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Formulation Development and *In-Vitro* Evaluation of Microsponges Gel Loaded with Anti Fungal Drug

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Abstract: ***Objective of this research work was to formulate and evaluate antifungal drug Miconozole loaded microsponges gel form for sustained topical drug delivery. In this study, efforts has been made to prepare microsponges containing Miconazole by quasi-emulsion solvent diffusion method using different polymers like Eudragit RL100, Eudragit L100 and Ethyl cellulose. Optimization of best suitable polymer was determined based on product production yield, loading efficiency and drug content of drug loaded microsponges. Prepared topical microsponges gels were evaluated for pH, viscosity measurement; spread ability, estimation of content of drug, drug release studies. Best formulation has to be chosen, depending on the criteria such as maximum drug release from the microspongesgel. Formulation with drug and polymerratio1:5 shows good sustained drug release up to 24 hours. Optimized formulation was studied for rate release kinetics.***

Keywords: Miconozole, Microsponges, Eudragit RL 100 and Quasi emulsion solvent diffusion method

1. Introduction

Microsponge delivery system is a unique technology for control release of topical agents and consists of micro porous beads to target specific drug delivery systems. The system consists of a polymeric bead having network of pores with active ingredient. On application to the skin it releases the active moiety at a time and response to stimuli to show final target.

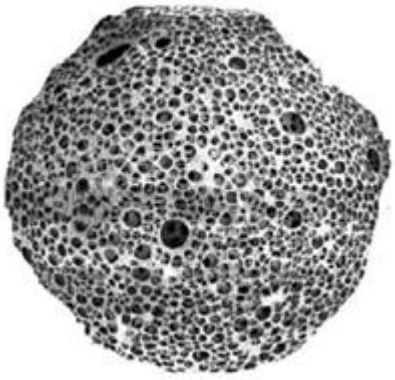

Figure 1: Structure of Microsponge

Microsponges are uniform, highly cross-linked, spherical, porous polymeric microsphere and particle size ranges between 5-300µm. These are compatible with most vehicles and ingredients [1].

In present study microspongeswere prepared by Quasi emulsion solvent diffusion method, it includes two steps internal and external phases: Internal phase contains drug, polymer and organic polymer solvent was dissolved in ethyl alcohol and then drug is added to the above solution and dissolved under ultra-sonication at 35◦c.External solution contains aqueous solution, internal phase is added to external phase followed by 60 min of stirring and the mixture is filtered to separate the microsponges, prepared microsponges are dried in hot air oven at 40◦ c for 12hours[2].

2. Materials and Equipment

Materials required for this study were received from diverse sources. Miconazole drug was gifted from Chandra labs, Hyderabad. EudragitRL 100 and Eudragit L 100 were procured from Mylon chemicals. Poly vinyl alcohol procured from standard chemicals. Ethyl cellulose procured from Rankem chemicals. All other chemicals and ingredients were of analytical grade and were used as procured. Equipments used in present study were Franz diffusion cell (Electro lab), UV visible spectrophotometer (Lab India), pH meter (Digisun electronics system), Mechanical stirrer (Remi motor), Digital balance (Mettler Toledo) and Glass ware (Cad mach).

3. Methods

3.1 Drug characterization

3.1.1 Organoleptic evaluation

These are preliminary characteristics of any substance which is useful in identification of specific material. It includes physical appearance, odour and colors.

3.1.2 Melting point

Melting point of Miconazole was determined by using Scientek digital melting point apparatus by capillary method. Fine powder of Miconazolewas filled in glass capillary tube (previously sealed on one end). The capillary tube is inserted into the melting point apparatus and observed the temperature at which drug started to melt.

3.1.3 Drug and excipient compatibility studies:

There is always possibility of drug-excipient interaction in any formulation due to their intimate contact. It is also necessary to determine any possible interaction between the excipients used in the formulations. This will also indicate success of Stability studies.

3.1.4 FTIR studies

Infrared spectroscopy deals with the infrared region of the electromagneticspectrum. FTIR is most useful tool for identifying chemicals that are either organic or inorganic by identifying the types of chemical bonds (functional groups). While organic compounds have very rich, detailed spectra, inorganic compounds are usually much simpler.

In FTIR spectroscopy, IR radiation is passed through a sample. Some of the infrared Radiation is absorbed by the sample (the wavelength of light absorbed is characteristic of the chemical bond) and some of it is passed through (transmitted).the resulting Spectrum represents the molecular absorption and transmission, creating a molecular Fingerprint of the sample. Like a finger print no two unique molecular structures produce the same infrared spectrum. By interpreting the infrared absorption spectrum, the chemical bonds in a molecule can be determined. The FTIR spectrum of Miconazole was recorded using FTIR spectrophotometer by KBr pellet technique.

3.1.5 UV spectroscopy

Linearity graph of Miconazole was plotted using phosphate buffer solution (PBS) of pH 7.4 by keeping concentrations in a range of 10-50 µg/ml. Drug was analyzed spectrophotometrically at 237nm.

3.2 Miconazolemicrosponges preparation [3]:

Internal phaseprepared by dissolving Miconazole in 10ml of dichloro methane and ethanol (1:1) completely and add dibutyl phthalate, it acts as a plasticizer. The external phase contains aqueous solution of poly vinyl alcohol in water 100ml of 1% (w/v).The external phase is placed in a magnetic agitator revolving on 600rpm. To this the internal phase is slightly add, and keep on continuous stirring up to 8 hrs to get rigid and stable microsponges after filter them by using whatmann filter paper 0.45µm. and washed with water and dried at hot air oven. Various formulations were prepared as per Table 1.

Table 1: Formulations of Miconazolemicrosponges

Ingredients (mg)	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Internal Phase												
Miconazole (mg)	200	200	200	200	200	200	200	200	200	200	200	200
EudragitRL100 (mg)	500	750	1000	1500	----	-----	----	-----	---	---	---	---
EudragitL100 (mg)	----	----	-----	-----	500	750	1000	1500	------	------	------	-----
Ethyl cellulose (mg)	------	-----	----	-----	-----	----	-----	---	500	750	1000	1500
Ethanol: DCM (ml)	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1
Dibutylphthalate (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
External phase												
PVA (gm)	1	1	1	1	1	1	1	1	1	1	1	1
Waterin (ml)	100	100	100	100	100	100	100	100	100	100	100	100
Total weight (mg)	700	950	1200	1700	700	950	1200	1700	700	950	1200	1700

3.3 Evaluation of Miconazolemicrosponges [4]

3.3.1 Percentageyield:

Each formulation of microsponges was taken separately and calculate yield by using below equation.

$$\text{Percentage Yield} = \frac{\text{Practical Weight}}{\text{Theoretical Weight}} \times 100$$

3.3.2 Percentage drug entrapment efficiency

40mg of Miconazolemicrosponges were powdered and dissolved in 100ml of methanol. Diluted this with PBS 7.4 buffer and examined for drug content using spectrophotometric method. Loading efficiency was calculated using below equation.

$$\text{Loading Efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

3.3.3 Preparation of Microspongesmiconazole gel:

Drug solution and polymer solution were prepared separately; polymer solution is prepared by dissolving 500mg of Carbopol 936 in water and drug solution (2%) prepared by dissolving microsponges in Guar gum 350mg.Further, first solution is added to the drug solution with continuous stirring, follow through adding 1ml Tween 80. Neutralize the Carbopol solution by slowly adding of tri ethanolamine solution with continuous stirring, to form a gel.

3.4 Evaluation of Microspongesgel[5]

3.4.1 pH of Formulation

Take 1mg of gel from each formulation is taken in a beaker and dilute with water make up to 25ml then pH of the solution be determine by digital pH meter and is noted.

3.4.2 Viscosity Measurement:

The viscosity measurements were carried out by using Brookfield programmable DV-II LV model (Brookfield Eng. Lab., Inc.USA). The gel sample was placed in tiny sample adapter. Temperature was increased in the range of 20^0C to 40^0C, using water circulation jacket. The temperature sensing probe was lowered in gel and temperature of gel was recorded. Viscosity at various temperatures was recorded.

3.4.3 Spreadability

It was determined by modified wooden block and glass slide apparatus. A measured amount (M) of gel was placed on fixed glass slide; the movable pan with a glass slide attached to it and was placed over the fixed glass slide, such that the gel was sandwiched between the two glass slides for 5min. The weight was continuously removed and note down the time in seconds (T). Spreadability was determined using the formula.

$$S = M/T$$

3.4.4 Evaluation of drug content:
Accurately weigh 40 mg of Miconazolemicrosponge gel of each formulation was dissolved in 100ml of methanol and filtrate, to the solution was diluted with pH 7.4 PBS and measure the absorbance at 237nm.

***3.4.5 In-vitro* Drug release studies:**
The drug release from microsponges was investigate (14ml) by using Franz Diffusion cell which contains PBS pH7.4 as a dissolution medium. Take a few amount of microsponge gel equivalent to 2% of Miconazole was taken in the donor chamber. At secure intervals, take 5 ml of sample is taken and replace with PBS pH 7.4. The removed samples were measured at different time gaps to determine the absorbance at 237 nm against blank.

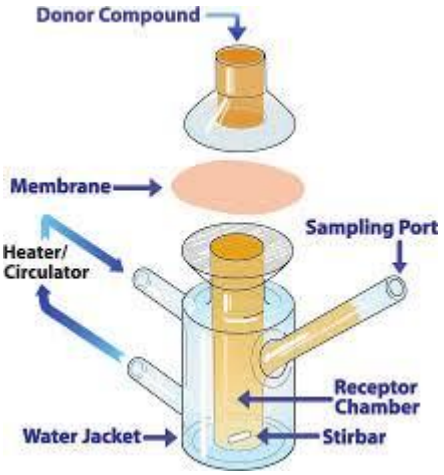

Figure 2: Franz diffusion cell

3.4.6 Release Kinetics [6]
The matrix systems were reported to follow the Peppas release rate and the diffusion mechanism for the release of the drug. To analyze the mechanism for unharness the discharge} and release rate mechanics of the dose kind, the data obtained was fitted in to, Zero order, First order, Higuchi matrix, Peppas and Hixson Crowell model. In this by comparing the r-values obtained, the best-fit model was selected.

4. Results

4.1 Characterization of drug:

White or almost white powder and free from odour. Drug freely soluble in methanol and very slightly soluble in water. Miconzole melting point was observed at 83-87^{0}c.

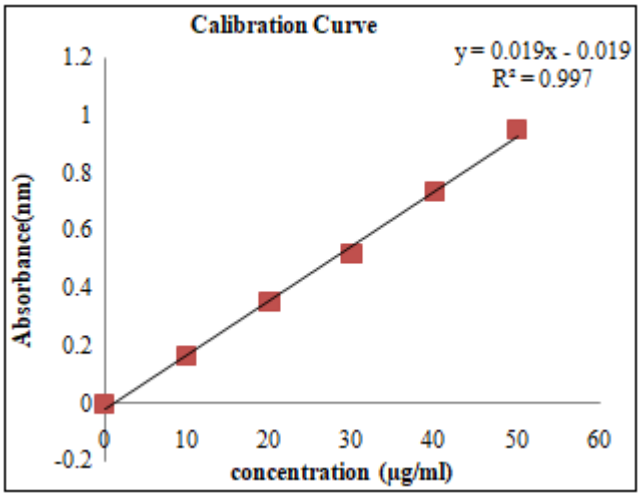

Figure 3: Calibration curve of Miconazole in PBS 7.4pH

4.2 FTIR studies

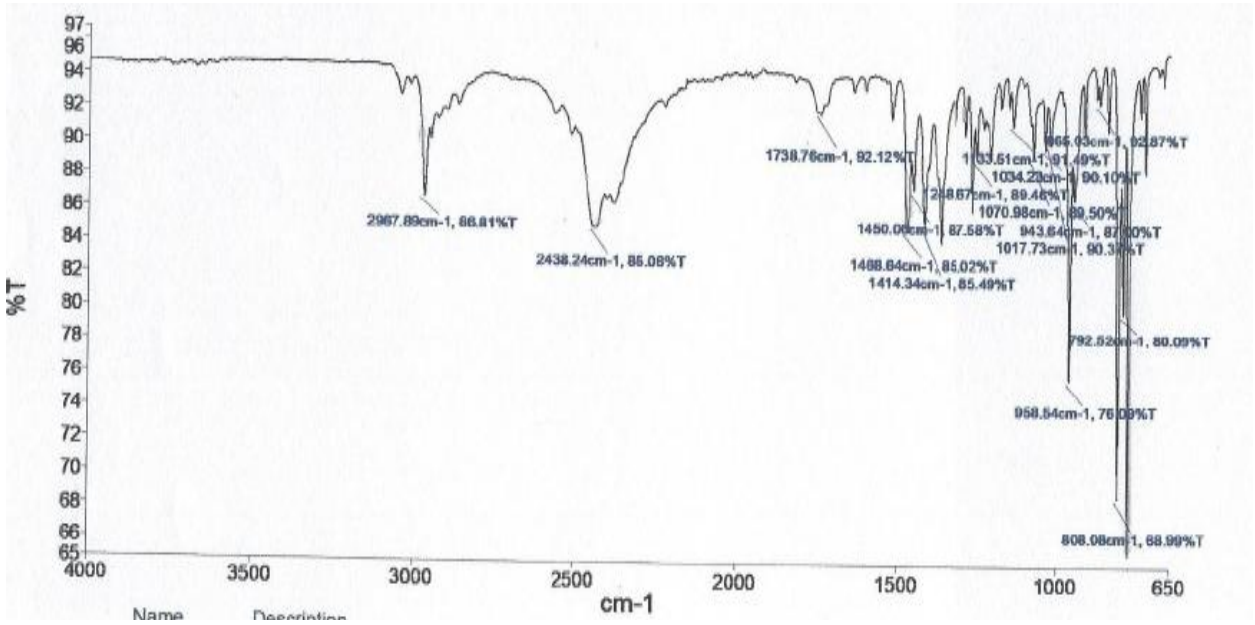

Figure 4: FTIR Spectra of Miconazole

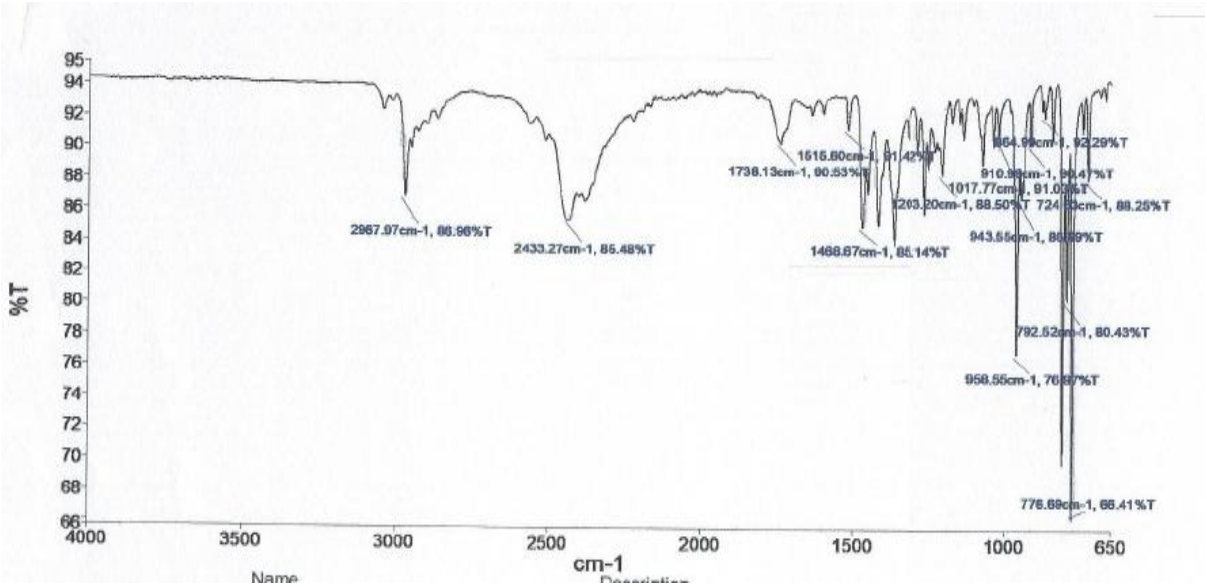

Figure 5: FTIR Spectra of Miconazole optimized formulation

4.3 Evaluation and Characterization of Microsponges

Table 2: Evaluation ofpercentage yield and% drug entrapment efficiency

Batch	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
% Yieald	78.21	80.34	91.25	84.21	88.42	82.42	85.42	86.02	83.46	79.53	82.43	84.36
% Entrapment efficiency	52.64	69.01	81.68	74.8	77.32	72.56	74.71	76.42	71.64	52.80	69.84	71.44

4.4 Evaluation Parameters of Miconazole Gel

Table 3: Evaluation parameters of all microsponges gels

Microsponges Formulation code	pH	Viscosity (cps)	Drug Content (%)	Spreadibility (g.cm/sec)
M1	6.0	1169	93.2	16.81
M2	5.8	1175	94.1	15.94
M3	6.56	1193	94.8	21.32
M4	6.5	1170	92.4	16.11
M5	6.6	1184	94.5	19.03
M6	6.5	1172	93.7	18.61
M7	6.2	1181	92.9	17.21
M8	6.4	1180	93.8	17.60
M9	6.6	1170	91.7	16.21
M10	6.4	1181	92.9	17.12
M11	6.2	1179	89.2	18.62
M12	6.7	1170	93.6	17.14

4.4.1 *In-Vitro* Drug Release Studies

The dissolution were performed by using pH 7.4 dissolution media. All the preparations were carriedout using Franz diffusion cell. The obtained values for prepared M_1- M_{12} formulations are shown in figure no. 6-8.

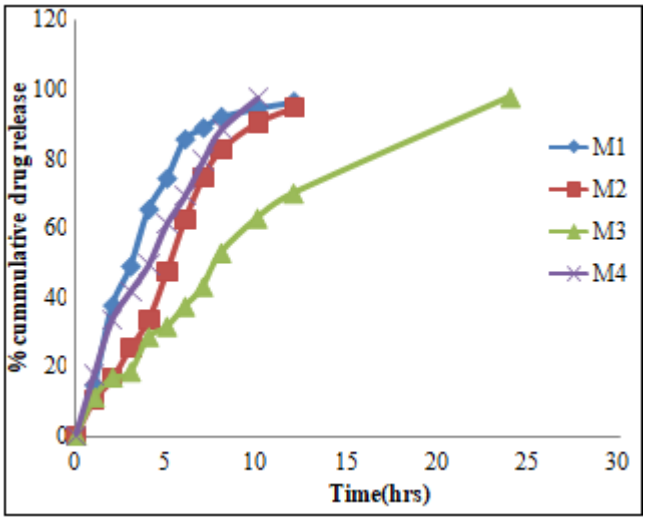

Figure 6: Drug release plot for formulation M1-M4

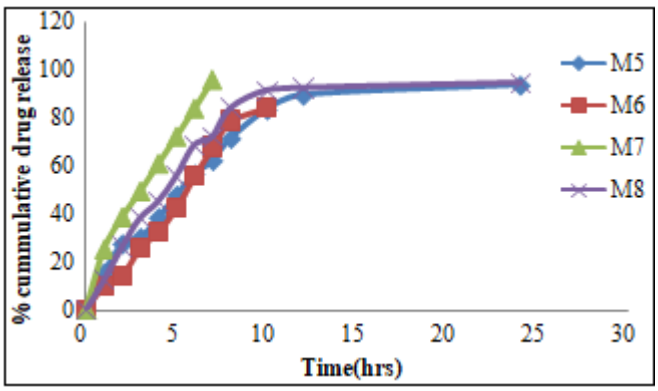

Figure 7: Drug release plot for formulation M5-M8

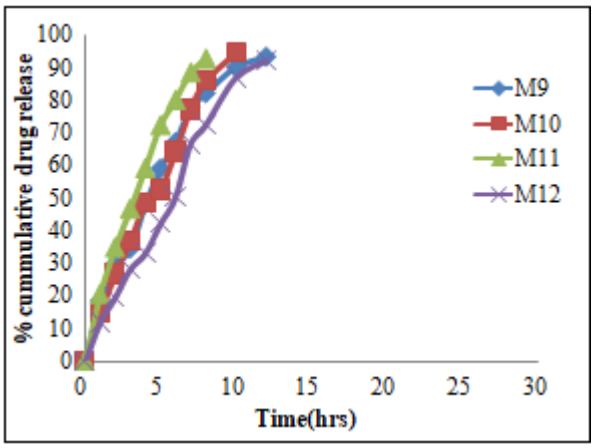

Figure 8: Drug release plot for formulation M9-M12

4.5 Kinetic Release Studies for all Formulations

4.5.1 In-Vitro Drug Release Kinetics

For understanding the mechanism of drug unharness and unharness rate mechanics of the drug from indefinite quantity kind, the in-vitro drug dissolution knowledge obtained was fitted to varied mathematical models such as zero order, First order, Higuchi matrix, and Korsmeyer-Peppas model and values were complied. The constant of determination (R^2) was used as an indicator of the simplest fitting for every of the models thought-about. The kinetic data analysis of all the formulations reached higher coefficient of determination with the Zero order (R^2 = 0.941).

4.5.2 Kinetic Release Studies

Table 4: Release kinetics for M3 formulation

M3	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	4.15019048	-0.06710504	21.74577107	-0.81696401
Intercept	10.87333333	2.134526617	-11.1859145	2.22012705
R 2	0.94195039	0.928865463	0.958287792	0.577218774

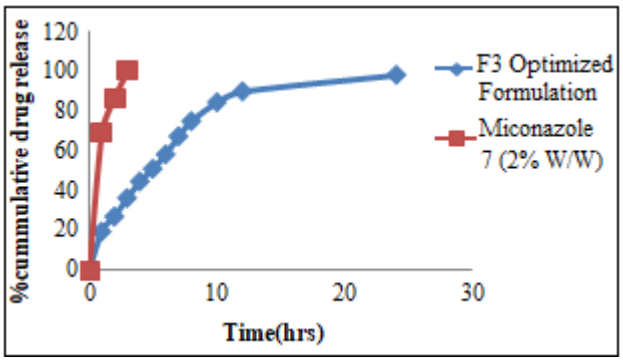

Figure 9: Comparison b/w marketed drug with optimized formulation (M3)

5. Conclusion

The present study is to formulate microsponges gel containing Miconazole with a goal to deliver the drug in sustained manner in topical application. The FT-IR spectral examination suggests that, there was no compatibility between the drug and excipients. All the prepared gels were passed to evaluation tests like pH, rheological properties, drug release content and *In-vitro* drug release studies. In-vitro drug release studies done by the Franz diffusion cell the dissolution was performed to all the preparations. Among all those formulations M3 illustrate highest drug liberation up to 24hrs in sustained manner. In all the cases the best fit model was found to be Zero order indicates drug release is independent upon concentration. *In-vitro* dissolution Comparison was performed between the marketed product and M3 optimized formulation. From the above marketed (MICONAZOLE 2% W/W) shows 100.2 % drug release within 3hrs but M3 optimized formulation was maintains their sustainability for 24hrs. Hence, M3 formulation shows prolonged action compared to marketed product, so it is considered as best formulation for control release of anti-fungal treatment, which also improves the patient compliance.

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