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Formulation and Evaluation of Posaconazole Microsponges for Controlled Topical Drug Delivery

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ABSTRACT

The Microsponges are Novel Approach for topical controlleddrug delivery system. To overcome conventional topical drug delivery problems like itching, skin irritation, redness, swelling, stickiness, greaseness etc & overcome the side effects. Most common technique for microsponge preparation is Quasi emulsion solvent diffusion method. In that Eudragit RS 100 mostly use because they forms best microsponges with suitable compatibility. Microsponges provide controlled release of drug for prolonged period of time increases solubility of BCS class II Drug. Posaconazole antifungal microsponges are treat the fungal skin infections like candida infections,Esophageal candidiasis, Amebiasis, Oropharyngeal candidiasis, Trichomoniasis etc .Effective treatment against topical fungal infections.As the polymer concentration increases the entrapment efficiency increases.Rate of drug release increases.

Keywords: Microsponges, Posaconazole, Eudragit RS100, Ethyl Cellulose, Controlled drug release, Topical drug delivery, 3^2 factorial design, antifungal activity etc

INTRODUCTION

- Topical drug delivery system has been used predominantly in the treatment of localized skin disease and other injuries.
- Local treatment requires only that, the drug permeate the outer layers of the skin to treat the specific area with the hope that this occurs with little or no systemic accumulation.
- The industries produces chemical entity specific for dermal or transdermal are ideally suited to retain on to the skin and should not uptake into and through the skin.
- This means considerable effort has to be expanded on the appropriate design or a device to deliver enough of the medicine with controlled, extended and target manner at its site of action.[1,2]
- A Microsponge drug delivery system (MDDS) is a patented, highly cross-linked, porous, polymeric microspheres polymeric system (10-25), consisting of porous microspheres particles consisting of a myriad of interconnecting voids within non-collapsible structures with a large porous surface that can entrap a wide range of actives (cosmetics, over-the-counter (OTC) skin care, sunscreens, and prescription products) and then to cause. A normal 25-mm sphere can contain up to 250000 holes, giving it a total pore volume of around 1 ml/g, and an internal pore structure that is 10 feet long. [3]
- The skin cannot be penetrated by micro sponges, which can hold four times their weight in skin secretions. Instead, they gather in the skin's minuscule crevices and release the medicine there as the skin requires it. The micro sponge system can stop components from building up too much in the dermis and epidermis. These products often have a high concentration of active chemicals and are offered to the consumer in customary forms such creams, gels, or lotions. Micro sponges are porous microsphere-based polymeric delivery devices. They include a variety of active components that they can contain, including emollients,

perfumes, essential oils, sunscreens, and anti-infective, anti-fungal, and anti-inflammatory medications. Compared to other technologies like microencapsulation and liposomes, the MDS has advantages. Typically, microcapsules are unable to regulate how quickly actives are released. The actives inside the microcapsules will be released once the wall is ruptured. Low payload, challenging formulation, limited chemical stability, and microbial instability are all problems for liposomes.[4]

- Posaconazole is a BCS (Biopharmaceutics Classification System) classII and imidazole derivative with antimycotic action across the board [5]. It inhibits the manufacture of sterol and ergostol, resulting in antifungal action. Posaconazole has a half-life of 15 hours. It has an8-47% oral bioavailability, which increases the drug's dose frequency. Side effects of increased dose frequency include erythema, edema, and skin irritation. Posaconazole topical hydrogel formulation is recommended to exert on the skin's outer layers, which may quickly absorb. The current study's purpose was to create a microsponge-based gel for topically regulated posaconazole delivery. Posaconazole-loaded microsponge-based gels can be employed for prolonged drug release and dosage form retention on the skin, minimizing drug concentration fluctuations, reducing medication toxicity, and enhancing patient compliance by extending dosage application intervals [6].

MATERIALS AND METHODS:

Materials:

Posaconazole was kindly gifted by Lee Pharma Distributors, Mumbai. Carbopol 940, Tween80, Methanol, Propyl Paraben, Methyl Paraben, Triethanolamine was available in SGRS College of Pharmacy, Saswad. All other reagents used were of analyticalgrade.

Formulation Of Posaconazole Microsponges:

- Posaconazole loaded microsponges was prepared by Quasi Emulsion Solvent Diffusion method.
- Porous microspheres (microsponges) are also prepared by a quasi-emulsion solvent diffusion method (two-step process) using an internal phase containing polymer such as Eudragit RS 100 and Ethyl Cellulose which is dissolved in methanol.
- Then, the Posaconazole drug is slowly added to the polymer solution and dissolved under ultra-sonication at 35ºC .
- The inner phase is then poured into external phase containing Tween 80 and distilled water with continuous stirring for 5 hours at 500rpm.
- Then, the mixture is filtered to separate the microsponges. The product (microsponges) was washed and dried in an air at 35°C for 24 hr.
- Collect it.

3^2 Full Factorial Design:

It is essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design. The number of experiments required for these studies is dependent on the number of independent variables selected. The response (Y) is measured for each trial.

$Y = \beta 0 + \beta 1X1 + \beta 2X\ 2 + \beta 12X\ 1X\ 2 + \beta 11\ X1 + \beta 22\ X2$

Where, β = Intercept = Constant

β1 and β2 = Co-efficient of X1 and X2 variable

β12 = Co-efficient of interaction

β11, β22 = Co-efficient of quadratic terms = Non linearity

X1 and X2 = Variables

A 3 full factorial design was employed to study the effect of independent variables, i.e., ratio of Ethyl Cellulose: (X1) and the ratio of Eudragit RS100 (X2) on dependent variables, i.e., %Transmittance (Y1), viscosity (Y2) and %cumulative drug release at 12 h (Y3) (Table 1). Refer (Table 2) for the composition of factorial batches F1 to F9.

Table 1: Coded value of factor in different batches of microemulsion formulations

Batch No.	X1	X2
F1	-1	-1
F2	-1	0
F3	-1	1
F4	0	-1
F5	0	0
F6	0	1
F7	+1	-1
F8	+1	0
F9	+1	+1

Factor and levels for 3 factorial designs

Variables level	Low (-1)	Medium (0)	High (+1)
Ethyl Cellulose (X1)	100mg	250mg	500mg
Eudragit RS100(X2)	1oomg	250mg	500mg

Table 2: Composition of factorial batches F1 to F9

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Posaconazole	500	500	500	500	500	500	500	500	500
Eudragit RS100	100	100	100	250	250	250	500	500	500
Ethyl Cellulose	100	250	500	100	250	500	100	250	500

Evaluation of posaconazole microsponges: [7-10]

Determination of %Transmittance:

The %Transmittance was checked against distilled water using UV-visible spectrophotometer at λmax 272 nm.
%T = Antilog (2 - Absorbance)

Detection of Microsponges by SEM(Scanning Electron Microscopy) Test:

Size and Shape of Microsponges are Detected by SEM test

Formulation of posaconazole microsponge based gel:.

A] Preparation of Gel:[11,12,13]

All the ingredients were accurately weighed. Carbopol 940 was soaked overnight withdistilled water to hydrate and then hydrated carbopol was again dispersed in distilled water bystirring on a magnetic stirrer for about 1 hour, then propylene glycol along with otherexcipients such as Butylated Hydroxy Toulene and Methyl paraben were added withcontinuous stirring to the carbopol 940 solution. Then the mixture was neutralized by thedrop-wise addition of triethanolamine which act as a neutralizing agent. Mixing wascontinued until transparent gel appeared, while the amount of base was adjusted to achieve agel with a pH value of about 6.1.

B] Incorporation of Microsponges into the Gel:

The prepared Microsponges of posaconazole was weighed and dispersedinto carbopol gel with continuous stirring on a magnetic stirrer for 20 minutes to getuniformly distributed microsponges into the gel base.

Evaluation of posaconazolegel:

Determination of physical parameter:

The gel formulations were inspected for visual color, homogeneity, consistency, texture and feel upon application such as grittiness, greasiness, stickiness, and smoothness characteristics. The color of formulation was checked against white and black background. The consistency of gel was checked by applying on skin.

pH Evaluation:

pH evaluation is the important criteria especially for the topical formulation. The pH of gel should be between 5.8 – 6 to mimic the skin condition. If the pH of the prepared gel is acidic or basic, it may cause irritation to the patient. pH of the prepared hydrogel was measured using digital pH meter by dipping the glass electrode into a gel. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Viscosity:

Brookfield Viscometer was used to determine viscosity of preparedgel formulation. For the determination of viscosity, prepared hydrogel formulation was added to the beaker and settled it for 30 minutes at 25-30 °C. Adjust the spindle in that way that spindle does not touch the bottom of the jar and rotate at a moderate speed 100 RPM for 10 minutes. The viscosity reading was noted."

Spreadability:

Spreadability is determined by apparatus which is suitably modified in the laboratory and used for the study. Spreadability was measured by two glass slides and a wooden block, which was provided by a pulley at one end based on Slip and Drag characteristics of gels. A ground glass slide was fixed on this block. "A 1 gm of gel of different formulations were placed on the ground slide. The gel was then sandwiched between this slide and another glass slide having the dimension of fixed ground slide. Excess of the gel was scrapped off from the edges. The top plate was subjected to pull of 50gms. If time taken for the separation of two slides is less then better the spreadability."

Spreadability is calculated by using the following formula:

$S = M \times L/T$

Where, S is the spreadability,
M is the weight in the pan (weight tied to the upper slide),
L = is the length moved by the glass slide,
T = time taken to separate the slide completely from each.

Drug Content Determination:
For drug content determination, about 1 g of microsponge based gel was weighed in a 10 ml volumetric flask and dissolved it in methanol and diluted properly. Methanol was taken as blank and analyzed spectrophotometrically at λmax 272 nm.
Drug Content = (Concentration × Dilution Factor × Volume taken) × Conversion Factor.

Swelling Index:
Swelling of the hydrogel was based on the concentration of the polymer, ionic strength, and the presence of water. To calculate the swelling index of optimized topical hydrogel formulation, 1 gm of hydrogel is kept on porous aluminium foil and then placed aside in a 50 ml beaker containing 10 ml 0.1 N NaOH. Then samples were withdrawn from beakers at specific time intervals and placed it on dry area for specific time, after this reweighed the sample.
Swelling index is determined by a formula:
Swelling Index (SW) % = [(Wt – W0) / W0] × 100.
Where, (SW) % = Equilibrium percent swelling,
W0 = Original weight of gel at zero time,
Wt = Weight of swollen gel after time t.

Stability study:
The optimized microemulsion based gel formulations were subjected to stability studies at different temperatures for a period of one month. Formulations were kept at different temperatures, 5 ± 3°C, 25 ± 2°C and 45 ± 2°C. Samples are withdrawn at each 10days as per ICH guidelines and analyzed for their physical appearance, pH, drug content, drug release profile etc."

In vitro drug diffusion study:
In vitro study was carried out using cellophane membrane. The cellophane membrane was activated in glycerine for 4h. This cellophane membrane was mounted on Franz diffusion cell using feviquick glue at the edge of the donor compartment to escape leakage of the test sample. The cellophane membrane was placed on the receiver chamber and the donor chamber was clamped in place. The receiver chamber was filled with 30 ml of phosphate buffer pH 7.4 as diffusion medium. The whole assembly was put on a magnetic stirrer. 1 gm of microsponges based gel was put on the cellophane membrane and stirring was started with note down of time. Samples were withdrawn from the receiver solution at predetermined time intervals, and the cell was replenished to their marked volumes with fresh buffer solution. The addition of the solution to receiver compartment was done with great care to escape air trapping. The samples were filtered and %drug release was calculated by taking absorbance at λmax 272 nm.

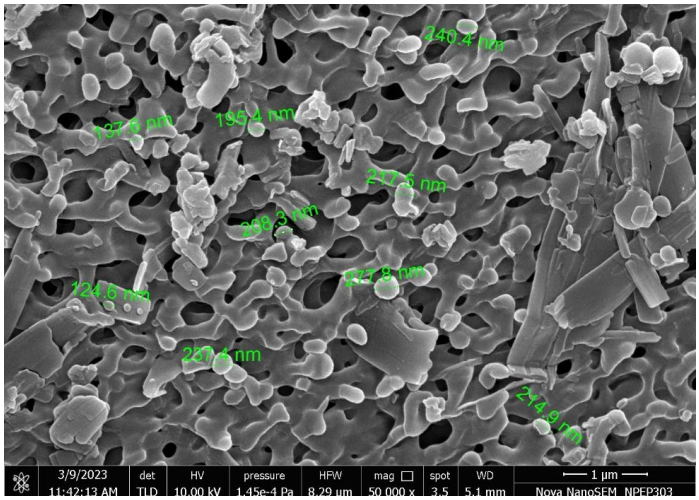
Antifungal activity:
Antifungal activity of the formulation was checked by cup-plate method. A certain volume of Candida albicans suspension was poured into sterilized dextrose agar media (cooled at 40°C) and mixed systematically. About 20 ml of this suspension was poured aseptically in a petri dish and kept till the solidification. The surface of agar plates was pierced by using a sterile corn borer. The prepare wells were filled with equal volume of the optimized batch of microsponge based gel and marketed hydrogel after that it was incubated at 18-24 ºC, for 72 h. Fungal growth was detected and the zone of inhibitions was measured using antibiotic zone reader.

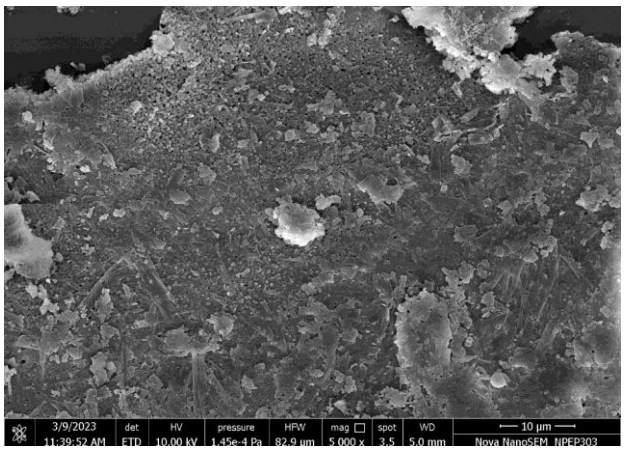
RESULTS AND DISCUSSIONS

Screening of Posaconazole solubility:
The higher solubility of the posaconazole in the oil phase is important because posaconazole is amorphous in nature and poorly water-soluble drug. Posaconazole solubility in the various solvents such as Ethanol, Methanol, Acetone were tested. Amongst the solvents tested, the maximum solubility of posaconazole was found in the Methanoland methanol as a solvent is selected for internal phase preparation.

1)Measurement of %Transmittance of posaconazole microsponges:
%Transmittance of posaconazole microsponges F1-F9 was found to be 96.37, 97.17, 98.01, 98.26, 98.53, 96.55, 98.12, 98.35 and 99.25, respectively. The clarity of microsponges was checked by transparency, measured in terms of transmittance (%T). Formulation F7, F8 and F9 have %Transmittance values greater than 99% indicate the high clarity of microsponges formulations.

2) Detection of Microsponges bySEM(Scanning Electron Microscopy) Test:
Size and Shape of Microsponges are detected by SEM. The microsponges found within 1 um to 10um.Shape is found to be Spherical and Sponge like structure is observed.





3)Measurement of physical appearance and pH of gel:
The prepared posaconazole microemulsion based hydrogel is transparent and white colour with a pleasant odour and smooth texture. The PH of optimized batch(F9) was found to be 5.6±0.25.

4)Measurement of viscosity of posaconazole gel:
Viscosity of posaconazole microsponge based gel was increasing as the speed increases.

Figure 2: Comparison of viscosity of various batches of posaconazole gel formulations at room temperature

5)Measurement of spreadability ofposaconazole gel:
Time taken for the separation of two slides is less then better the spreadability of F9 batch.

Figure 3: Comparison of spreadability of various batches of posaconazolegel formulations at room temperature

6) Measurement of percentage drug content of posaconazole gel:
Percent drug content F9 was found to be 89.23%

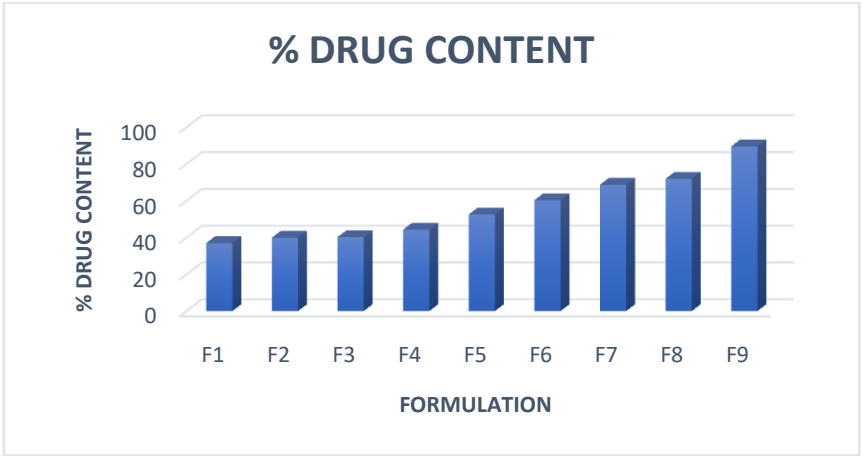


Figure 4: Comparison of % Drug content of various batches of posaconazole gel formulations

7) Measurement of In-vitrodrug diffusion study:
%CDR increases with an increase in the ratio ofEthyl cellulose:Eudragit RS100, as compared to batch F1-F9

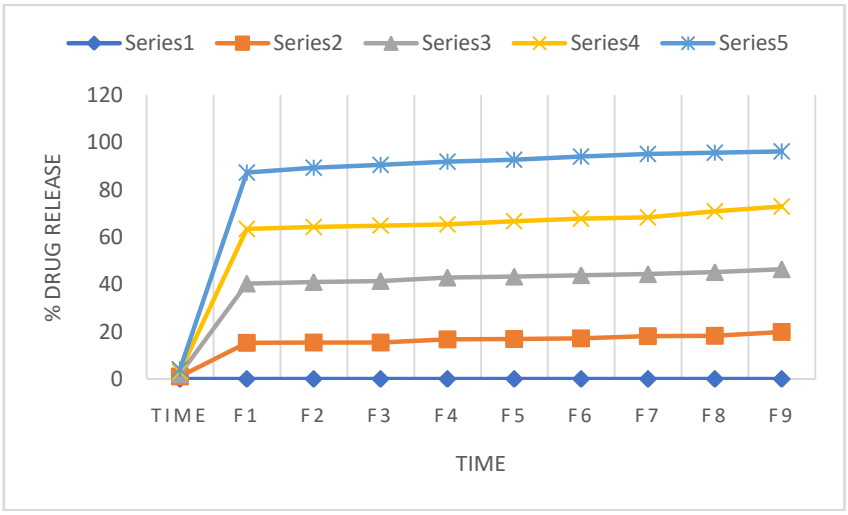


Figure 5: % Cumulative drug release of Posaconazole gel formulation (F1-F9)

8**) Measurement of antifungal activity of posaconazole gel:**

The values of mean zone of inhibition (in vitro antifungal activity) of optimum microemulsion based hydrogel batch (F9) Hence the optimized formulation had highest zone of inhibition (3.8cm) So, it is clearly indicated that the optimized formulation had good antifungal activity.

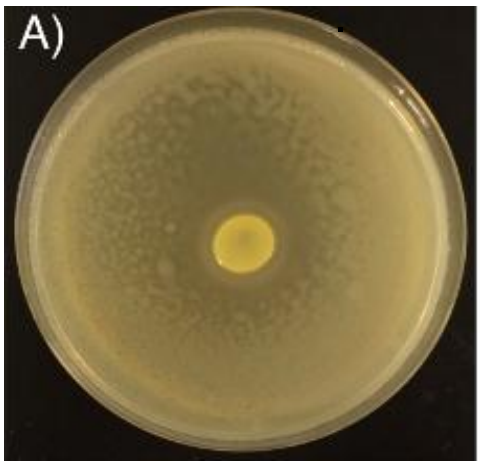


Figure 6: Zone of inhibition of optimized batch (F9)

CONCLUSION

Microsponge formulation was used to increase the solubility of posaconazole. The findings of a 3^2 factorial design revealed that the ratio of Ethyl Cellulose to Eudragit RS100 had a significant effect on the dependent variables such as % Transmittance (Y1), Production Yield (Y2), and CDR after 4 hours. (Y3). The optimised batch F9 has demonstrated in vitro drug release for up to 5 hours. The antifungal efficacy of the optimised microsponge-based gel formulation was high. After one month, a stability analysis of the optimised sample revealed a negligible change in pH, viscosity, transparency, and drug contents.

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