Formulation and Evaluation of Microemulsion Based Hydrogel for Topical Delivery

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Abstract: The purpose of this study was to construct a posaconazole hydrogel based on a microemulsion and characterize it in order to use it as a topical administration system. The solubility of posaconazole was done in different excipients. FTIR spectroscopy was used to conduct a study on the compatibility of drugs and excipients. Pseudoternary phase diagrams were built to determine the region of existence of microemulsions. Posaconazole loaded oil in water (o/w) microemulsion was made by phase titration method. To study the impact of independent variables, such as the ratio of surfactant to co-surfactant and the ratio of oil to water, on dependent variables, such as %transmittance, viscosity, and %cumulative drug release at 4 hours, a 3^2full factorial design was used. The improved formulation F9 demonstrated in vitro drug release for up to 4 hours. The physical appearance, pH, viscosity, spreadability, and in vitro permeability of a posaconazole microemulsion-based hydrogel were all adjusted. Antifungal activity was high in the optimized formulation. The results of the stability research demonstrated that the optimized formulation was sufficiently stable for one month.

Keywords: Topical drug delivery, pseudoternary phase diagrams, microemulsion based hydrogel, posaconazole, 3^2 factorial design, antifungal activity.

INTRODUCTION

Because of their ability to solubilize poorly water-soluble drugs and improve systemic and topical availability, microemulsions, which are thermodynamically stable and optically isotropic systems of water, oil, surfactant, and/or co-surfactant, have been studied as drug delivery systems. It aids in the solubilization of lipophilic drug moiety and provides quick and effective skin penetration. As a result, it is advantageous for medication administration via topical application. Microemulsion is embedded in a polymer hydrogel substrate for topical distribution to increase local interaction with the skin. Creams, ointments, and lotions are often used topical medicines that have several drawbacks, including causing discomfort to the patient when applied, being sticky when administered by rubbing, and having a lack of stability. Because of its low viscosity, microemulsion has a low stability, but this can be solved by putting it into a topical drug delivery system, which improves viscosity and hydrates the stratum corneum, increasing drug dermal permeability and skin flux. Because of all these aspects within the main category of semisolids, the usage of transparent hydrogels in medicinal preparations and cosmetics has increased. Despite the various benefits of hydrogels, the administration of lipophilic medicines is limited. As a result, a microemulsion-based technique is used to circumvent this limitation, and even a hydrophobic medicinal moiety can be efficiently integrated and administered using hydrogels. Using drug/oil/water emulsions, hydrophobic medicines can be integrated into microemulsion-based hydrogels. Hydrogel based on microemulsions aids in the integration of hydrophobic medicines in the oil phase, after which oily globules are disseminated in the aqueous phase, resulting in an oil/water emulsion. [1-5]

Posaconazole is a BCS (Biopharmaceutics Classification System) classII and imidazole derivative with antimycotic action across the board

[6]. It inhibits the manufacture of sterol and ergostol, resulting in antifungal action. Posaconazole has a half-life of 15 hours. It has an 8-47% 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 microemulsion-based hydrogel for topically regulated posaconazole delivery. Posaconazole-loaded microemulsion-based hydrogels 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 [7].

MATERIALS AND METHODS

MATERIALS:

Posaconazole was kindly gifted by Tapadiya Distributors, Pune. Geranium oil was purchased from Sun International, Kolhapur. Carbopol 934, Tween80, Methanol, Propyl Paraben, Triethanolamine was available in SGRS College of Pharmacy, Saswad. All other reagents used were of analytical grade.

SCREENING OF OILS, SURFACTANTS AND CO-SURFACTANTS:

Solubility of posaconazole was determined in different oils, surfactant, and co-surfactant. Posaconazole was added in excess to different oils, surfactant and co-surfactant and stirred for 24 h on a magnetic stirrer. After stirring, samples were centrifuged at 1500 RPM for 10 min and drug in the supernatant was analyzed at λmax 261 nm.[8]

CONSTRUCTION OF PSEUDOTERNARY PHASE DIAGRAM:

The pseudoternary phase diagrams were constructed with screened oil, surfactant/co-surfactant and water using the water titration method at room temperature by ProSim ternary diagram software. The procedure consists of preparing solutions containing tween 80 to methanol (surfactant to co-surfactant) in the ratios 1:1, 1:2 and 1:3. Add water to each mixture and vortexed for 5 min and then placed in a water bath at 37 °C for 24 h with gentle shaking. The mixtures were observed against a dark background after illuminating the samples with white light. To such isotropic solutions a further 5% water was added and vortexed for 5 min, followed by calibration at 37°C for 24 h with gentle shaking. Above procedure was continued until transparent microemulsion was formed.[9]

FORMULATION OF POSACONAZOLE MICROEMULSION

Posaconazole loaded o/w microemulsion was prepared by phase titration method. Surfactant and co-surfactant were mixed in fixed ratio and added into the water drop wise. The drug was dissolved in oil phase and added drop wise in the above solution with continuous stirring. Allowed the solution to form clear and transparent liquid, which was microemulsion.

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 [10-11].

$Y = \beta0 + \beta1X1 + \beta2X\ 2 + \beta12X\ 1X\ 2 + \beta11\ X1 + \beta22\ X2$

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 surfactant: co-surfactant (X1) and the ratio of oil: water (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)
Ratio of surfactant: co-surfactant (X1)	2:1	4:3	5:3
Ratio of oil: water (X2)	1:1	1:2	1:3

Table 2: Composition of factorial batches F1 to F9

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Posaconazole	100	100	100	100	100	100	100	100	100
Surfactant and Co-surfactant ratio	2:1	2:1	2:1	4:3	4:3	4:3	5:3	5:3	5:3
Oil and water ratio	1:1	1:2	1:3	1:1	1:2	1:3	1:1	1:2	1:3

Evaluation of posaconazole microemulsion: [12-15]
Determination of %Transmittance:
The %Transmittance was checked against distilled water using UV-visible spectrophotometer at λmax 272 nm.
%T = Antilog (2 - Absorbance)

Formulation of posaconazole microemulsion based hydrogel:
I made a polymer solution (Carbopol 934) and let it kept for 4 hours to swell. Drop the microemulsion into the gelling solution, stirring continuously with a magnetic stirrer. Finally, add Triethanolamine as a neutralising agent to the formulation to alter the pH.

Evaluation of posaconazole hydrogel: [16-19]
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 hydrogel was checked by applying on skin.

pH Evaluation:
pH evaluation is the important criteria especially for the topical formulation. The pH of hydrogel should be between 5.8 – 6 to mimic the skin condition. If the pH of the prepared hydrogel 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 hydrogel. 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 prepared hydrogel 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 microemulsion based hydrogel 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 hydrogel at zero time,
Wt = Weight of swollen hydrogel 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 microemulsion based hydrogel 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 microemulsion based hydrogel 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 oils, surfactants, and co-surfactants:
The higher solubility of the posaconazole in the oil phase is important because posaconazole is poorly water-soluble drug. Posaconazole solubility in the various oils such as geranium oil, olive oil and mentha oil were tested. Amongst the oils tested, the maximum solubility of posaconazole was found in the geranium oil and Tween 80 as a surfactant, methanol as a co-surfactant.

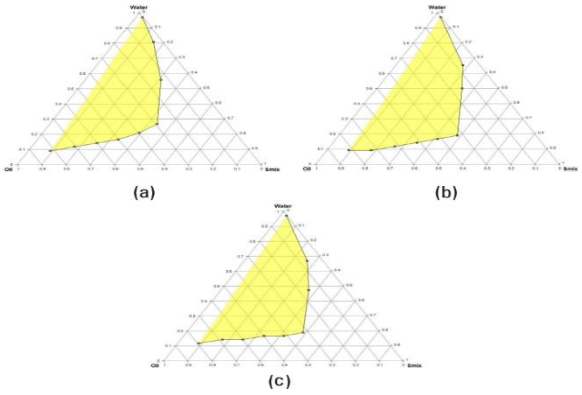

Figure1: Pseudoternary phase diagram with ratio of surfactant: co-surfactant

The results of phase diagram revealed that formulation F9 has shown clear and stable microemulsion formulation

1)Measurement of %Transmittance of posaconazole microemulsions:

%Transmittance of posaconazole microemulsions F1-F9 was found to be 97.37, 98.17, 98.12, 98.46, 98.83, 96.85, 99.12, 99.35 and 99.85, respectively. The clarity of microemulsions 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 microemulsion formulations.

2)Measurement of physical appearance and pH of hydrogel:

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 5.9±0.25.

3)Measurement of viscosity of posaconazole hydrogel:

Viscosity of clotrimazole microemulsion based hydrogel was increasing as the speed increases.

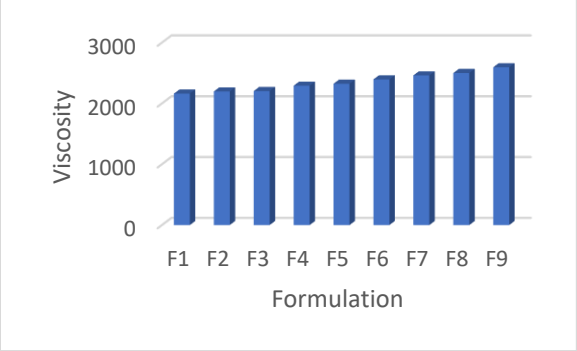

Figure 2: Comparison of viscosity of various batches of posaconazole hydrogel formulations at room temperature

4)Measurement of spreadability of posaconazole hydrogel:

Time taken for the separation of two slides is less then better the spreadability of F9 batch.

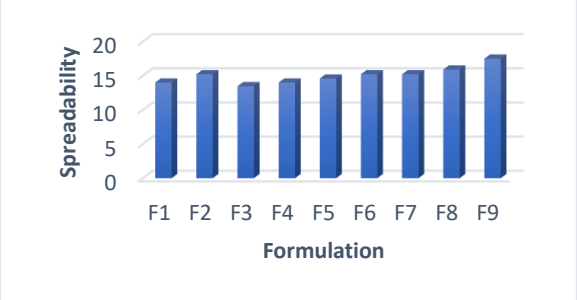

Figure 3: Comparison of spreadability of various batches of posaconazole hydrogel formulations at room temperature

5) Measurement of drug content of posaconazole hydrogel:

Percent drug content F9 was found to be 82.23%

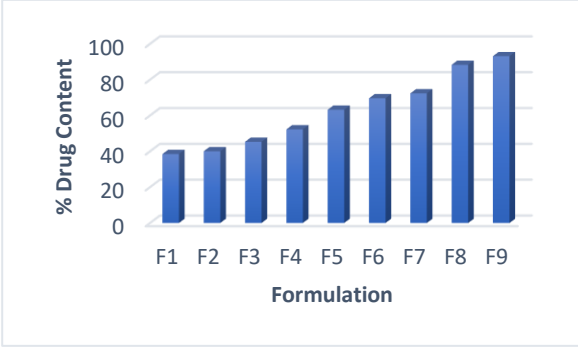

Figure 4: Comparison of % Drug content of various batches of posaconazole hydrogel formulations

6) Measurement of In-vitro drug diffusion study:

%CDR increases with an increase in the ratio of oil: water as well as the ratio of surfactant: co-surfactant, as compared to batch F1-F9

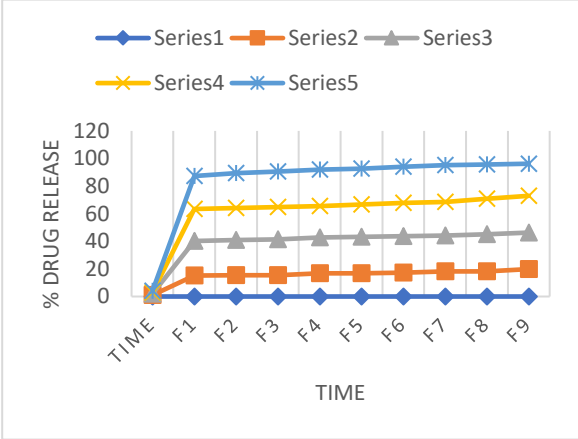

Figure 5: % Cumulative drug release of Posaconazole hydrogel formulation (F1-F9)

7) Measurement of antifungal activity of posaconazole hydrogel:

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 (4.4 cm) So, it is clearly indicated that the optimized formulation had good antifungal activity.

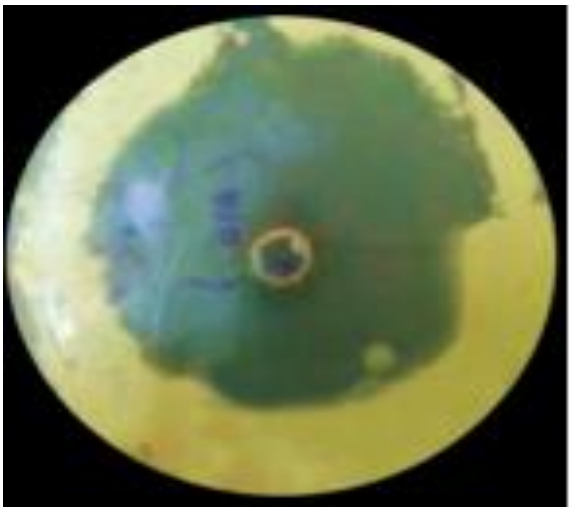

Figure 6: Zone of inhibition of optimized batch (F9)

CONCLUSION

Micro emulsification was used to increase the solubility of osaconazole. The findings of a 3^2 factorial design revealed that the ratio of surfactant to co-surfactant and the ratio of oil to water had a significant effect on the dependent variables such as % Transmittance (Y1), viscosity (Y2), and CDR after 4 hours. (Y3). The optimised batch F9 has demonstrated in vitro drug release for up to 4 hours. The antifungal efficacy of the optimised microemulsion-based hydrogel 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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