Development and characterization of oral posaconazole microemulsion for treatment of systemic fungal infections

Bhavesh Patel[*1,2], Rakesh Patel[3]
[1]PhD Research Scholar, Parul University
[2]Formulation Head,Precise Bio Pharma.Pvt.Ltd
[3] Professor, Department of Pharmaceutics, Parul University
*Corresponding Author :Bhavesh Patel
Institution(s) at which work was performed: Parul University
e-mail address:patel_bhavesh1520@yahoo.co.in
Institutions address: Parul University, P.o.Limda, Tal. Waghodia-391760, Dist. Vadodara, Gujarat (India)

Abstract

Objective: Concurrent fungal infections in the current area have been an unaddressed issue due to the resistance of the host fungal organism to the present antifungal ailments available in the market. Posaconazole is the drug of choice for prophylactic fungal infection and is also recommended in immune-compromised patients in prophylaxis of candida and aspergillus infections including patients undergoing hematopoietic stem cell transplantation that has graft versus host disease. Hence the aim is to formulate a microemulsion based formulation of posaconazole to deliver the drug at the site of action with a quick onset of action compared to suspension formulation at an affordable cost.

Methodology: Posaconazole microemulsion was formulated using a pseudo ternary phase diagram and optimized using a D-optimal design. The formulation was characterized for % drug content, pH, globule size, zeta potential, PDI value and i*n-vitro* drug release and stability study at 40°C/75% RH for six months.

Results: The oral posaconazole microemulsion had a drug content of more than 95%, pH of 7.2. The globule size, zeta potential and PDI value were found to be 74 nm, 12.45 mV and 0.122 µs.cm-1 indicating a stable microemulsion. The drug release of the ME was more than 90% in fifteen minutes indicating the quick onset of action and availability at the site of action.

Conclusion: From the obtained results, it can be said that a stable posaconazole oral microemulsion with a quick onset of action and better bioavailability can be manufactured at affordable cost which can enhance patient compliance.

Key words : Posaconazole, microemulsion, anti-fungal

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Introduction

Fungal infections have an olderexistence about centuries ago and more than 50000 species of fungi have been in existence. Yet, the frequency of the pathogenic fungi infecting the host also has increased remarkably (Achterman and White 2012).The present medications to treat the fungal infections are using either of the dermal applications flooded in the market like creams, gels, sprays and lotions or the oral medications containing these active pharmaceutical moieties like triazole derivatives viz fluconazole, eberconazole, sertaconazole, ketoconazole, luliconazole or oral antifungal medications like tablets, capsules, suspensions containing fluconazole, itraconazole, micafungin. Newer species of fungi like *candida glabrate, trichophytonmegantrophes, candida parapsilosis, candida krusei, trichophytonbenhamie, trichophytonspiraliforme, trichophytonpersicum, trichophytonjaponicum, trichophytonafricanum* to name a few are evolved which the current line of treatment does not serve the purpose. Concurrent fungal infections in the current area have been an unaddressed issue due to the resistance of the host fungal organism to the present antifungal ailments available in the market. Newer species of fungi developing as a consequence of mutation possessing an inherent resistance to the available antifungal medications have also been lacuna in the therapeutic regimen (Richardson, Lass-Flörl et al. 2008).

There is a need of either proving the newer antifungal agent with a broad spectrum of action against the fungi pathogens or delivering an existing antifungal agent which has a broad spectrum of action that would have a quick onset of action, low microbial minimum inhibitory concentrationwith maximum fungicidal efficacy to the site of infection. The faster the ability of the drug the cross the systemic circulation the faster is the absorption drug at the site of action (Rodrigues and Nosanchuk 2021). Posaconazole is the drug of choice for prophylactic fungal infection caused by *cryptococcusneoformans, Aspergillus species,* Scedosporium *species,* Fusarium *species and candida species, etc.*Posaconazole is not only recommended drug of choice in immune-compromised patients in the prophylaxis of candida and aspergillus infections but also includes patients undergoing hematopoietic stem cell transplantation who has graft versus host disease (Greer 2007). Chemically, posaconazole is a triazole molecule with a poorly soluble molecule having a solubility of 0.027 mg/ml. and a log P value of 5.5 indicating poor permeability with a high efflux potential. Posaconazole exhibits pH dependent solubility i.e. below pH 1. It has a solubility of 790 mcg/ml while at pH more than 4 it has solubility less than 1 mcg/ml (Hens, Brouwers et al. 2015). Mechanism of action of posaconazole is an inhibitor of lanosterol an alpha demethylase enzyme which inhibitsergosterol synthesis. The later is vital for formation of fungal cell walls. This causes cell wall death and leads to leakage of cellular components and cell death (Hof 2006).

The onset of the delivery of the active plays a crucial role in minimizing the spread of infection, providing quick relief and improving patient compliance and ensuring adherence to the therapy. Microemulsions are considered thermodynamically unstable clear transparent or translucent systems containing a dispersed phase dispersed in a dispersion phase along with a surfactant and co-surfactant where the globule size of the dispersed phase is not more than 100 nm. Microemulsions are better in terms of emulsions in terms of duration of action, providing targeted delivery to the site of action and stability (Kale and Deore 2017). In the current scenario Noxafil tablet and Noxafil suspension are available in the market containing 100 mg and 40mg/ml of posaconazole respectively. The marketed formulation of posaconazole is heavy on cost due to complex processes and specialized equipment increasing the cost of production (Gandhi, Suthar et al. 2021) . Hence, the current hypothesis is to deliver a microemulsion based formulation of posaconazole to deliver the drug to a site of action with a quick onset of action compared to the tablet and suspension formulation. Also, as there is no complex machinery involved the cost of production is reduced and the product can be made available at a low cost.

In the macroemulsion system, average globule size increase with fractions of time and thus phase separation ultimately occurs under gravitational force, which makes them thermodynamically unstable and their formation requires input of work, whereas in the case of microemulsions the formation of the system is extemporous that depends on the structure and nature of the surfactant involved which sufficiently lowers the energy required to raise the surface area hence the spontaneous dispersion of water or oil droplets makes the system thermodynamically stable (Kale and Deore 2017).

For a while, the regulatory requirements have focused on the product development by the approach of the quality by design concept to ensure the robustness and building quality into the product rather than getting the quality tested for the finished product. Hence as per the quality by design framework, critical quality attributes were chosen from the quality target product profile (QTPP) which were defined enlisting properties that affect the finished product quality for formulating posaconazole microemulsion to achieve the maximum therapeutic efficacy at the site of action (Singh, Kumar et al. 2005).

Materials

Posaconazole was received as a gift sample from BDR Pharmaceuticals international private limited, Vadodara, India. Tween 80 was purchased from Sulab chemicals, Vadodara, India. Polyethylene glycol was obtained from Indian glycols, India. Sodium saccharin was obtained from N.S. chemicals private limited, Mumbai, India. Sodium saccharin was obtained from IFF private limited, Mumbai, India.

Methods

1. Defining QTPP and CQA's

As the quality based design framework is to be applied in the development of posaconazole oral microemulsion, Quality target product profile needs to be defined that enlists the targeted quality characteristics of a microemulsion. The quality target product profile (QTTP) for the oral posaconazole microemulsion is described in Table 1. critical quality attributes (CQA) are the ones that define the attributes that impact the finished product quality and are derived from the set of enlisted QTTP like strength, globule size, *in-vitro* drug release, zeta potential, % drug loading, assay or dug content and *ex-vivo* permeation of the drug. The list of critical quality attributes for posaconazole oral microemulsion is shown in Table 2.

Table 1: Quality target product profile (QTTP) of oral posaconazole microemulsion

QTPP elements	Target	Justification
Dosage form	Microemulsion (ME)	Selection of phospholipid based ME helps in the enhanced permeation through mucosal layer
Dosage type	Rapid release	Quick onset of action leads to enhanced therapeutic effects
Route of administration	Oral	Most preferred route of administration
Dosage strength	300 mg	300 mg Posaconazole was incorporated in a single formulation of ME
Ex vivo permeation	Higher permeation and muco-adhesion	Required for achieving higher drug concentration in blood stream
Stability	At least 6 months at various storage temperatures	To maintain therapeutic potential of the drug during storage period
Container closure system	System qualified as suitable for this drug product	Needed to achieve the targeted shelf life

Table 2: Critical quality attributes (CQA) of oral posaconazole microemulsion

Quality attributes of the drug products	Target	Is this a CQA?	justification
Physical attributes color Odor appearance	Transparent No unpleasant odor	No	Physical attributes of the formulation were not considered as critical as they are not directly linked to efficacy and safety

	Acceptable to patients		
Assay and content uniformity	Assay: 95-105 Content uniformity: 80-95	No	MEs are being considered as homogenous dispersions containing drug present in solubilized in the blend of excipients, so regarded as moderately critical
Globule size	Less than 100 nm	yes	Smaller globule size of ME will facilitate better permeation in the mucosal layer
Permeation	High	Yes	The components of microemulsion can interact with transmucosal layers, changes its structural integrity leading to reducing the diffusion barrier and thus enhancing the permeation
Drug loading	High	Yes	Large amount of drug can be incorporated due to high solubilization capacity
Zeta Potential	Between +40mV to -40mV	Yes	As indication of stability of ME zeta potential is considered as critical quality attribute

An Ishikawa diagram is the tool tom access the risk involved in the process design and formulation design and the factors contributing to the same. An Ishikawa diagram (also called as fishbone) diagram was prepared using Microsoft Visio® pro software tool as an indicative of the cause and effect of a particular critical attribute on CQA of the oral posaconazole microemulsion formulation shown in figure 1.

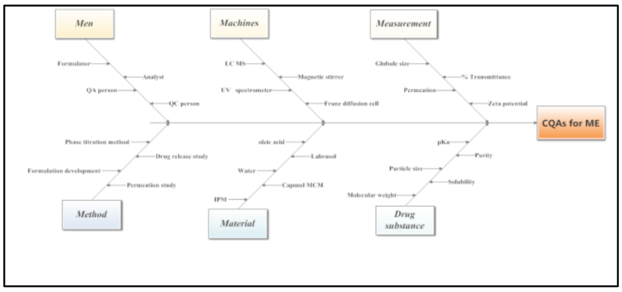

Figure 1: Ishikawa diagram of oral posaconazole microemulsion

2. Preformulation study of posaconazole (Gandhi, Suthar et al. 2020)

Preformulation study for the development of posaconazole microemulsion formulation involves determining the aqueous solubility study and drug excipient compatibility study. Solubility of posaconazole was tested in water. Water was added per ml to 10 mg of posaconazole in a test tube and aqueous solubility was determined. Also, the solubility study of posaconazole was carried out to screen the oil phase, surfactant and co-surfactant suitable in the microemulsion formulation. The oil phase components selected for solubility study are soybean oil, cotton seed oil, Transcutol P, Captex 200, Labrasol, Labrafil, Captex 355 NF, Capmul MCM, Isopropyl myristate. Surfactants screened were Tween 80, Span 80 and Pecol and co-surfactants screened were PEG 400 and isopropyl alcohol. A drug excipient compatibility study was conducted by preparing a physical mixture of drug and excipients in a 1:1 ratio and subjecting them to 40ºC / 75% RH for one month and a Fourier transformation infra-red spectrophotometer was used to confirm the compatibility of the drug and formulation samples (Rakesh and Charmi 2014).

3. Development of posaconazole microemulsion (Moghimipour, Salimi et al. 2013, Negi, Singh et al. 2016)

Generally,the development of microemulsion formulation requires construction of a pseudo ternary phase diagram to optimize the ratio of Surfactant: Co-surfactant ratio required for the preparation of a stable microemulsion. Pseudo ternary phase diagrams were constructed using a Phase titration method. As per the miscibility of posaconazole in various oils, surfactants and co-surfactants, posaconazole dissolved in labrasol was chosen as oil phase, Tween 80 was chosen as surfactant and PEG 400 was chosen as co-surfactant. In phase titration method, varied combinations of Tween 80 as a surfactant and PEG 400 as co-surfactant were taken to obtain a suitable S_{mix} ratio, posaconazole dissolved in labrasol was used as oil phase and purified water as water was utilized to investigate the phase behavior by employing titration method. The S_{mix} ratios containing a Oil: surfactant- co-surfactant (S_{mix}) were altered at 1:1, 1:2, 1:3, 1:4, 2:1, 3:1 and 4:1 to construct pseudo ternary phase diagrams for Smix ratio optimization. The ME area of the ternary system was prepared as a triangular phase diagrams using CHEMIX® software (Ver. 3.5.1) and the ratio with the maximum area coverage in the phase diagram is suitable to formulate posaconazole microemulsion formulation.

Method of preparation of posaconazole microemulsion

Posaconazole microemulsion was prepared using labrasol as oil phase, Tween 80 as surfactant and polyethylene glycol 400 as co-surfactant. Posaconazole was dissolved in predetermined concentration of oil and this was mixed with the optimized concentration of surfactant co-surfactant mixture in a glass beaker under continues stirring using a magnetic stirrer. Flavour and sweetener were added to specific quantity of water which was added to the drug surfactant mixture. The mixture was continuously until clear transparent microemulsion is obtained.

Every experiment requires a scientific tool in order to justify the validation of the experiment. To optimize the microemulsion scientifically, D-optimal design of experiment was used to obtain robust, reproducible and optimized formulation. A D-optimal design of experiment is a constrained design containing three factors (i.e. Oil, S_{mix} and water), and is model independent, which leads to optimization based on suitable fit model that can be attained based on factors and hence is a suitable design for optimization of microemulsion formulation. The levels of the three independent variables i.e. oil (X_1), Smix (X_2) and water (X_3) are chosen based on the pseudo ternary phase diagrams. The ranges of the independent variables chosen for the D-optimal design are defined as below.

3ml_ X1_5 ml

30ml_ X2_42ml

55ml_ X3_65 ml

Table 3 describes the details of the thirteen experimental runs suggested by the design of experiment based on the constraint values in factor runs. The globule size (Y_1, nm) zeta potential (Y_2, nm) and % drug loading (Y_3, %) were chosen as the responses (CQA's).

Table 3: Factors and responses of D-optimal design

Experimental runs	X_1	X_2	X_3
1	3.00	42.00	55.00
2	4.42	30.58	65.00
3	5.00	40.00	55.00
4	4.42	30.58	65.00
5	3.00	40.03	56.97
6	3.00	35.46	61.54
7	5.00	37.92	57.08
8	3.87	36.78	59.35
9	3.87	36.78	59.35
10	3.00	32.00	65.00
11	5.00	33.21	61.79
12	5.00	34.92	60.08
13	3.09	33.62	63.28

Data analysis via the design of experiment

Data variables in response surface approaching the design of the experiment were analysed using Design expert® 7.0 software (version 7.0, Stat-ease.Inc, Minneapolis, USA) to fit the equations of linear, quadratic or cubic model using D-optimal design. The polynomial equations were derived using those coefficients which were found significant by using analysis of variance (ANOVA) as a statistical tool. The results of polynomial regression were represented in form of an arithmetic equation as well as contour plots using the design expert software shown in figure 3. The prediction of optimized formulation was done initially by using an overlay plot obtained by superimposing the counter plots over each other in the software to find the best composition. The region of the overlay-plot where all the value ranges fall in the acceptable range is called design space. The optimized formulation wasflagged within the overlay plot such that all the parameters (globule size, zeta potential and % drug content) fall in the desirable range and further a check point batch was formulated from the overlay plot to validate the design of experiment. The results of checkpoint batch and an executed batch was compared and the closeness to desirability plot values were confirmed to validate the design of experiment.

4. Characterization of microemulsion

4.1. % Transmittance

% Transmittance of posaconazole microemulsion formulation was all the batches were measured using a UV visible spectrophotometer (UV series 1800 Shimadzu, Kyoto, Japan) at 650 nm keeping distilled water blank.

4.2. pH of microemulsion

The pH of the posaconazole microemulsion was measured using a digital pH meter (Electro-lab, India).

4.3. Zeta potential

Zeta potential and PDI are the stability indicating parameters of microemulsion were measured using a Malvern zeta sizer ZS90 (Zetatrac software 10.6.2 by microtrac.inc, India). The samples of microemulsion were diluted 10 folds before analyzing the globule size and zeta potential. The mean value of triplicate measurements for each sample was reported as the final result.

4.4. Globule size

Globule size of the microemulsion was done using transmission electron microscopy using water as a dispersing agent (Indian Institute of Technology, Mumbai, India).

4.5. Drug content

Drug content of posaconazole microemulsion was evaluated using a UV Visible spectrophotometer (UV 1800, M/s Shimadzu, Kyoto, Japan) at 264 nm, where the content of clove oil in the formulation was calculated using the clove oil as standard by the equation given below.

$$Cu/Cs = Au/As$$

Where Cs is the concentration of the standard sample, Cu is the concentration of a test sample, Au is the absorbance of a test sample and As is the absorbance of the standard sample.

4.6. *In-vitro* drug release (Constantinides 1995)

The *in vitro* release of Posaconazole optimized formulation through dialysis membranes (MWCO: 10,000–16,000) was performed in phosphate buffer for 15 min at 37 ± 1 °C using a dialysis membrane as barrier and magnetic stirrer plate assembly method. Briefly, the polycarbonate dialysis membrane (pore size 0.22 mm) was soaked in the dissolution medium for 24 h before the commencement of each release experiment. Approximately 3–5.0 mL emulsions were added into the dialysis membrane containing 2.0 mL of the release medium. Thereafter, it was suspended in a 250-mL beaker containing 150 mL of dissolution medium and agitation was provided magnetically using a magnetic stirrer at 100 rpm (Remi Instruments, Mumbai, India). At predetermined time intervals, a 5.0 mL sample was withdrawn using a 5 ml needle and syringe. The same volume of medium was replaced immediately to maintain sink condition. The amount of Posaconazole in the withdrawn samples was determined.

4.7. Stability study

Posaconazole microemulsion was subjected to a stability study at 40±2̊C/75± 5% RH for six months as per ICH. The Formulation was

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analysed for any sign of degradation i.e. changes in appearance, globule size, zeta potential, PDI value and drug content.

Results and Discussion

Results of preformulation study

The solubility study of the posaconazole in various oils depicted that amongst soybean oil, cotton seed oil, Transcutol P, Captex 200, Labrasol, Labrafil, Captex 355 NF, Capmul MCM, Isopropyl myristate the solubility of posaconazole was highest in Labrasol and hence was chosen as an oil phase. Amongst the surfactant and co-surfactant, miscibility of oil phase was highest in tween 80 and polyethylene glycol 400. Hence tween 80 was chosen as surfactant and PEG 400 was chosen as co-surfactant. The solubility of posaconazole in various oils, surfactants and co-surfactants is shown in figure 2.

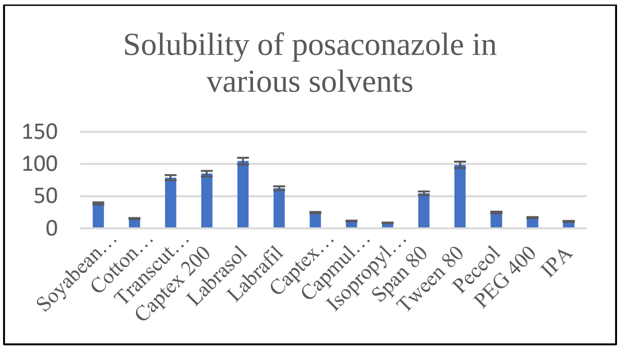

Figure 2: Solubility of posaconazole in various solvents

Also, constructed Pseudo-ternary phase diagrams to obtain the appropriate concentration range of components in a microemulsion depicted that the ratio of 2:1 was chosen appropriatly for the preparation of microemulsion as shown in figure 3.

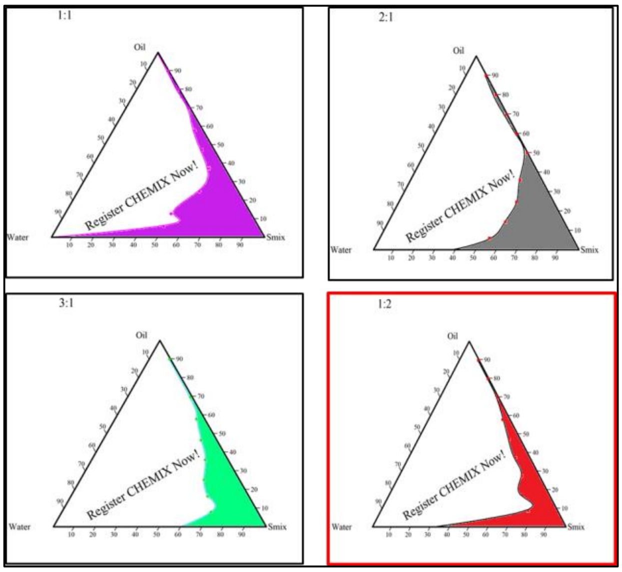

Figure 3: pseudo ternary phase diagram for oral posaconazole ME formulations

As a part of a drug excipient compatibility study, the FTIR was taken performed on the samples initially and after one month (placed at 40°C/75% RH). The results indicated that there was no shift in the wave numbers of the functional groups when compared to initial sample FTIR's. The FTIR's of pure drug and drug with excipients are shown in figure 4. Hence, it can be said that the drug is compatible with the excipients.

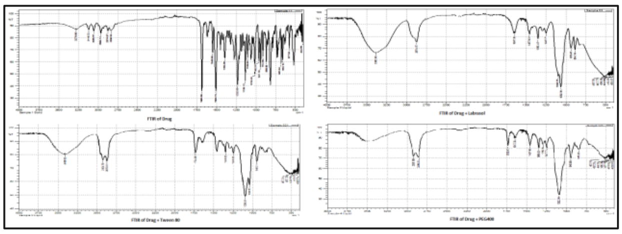

Figure 4: Results of Drug excipient compatibility study

Formulation by design

Posaconazole oral microemulsion formulation was optimized by applying a D-optimal design as a nature of a response surface relationship and deriving a finalized formulation. The factors or the independent formulation variables were chosen for the design were oil phase (x_1), Smix phase (X_2) and Water (X_3) whileglobule size (Y_1, nm) zeta potential (Y_2, nm) and % drug loading

(Y_3, %) waschosen as a critical quality attribute or the responses. The relationship of the factor to the response variables were studied individually as well as the interaction of each factor in combination with the response was studied.

Table 4 describes the details of the thirteen experimental runs suggested by the design of the experiment based on the constraint values in factor runs and the experimental values of the responses obtained conducted by executing the runs.

Table 4: Factors and response values of D-optimal design

Batch No.	X_1	X_2	X_3	Globule Size (nm)	Zeta potential (mv)	Drug Loading (%)
1	3.00	42.00	55.00	69	8	78
2	4.42	30.58	65.00	98	15	99.6
3	5.00	40.00	55.00	156	11	95
4	4.42	30.58	65.00	89	15	99.9
5	3.00	40.03	56.97	81	7	72
6	3.00	35.46	61.54	78	9	76
7	5.00	37.92	57.08	199	5	92
8	3.87	36.78	59.35	67	12	97
9	3.87	36.78	59.35	65	8	93
10	3.00	32.00	65.00	50	7	80
11	5.00	33.21	61.79	187	25	97
12	5.00	34.92	60.08	205	18	91
13	3.09	33.62	63.28	121	9	76

By placing the values of the responses variables in the runs suggested by the design of the experiment, the design was run to select the best model from either linear, quadratic or cubic that leads to the derivation of the correct polynomial regression equation for optimization of the posaconazole microemulsion and to derive a suitable polynomial equation that predicted a sum of residual squares for three response variables (Y_1 to Y_3) to determine the suitability of a right model fit and usually the minimum the PRESS value more suitable is the model.

The analysis of variance evaluated for the responses ensured the r square value near 1.0 confirming the suitability of the selected model. Also, the Probability value of the F value for each variable was less than 0.05 which indicated the suitability of the model. Following were the polynomial regression equations derived and used to demonstrate the relationship between the formulation components oil (X_1), S_{mix} (X_2), water (X_3), and the response variables Y_1 to Y_3. The equation derived for each of the variables is given below. The coefficients of each are mentioned in table 5 below.

Table 5: Model summary statistics

Response	Y_1	Y_2	Y_3
Model	Linear	Linear	Linear
A	0.0038	-22.28	-1225.38
B	68.69	7.43	76.31
C	27.3	6.19	80.7
AB	-0.005	61.36	1694.34
AC	-0.0028	64.5	1680.94
BC	128.98	5.92	-15.6
ABC	0.0285	128.47	0

Other than the polynomial regression equation, another way to determine the optimized formulation is the counterplots or also represented as response surface curves that depict the effect of factor variables on the response chosen. Counter plot for the globule size reveals that increase in the concentration of X_2 (S_{mix}) and X_3 (water) increases the globule size significantly and with the decrease in the concentration of water and S_{mix} the size of globules increases. The increase in the concentration of oil and water reduced the zeta potential while the increase in the concentration of oil-Smix and water Smix increased the zeta potential. The increase in the concentration of oil increases the drug loading and reduces the concentration of Smix and water in the formulation. The counterplots of all the three factors and responses interactions and the overlay plot is shown in figure 5.

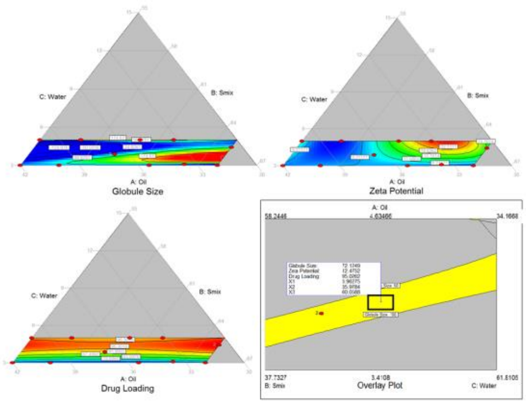

Figure 5: Counter plots and overlay plot of D-optimal design

The final formulation was derived based on the point prediction from the design of the experiment by all the values that were confined within the desirability plot and overlay plot. Table 6 mentions the final formulation of oral posaconazole formulation.

Table6: Oral Posaconazole formulation

Sr. no	Ingredient	Concentration	Function
01	Posaconazole	200mg/ 5ml	Drug
02	Oil	4%	Oil phase
03	Tween 80	12%	Surfactant
04	PEG	24%	Co-surfactant
05	Double distilled water	60%	Aqueous phase
06	Sucralose	0.1%	Sweetener
07	Vanila extract	0.015%	Flavoring agent

The posaconazole oral microemulsion was a clear transparent microemulsion with a sweet taste and aromatic smell. The viscosity of the micro emulsion was 154.2 ± 0.51 cps and the pH of the microemulsion was 7.19 i.e. isotonic to the systemic pH. The transmission electron microscopy of the microemulsion depicts the dak spherical globules in the transparent light background shown in figure 6. The % transmittance of microemulsion measured using a UV visible spectrophotometer (UV series 1800, M/s Shimadzu, Kyoto, Japan) at 650 nm was 99.68% indicating a clear transparent microemulsion. The conductivity of microemulsion measured via conductometer was 127.5 ± 3.4µS.cm^{-1} indicating oil in water nature of microemulsion. The zeta potential of the microemulsion formulation was +12.45 mV and the PDI value was suggested as 0.00148 indicating a stable microemulsion. The globule size of microemulsion was 74.28 ± 4.1 nm.

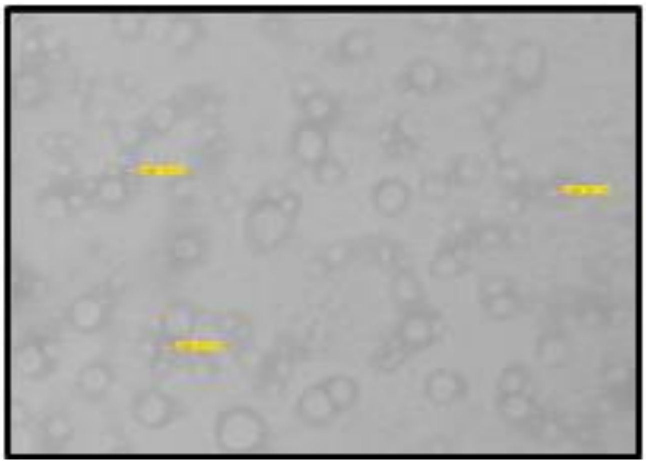

Figure 6: TEM of posaconazole microemulsion

The drug release of the microemulsion formulation was performed using a dialysis membrane(MWCO: 10,000–16,000) was performed in phosphate buffer for 15 min at 37 ± 1 °C. The % drug release of the microemulsion showed complete drug release within fifteen minutes. 94.57% of posaconazole was released within fifteen minutes in a dissolution apparatus indicating the quick onset of action. The drug release of the posaconazole microemulsion was compared with Noxafil® suspension marketed by Merck Shape Dohme and is shown in figure 7. The comparative *in-vitro* drug release showed that posaconazole microemulsion had a faster drug release than the marketed posaconazole suspension indicating faster drug release, quick onset of action and faster availability of the drug at the site of action.

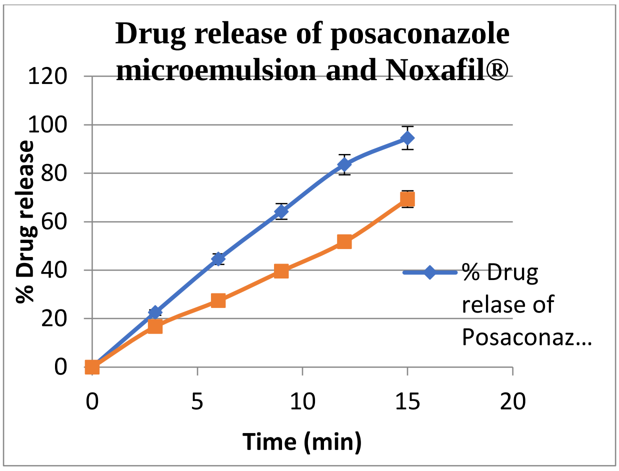

Figure 7: Drug release of posaconazole microemulsion and Noxafil® suspension.

The posaconazole oral microemulsion was subjected to a stability study at 40±2̊C/75± 5% RH for six months. The results shown in table 7 indicated that the posaconazole microemulsion was stable after six months even in accelerated conditions, as there was no marginal degradation observed in drug content as well as zeta potential and PDI values were indicative of a stable microemulsion. Thus posaconazole microemulsion can be considered stable and stored for 24 months below 25°C in a cool and dry place.

Table 7: Stability data of posaconazole microemulsion at 40°C/75%RH

Parameters	Optimized Batch - Accelerated Stability study 40□/75% RH			
	Initial	1 month	3 months	6 months
Drug Content	99.25.±0.045	100.24±0.018	99.76±0.034	99.18±0.074
Sign of physical degradation	No	No	No	No
Globule size	74.29±2.34	78.64±3.24	79.11±2.11	80.24±1.38
Zeta potential	12.45±1.23	13.24±2.05	10.34±1.14	14.59±1.37
PDI	0.122	0.113	0.124	0.126

Conclusion

The posaconazole oral microemulsion was clear and transparent with a globule size of 74nm and pH isotonic to the systemic pH. Zeta potential and PDI values indicated the stability of the microemulsion. The drug loading of the API in the microemulsion was achieved as desired. The posaconazole microemulsion showed better and faster drug release as compared to Noxafil suspension. Also, the microemulsion formulation was stable for six months. Hence it can be said that a stable posaconazole oral microemulsion with a quick onset of action and better bioavailability can be manufactured at an affordable cost which can enhance patient compliance.

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