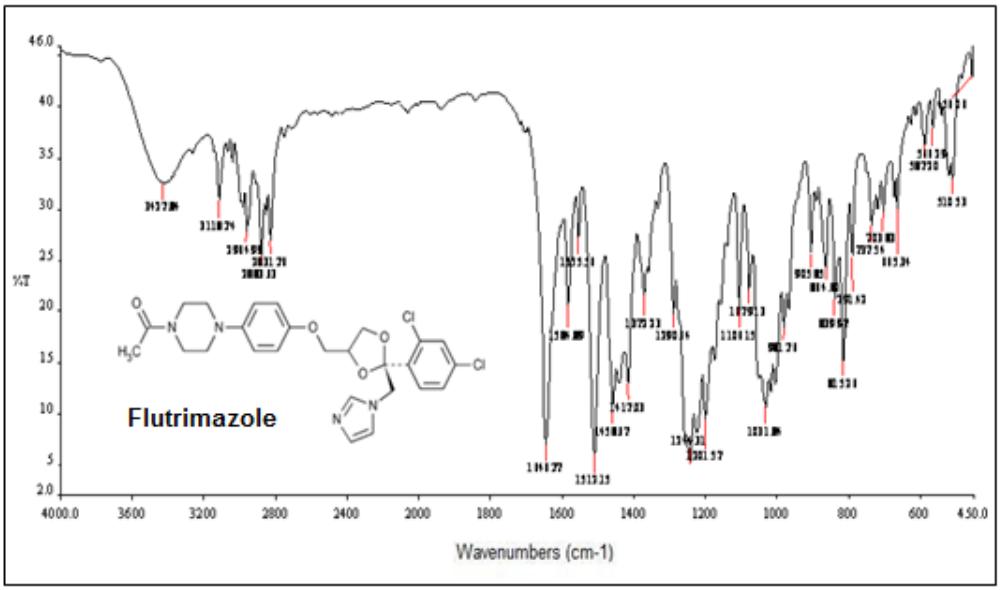


***Figure 1 : IR Spectra of Flutrimazole***

**Table 5: IR Spectrum interpretation of Flutrimazole**

| Functional group | Wave number observed($cm^{-1}$) |
|---|---|
| C=O(carbonyl group) | 1646.77 |
| C-O(aliphatic ether group) | 1031.84 |
| C-O(cyclicether) | 1244.31 |

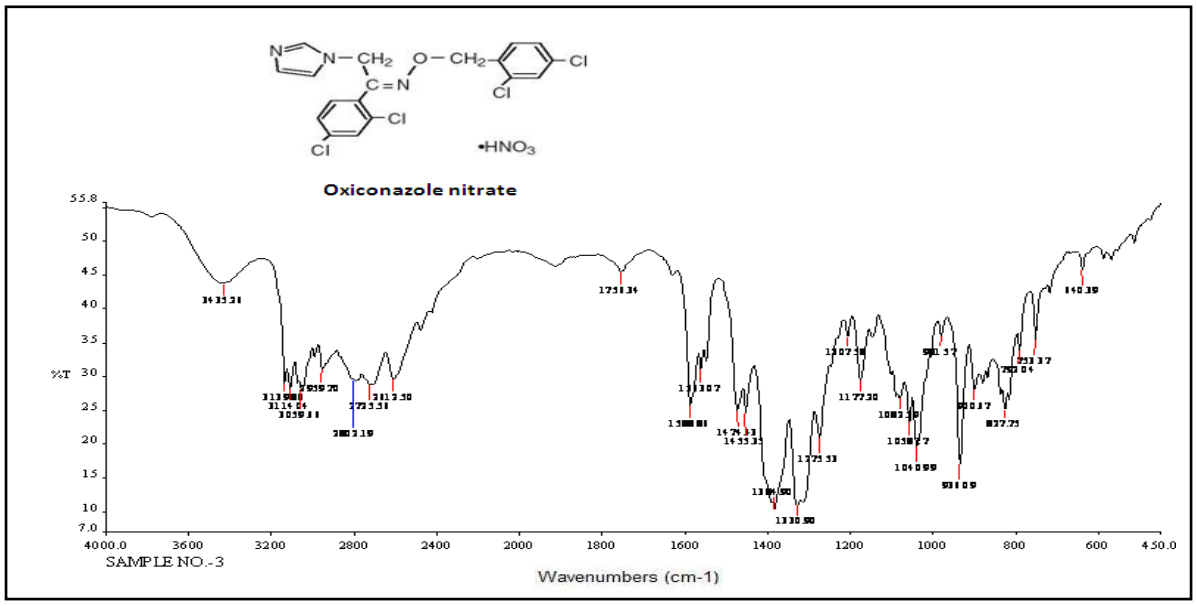


***Figure 2: IR Spectra of Oxiconazole nitrate***

**Table 6: IR spectrum interpretation of Oxiconazole nitrate**

| Functional group | Wave number observed($cm^{-1}$) |
|---|---|
| C-H (methylene, $CH_2$) | 2959 |
| C=N | 1474,1455 |
| N-O(of cis isomer) | 1330–1384 |
| C-H (aromatic) | 3139–3059 |

## Drug-Excipient Compatibility Studies

### Physical Change

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

### 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 3,4

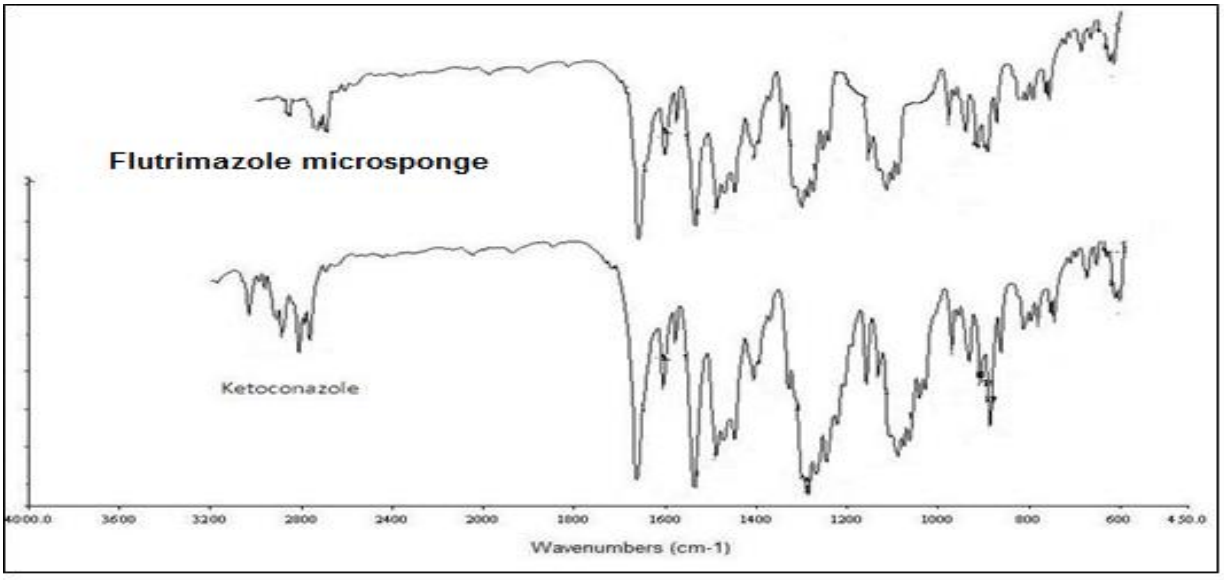


***Figure 3: Compatibility study of Flutrimazole by IR***

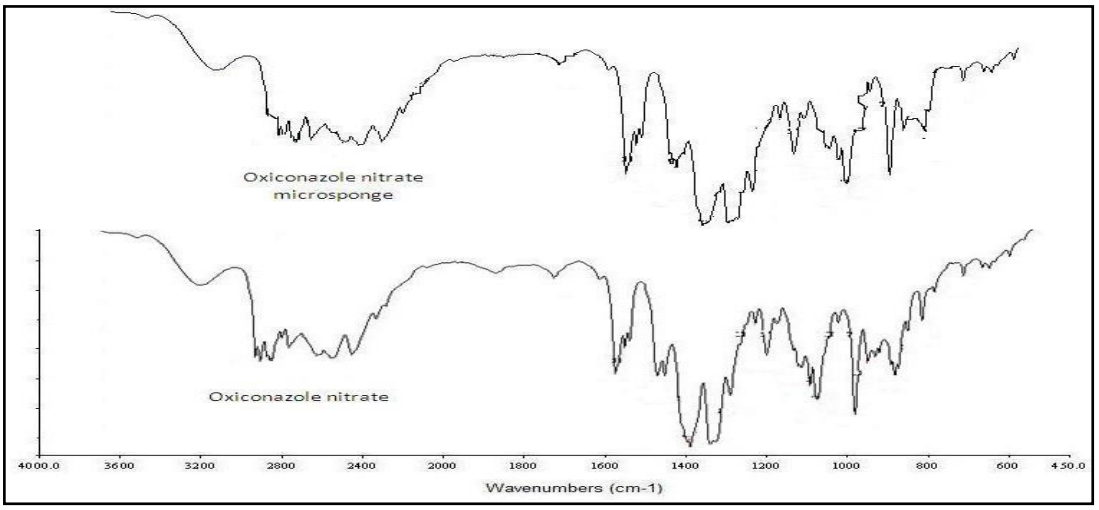


***Figure 4 : Compatibility study of Oxiconazole nitrate by IR***

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.

**Evaluationof Microsponges**

**Production yield**

Table 7: Production yield of Flutrimazole microsponge

| Formulation code | Production yield(%) |
|---|---|
| F1 | 77.19±2.13 |
| F2 | 80.23±1.17 |
| F3 | 82.21±1.23 |
| F4 | 85.12±2.01 |
| F5 | 87.25±1.14 |
| F6 | 89.14±1.90 |
| F7 | 90.17±2.16 |

*****Each value is average of three separate determinations ±SD

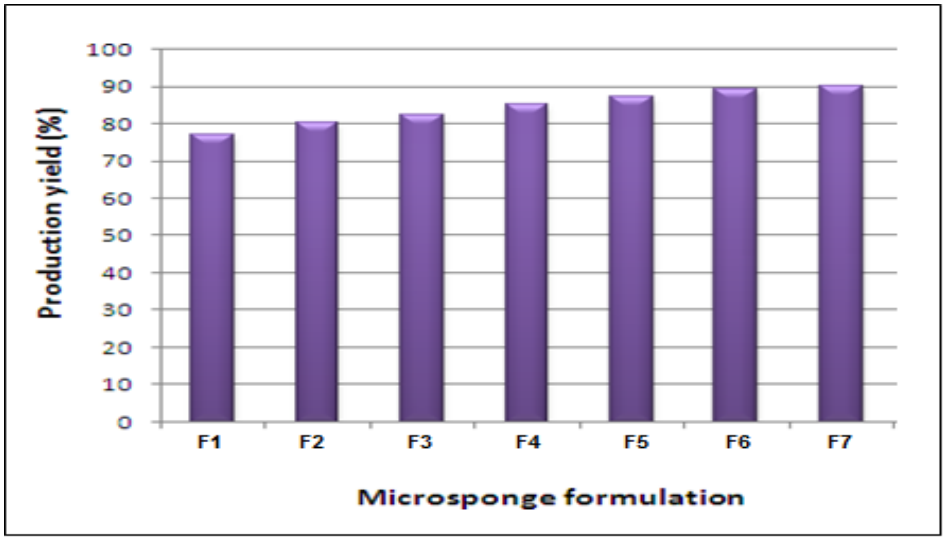


***Figure 5: Production yield of Flutrimazole microsponge formulations***

**Table 8: Production yield of Oxiconazole nitrate microsponge**

| Formulation code | Production yield(%) |
|---|---|
| F8 | 72.45±1.36 |
| F9 | 75.35±2.14 |
| F10 | 78.21±2.84 |
| F11 | 83.17±2.31 |
| F12 | 86.45±1.38 |
| F13 | 89.01±2.12 |
| F14 | 91.47±2.81 |

*****Each value is average of three separate determinations ±SD

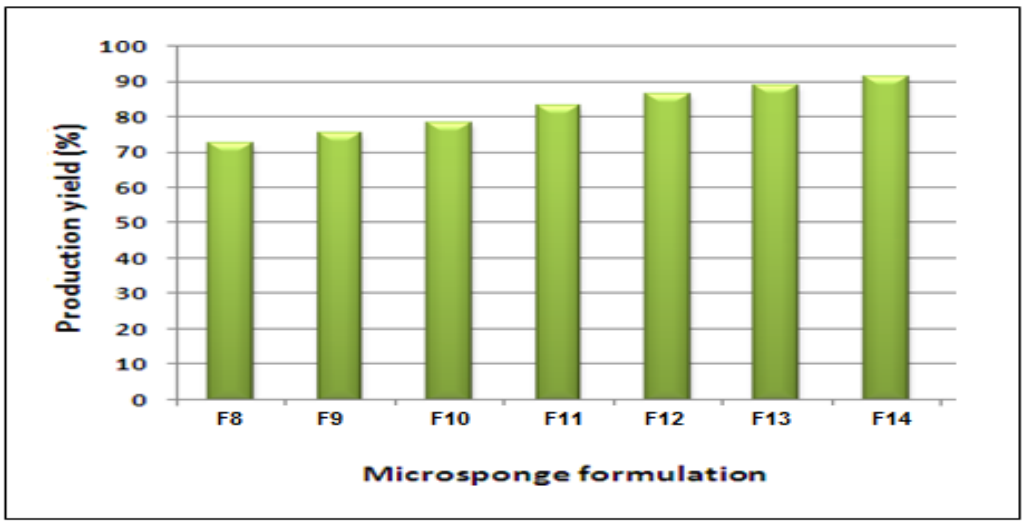


***Figure 6:Production yield of Oxiconazole nitrate microsponge formulations***

Production yield of Flutrimazole microsponges were between 77.19 to 90.17% (Table14).Production yield of Oxiconazole nitrate microsponges were between 72.45 to 91.47 % (Table 15). 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.

## Drug Loading Efficiency

**Table 9: Drug loading efficiency of Flutrimazole microsponge formulations**

| Formulation code | Drug Loading efficiency(%) |
|---|---|
| F1 | 85.36±1.32 |
| F2 | 86.45±0.69 |
| F3 | 88.49±2.01 |
| F4 | 90.86±0.27 |
| F5 | 92.38±1.26 |
| F6 | 94.21±0.39 |
| F7 | 94.89±0.16 |

*Each value is average of three separate determinations ±SD

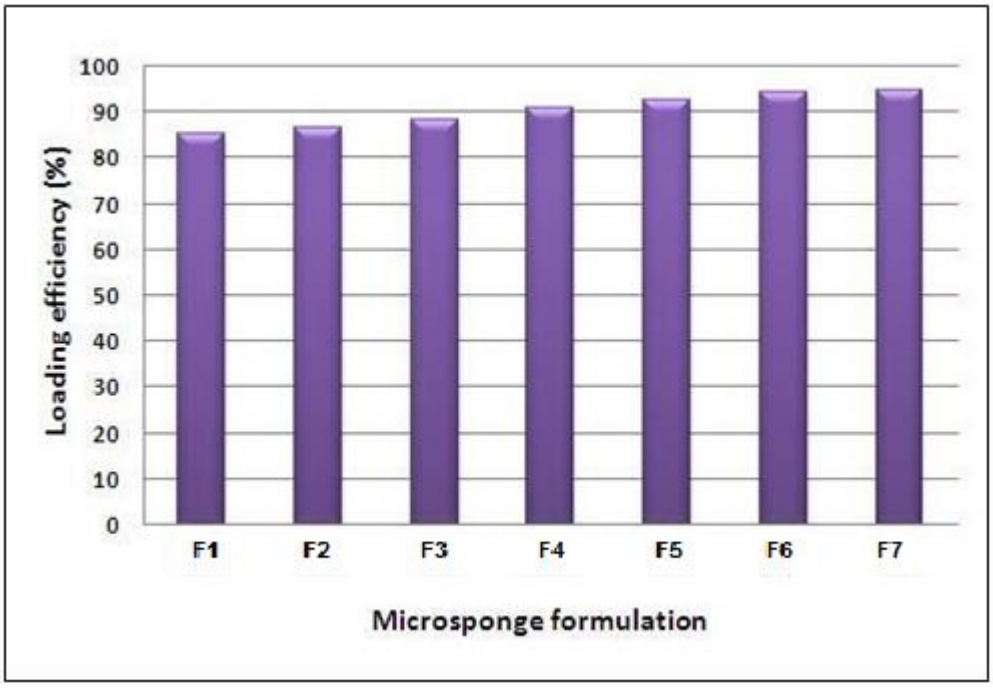


***Figure 7: Drug loading efficiency of Flutrimazole microsponge formulations***

**Table 10: Drug loading efficiency of Oxiconazole nitrate microsponge formulations**

| Formulation code | Drug Loading efficiency(%) |
|---|---|
| F8 | 52.65±0.28 |
| F9 | 65.69±2.84 |
| F10 | 70.86±1.08 |
| F11 | 73.84±1.84 |
| F12 | 78.49±0.37 |
| F13 | 81.59±1.86 |
| F14 | 84.57±1.89 |

*Each value is average of three separate determinations ±SD

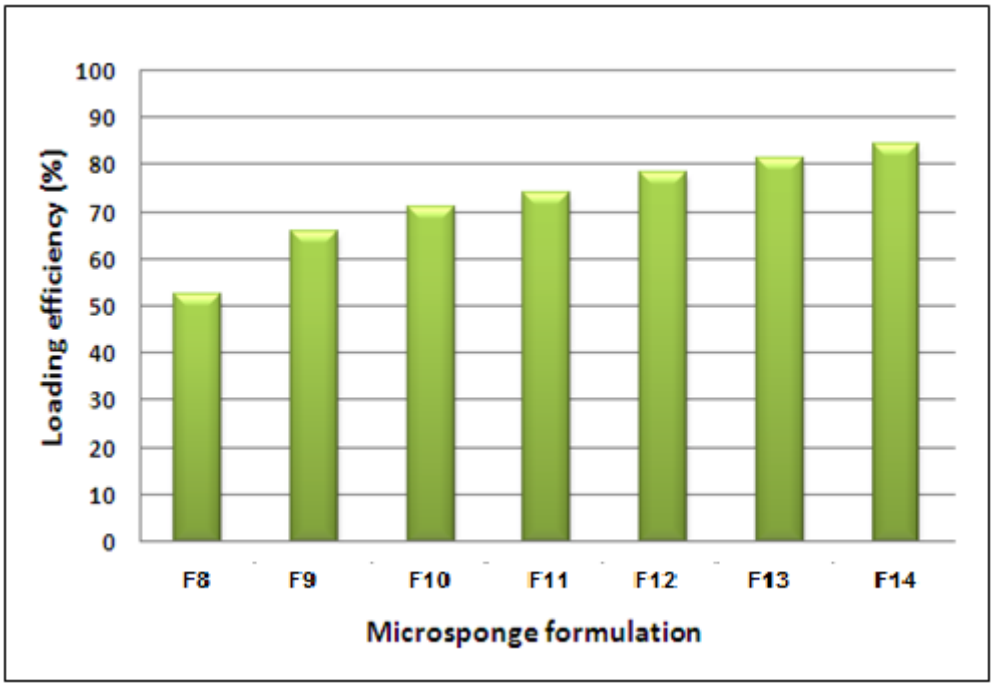


***Figure 8: Drug loading efficiency of Oxiconazole nitrate microsponge formulations***

Table No. 9, 10 shows the drug loading efficiencies of Flutrimazole & Oxinazole nitrate microsponges respectively. The loading efficiency was found to be high i.e. 85.36 to 94.89% in Flutrimazole microsponges and 52.65to 84.57% in Oxiconazole nitrate microsponges. In case of Eudragit RS 100 microsponges, it was found that as drug: polymer ratio increases, drug loading efficiency also increases.

## Particle Size Analysis:

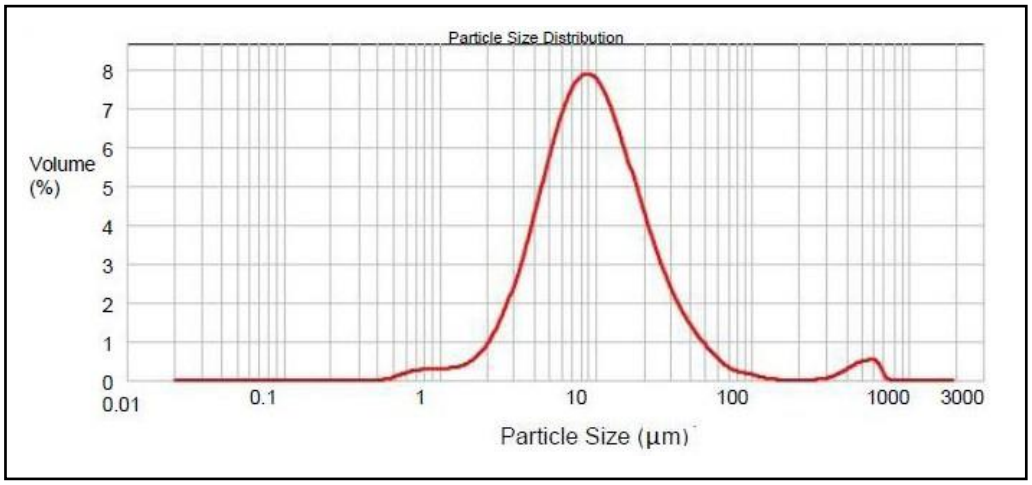


***Figure 9:Particle size distribution of Flutrimazole microsponges (Mean particle size 12.06µm)***

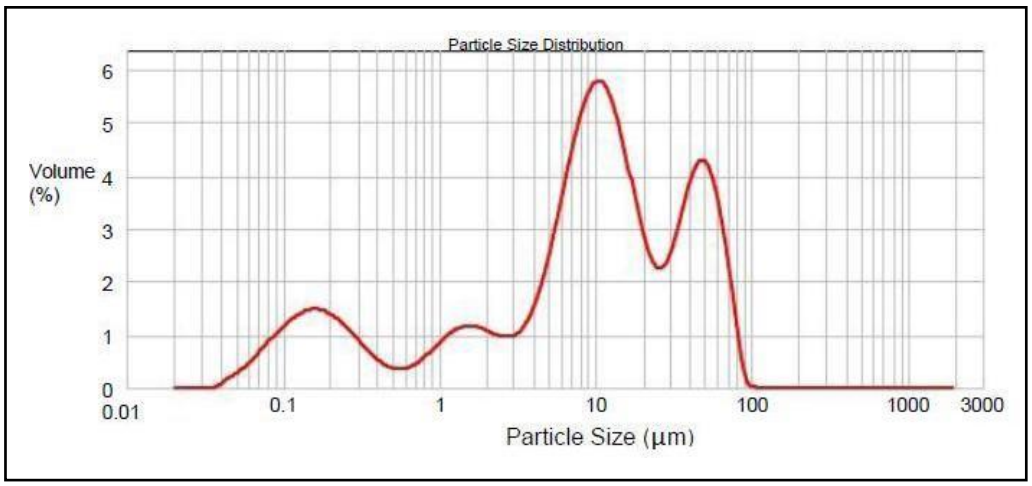


***Figure 10: Particle size distribution of Oxiconazole nitrate microsponges (Mean particle size 10.11µm)***

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 Eudragit based microsponges (Flutrimazole and Oxiconazole nitrate microsponge) are shown in Figure 9, 10. The mean particle size Flutrimazole and Oxiconazole nitrate was found to be 12.06 µm and10.11µm respectively.

## Infrared Spectroscopy

FTIR spectra of Flutrimazole / Oxiconazole nitrate, Eudragit RS 100 and microsponges prepared by Eudragit method (F7 and F14) and overlay spectra are, as shown in Figure 11,12. All characteristic peaks of drugs in the IR spectra of F7 and F14 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.

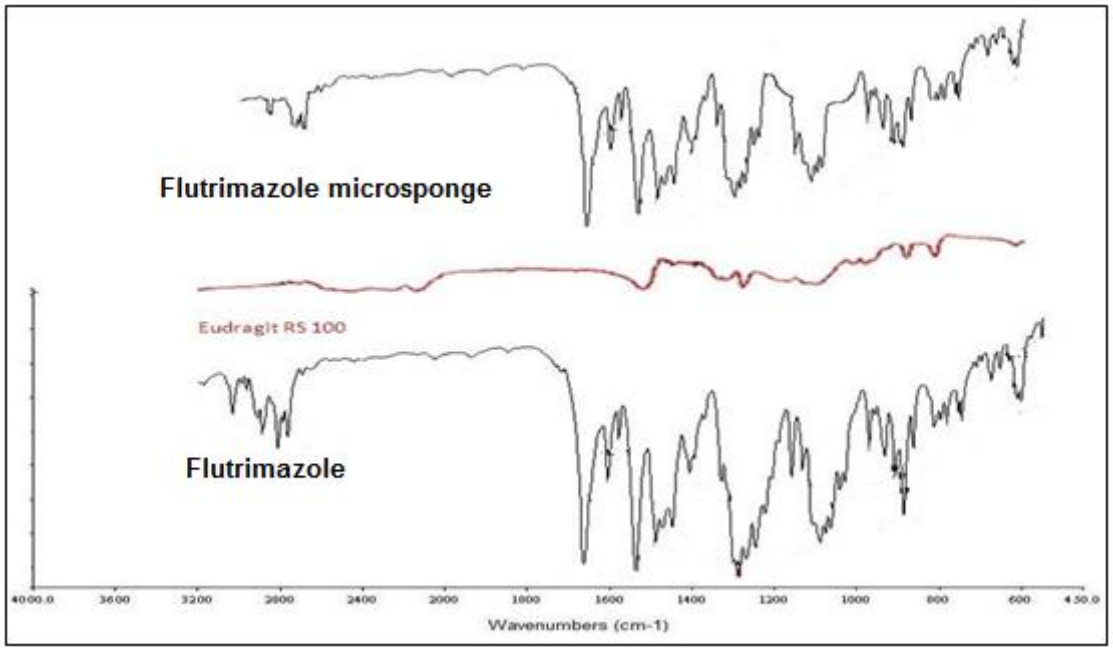


***Figure 11: Overlay FTIR Spectra of: Flutrimazole ,Eudragit RS100 and Eudragit microsponges containing Flutrimazole***

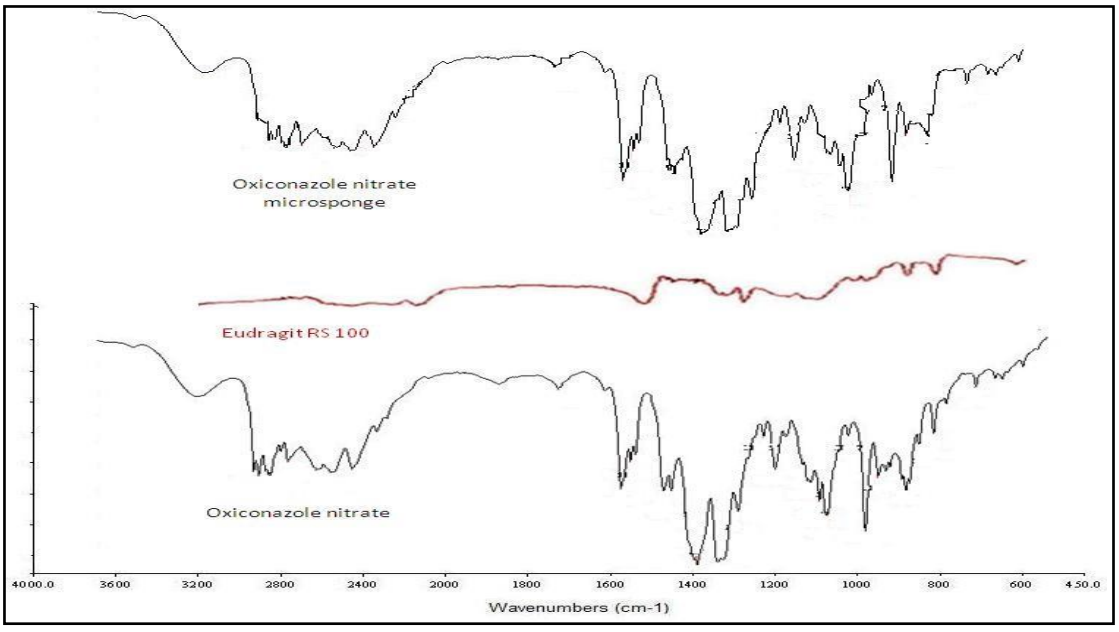


***Figure 12 :Overlay FTIR Spectra of : Oxiconazole nitrate,Eudragit RS100and Eudragit*** *microsponges* ***containing Oxiconazole nitrate***

## Differential Scanning Calorimetry(DSC)

In the DSC curves of F7 and F14 formulations, characteristic peaks of Flutrimazole , Oxiconazole nitrate and Eudragit RS 100 were seen. The thermograms of F7 and F14 formulation showed that there was no interaction between the drugs and the polymer in fig 13 & 14

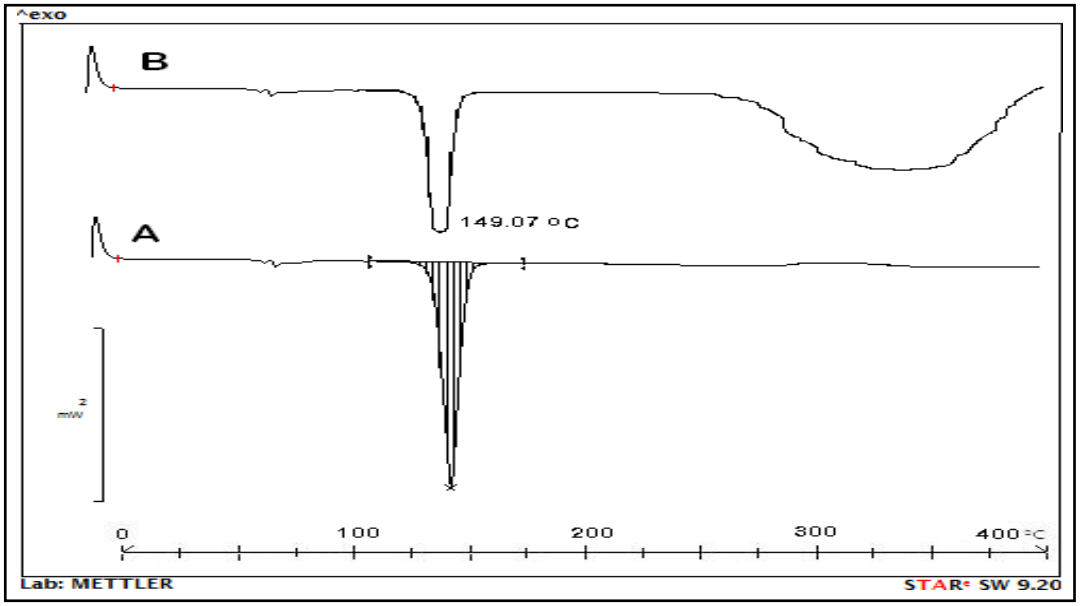


***Figure 13:Overlay DSC Thermograms of A:Pur eFlutrimazole ,B:Eudragit microsponges containing Flutrimazole***

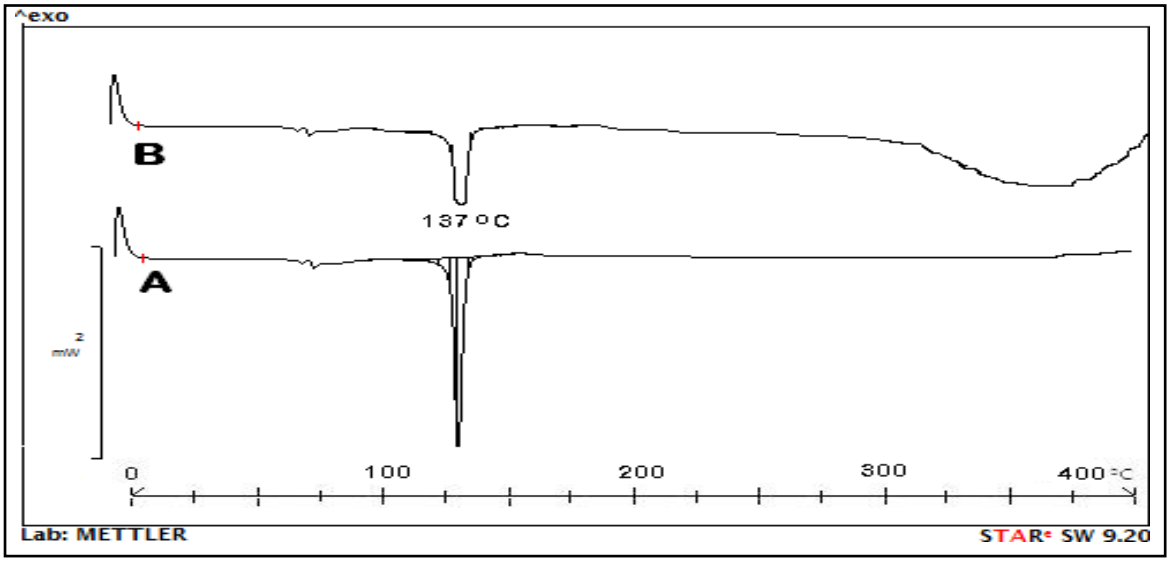


***Figure 14:Overlay DSC Thermograms of A:Pure Oxiconazole nitrate, B:Eudragit microsponges containing Oxiconazole nitrate***

## *In-vitro* Release Study of Microsponge

The drug release profiles of the Flutrimazole microsponge formulations are illustrated in Table 11. Drug release from Flutrimazole microsponge was found to range from 68.32 % to 77.25 % from all the formulations. The drug release profiles of the Oxiconazole nitrate microsponge formulations are illustrated in Table 12. Drug release from Oxiconazole nitrate microsponge was found to range from 57.42 % to 70.55 % for all the formulations.The microsponges differ from regular microspheres with their highly porous surface. This characteristic gives property to release the drug at a faster rate through the pores. Kawashima reported that microsponges having a moreporous internal structure, exhibited a faster drug release rate than that of rigid microspheres

**Table No 11. In-vitro release study of Flutrimazole microsponges**

| Time (Min) | Cumulative % drug release | | | | | | |
|---|---|---|---|---|---|---|---|
| | F8 | F9 | F10 | F11 | F12 | F13 | F14 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | 10.36±0.80 | 10.25±1.86 | 11.68±1.27 | 9.82±0.39 | 13.62±1.41 | 15.63±1.52 | 16.94±1.85 |
| 30 | 16.84±1.28 | 16.63±1.14 | 14.68±1.15 | 12.63±1.41 | 16.86±1.54 | 21.87±1.28 | 22.01±1.29 |
| 45 | 22.69±1.74 | 20.58±1.37 | 17.86±0.96 | 17.54±1.53 | 20.51±1.70 | 29.93±1.53 | 26.32±1.34 |
| 60 | 28.88±0.20 | 26.64±1.74 | 21.62±1.54 | 23.68±1.84 | 26.81±1.56 | 35.62±1.08 | 31.54±1.75 |
| 120 | 33.62±0.86 | 32.52±0.90 | 26.87±1.63 | 29.09±068 | 33.04±0.57 | 39.52±1.01 | 38.11±0.58 |
| 180 | 40.87±1.71 | 41.86±037 | 32.91±0.84 | 38.21±1.38 | 43.91±1.14 | 45.92±1.28 | 49.82±1.27 |
| 240 | 49.65±0.31 | 50.92±1.14 | 40.72±0.93 | 48.62±1.45 | 54.45±0.41 | 51.66±0.63 | 58.65±1.46 |
| 300 | 55.45±1.56 | 56.99±1.18 | 49.66±1.41 | 53.77±1.39 | 62.14±1.04 | 55.21±0.96 | 61.32±1.32 |
| 360 | 66.86±1.31 | 62.58±1.33 | 60.33±1.27 | 57.42±0.09 | 70.55±1.01 | 62.63±0.47 | 70.42±0.81 |

**Table No 12. In-vitro release study of Oxiconazole nitrate microsponges**

| Time (Min) | Cumulative % drug release | | | | | | |
|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | 19.96±1.52 | 22.13±1.13 | 19.36±1.53 | 19.65±1.58 | 22.18±1.27 | 23.83±1.60 | 18.35±0.40 |
| 30 | 27.63±1.16 | 29.48±1.52 | 26.35±1.30 | 26.54±1.12 | 29.54±1.70 | 31.52±1.66 | 26.52±1.33 |
| 45 | 36.48±1.53 | 35.41±1.50 | 35.87±1.57 | 33.65±1.52 | 37.56±1.49 | 36.84±1.73 | 38.47±1.28 |
| 60 | 46.98±1.20 | 44.32±1.35 | 41.28±1.50 | 41.74±1.19 | 44.54±1.73 | 41.68±1.43 | 45.92±1.63 |
| 120 | 58.68±1.51 | 50.91±1.18 | 49.86±1.88 | 48.92±1.52 | 48.92±1.58 | 49.63±1.52 | 50.45±0.28 |
| 180 | 64.21±1.44 | 58.54±1.40 | 54.64±1.31 | 52.63±1.85 | 51.36±1.97 | 52.36±1.52 | 56.69±0.37 |
| 240 | 67.85±1.55 | 64.86±1.42 | 61.24±1.59 | 59.87±2.15 | 57.62±1.52 | 57.85±1.58 | 60.36±0.78 |
| 300 | 71.52±1.51 | 72.52±1.54 | 68.87±1.09 | 66.32±1.52 | 65.21±1.52 | 62.96±1.52 | 64.12±1.16 |
| 360 | 75.62±1.48 | 77.25±1.29 | 73.65±1.09 | 71.96±0.75 | 74.85±1.53 | 68.32±1.53 | 75.85±1.18 |

**Determination of Viscosity:**

Results of viscosity determination of gel showed that gel loaded with microsponge is more viscous than gel loaded with plain drug. Gels containing Eudragit microsponges loaded with Flutrimazole and Oxiconazole microsponges were found gritty .

**Table 13:Viscosity of different gel formulations**

| **Gel for mulation** | **Viscosity(cps)** |
|---|---|
| Gel containing F7 microsponge | 302478±1.21 |
| Gel containing free Flutrimazole | 232345±0.69 |
| Gel containing F14 microsponge | 351650±1.80 |
| Gel containing free Oxiconazole nitrate | 211584±1.30 |

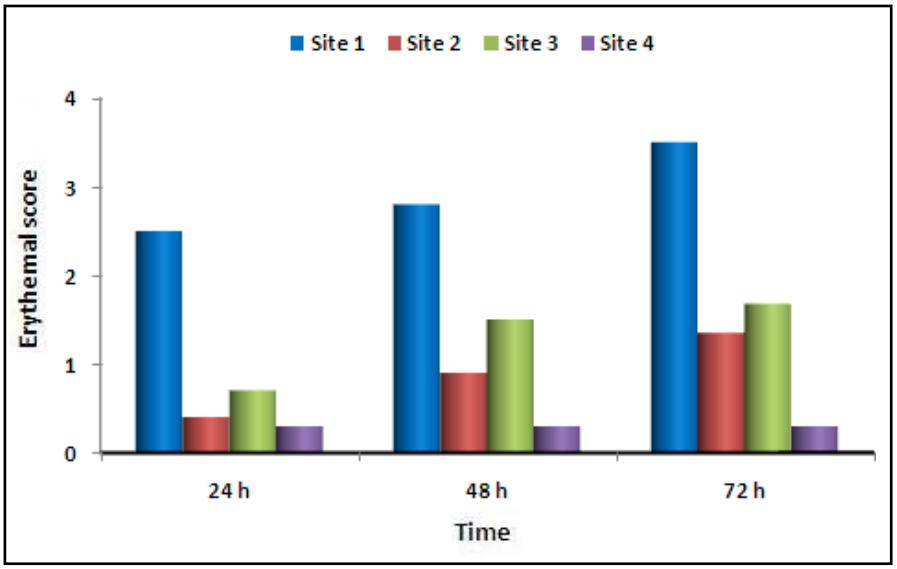


***Figure 15:Erythema scores observed for Flutrimazole formulations, recorded at 24, 48 and 72 hrs.***

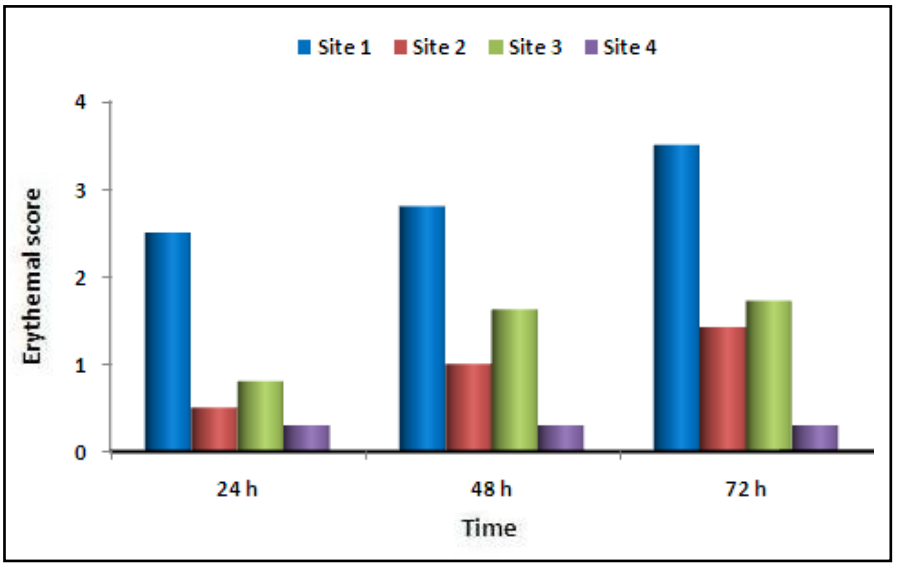


***Figure 16:Erythe ma scores observed for Oxiconazole nitrate formulations, recorded at 24, 48 and 72 hrs.***

PDIIs of all the marketed gels and gels containing entrapped drug are given in Figure 15,16. It was observed that the marketed gel shows more irritation than all the gels containing drug entrapped in microsponge drug delivery system.

**Table 12:Anti-fungal activity of microspongic gels in comparison to reference standard using Candida albicans (n=5), P value (<0.05)**

| **Formulation** | **Zone diameters(mm)** | | | | | **Mean zone diameter ±SD(mm)** |
|---|---|---|---|---|---|---|
| Flutrimazole Marketed Formulation | 18 | 19 | 21 | 18 | 22 | 18±1.82 |
| Free Flutrimazole gel | 17 | 21 | 22 | 19 | 18 | 17±2.07 |
| F7gel | 22 | 23 | 26 | 24 | 25 | 22±1.58 |
| Oxiconazole nitrate Marketed Formulation | 17 | 18 | 21 | 17 | 22 | 19±2.40 |
| Free Oxiconazole nitrate gel | 18 | 16 | 20 | 17 | 21 | 16±2.07 |
| F14gel | 23 | 21 | 24 | 26 | 25 | 21±1.92 |

Table 12 manifested that the antifungal activity of tested microspongic gels was larger than that of the gels containing free drug and marketed formulation. The ANOVA and Dunnett's Multiple Comparision Test showed that there was a significant difference in the microspongic gel zone of inhibition in comparison to the gels containing free drug and marketed formulation at P<0.05.

## Conclusion

Suspension polymerization conditions traditionally used in the preparation of microsponges were found to be compatible with salicylic acid. The encapsulation efficiency and drug release profile depend on the cross-linking of microsponges. Quasi-emulsion solvent diffusion is currently the preferred method for the preparation of porous microparticles. Since flutrimazole and oxiconazole nitrate have been shown to be incompatible with liquid–liquid suspension polymerization reactions, Eudragit RS100 microsponges containing flutrimazole and oxiconazole nitrate have been successfully used in this method. 7. Chemical:polymer ratios (1:1, 3:1, 5:1, 7:1, 9:1, 11:1 and 13:1) of Eudragit-based MDS were examined.

It was determined that the average particle size increased as the amount of polymer decreased in microsponge-based Eudragit. Using a three-faceted centrifugal mixer, microsponges introduce different particles. Mixing speed and time have a significant impact on the size and shape of microsponges. Increasing the mixing speed causes the average particle size to decrease. The drug loading efficiency showed that a higher drug-to-polymer ratio would lead to a higher drug loading efficiency.Eudragit RS100 microsponges show that both methods have good results and chemical properties. It is suitable for preparing micro sponges. The semi-emulsion solvent diffusion method is preferred because it is easier, takes less time and has better components than the free radical polymerization method and hence more preferred.The structure of the Eudragit RS 100 microsponge may deteriorate during the release of the drug during the injection process. Drug released from all gels was the best for the Higuchi model. Gels containing microsponges encapsulating flutrimazole and oxiconazole nitrate showed retention of anti-fungal properties and were compared to gels containing free drug

and commercial samples. It is stored for 6 months at 40 ± 2 °C and 75 ± 5% relative humidity, there is no significant change in surface morphology and drug release. > Thus, the micro sponge drug delivery system can improve the treatment of topical keratolytic drugs such as flutrimazole and oxiconazole nitrate, because it is micronized and semi-amorphous, and also has the following properties: No irritation due to controlled release on the skin. reduction advantage.

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