Original Article

Formulation And Development Of Posaconazole Loaded Microemulsion Based Gel For Treatment Of Fungal Infections

[1]Mr. Dinesh Prabhakar Patil*, [2]Dr. Rashid Ahmad [3]Dr. Vivek

1. Research Scholar, Shri JJT University, Jhunjhunu, Rajasthan-333001, India
2. Shri JJT University, Jhunjhunu, Rajasthan-333001, India
3. Shri JJT University, Jhunjhunu, Rajasthan-333001, India

*Corresponding author:

Mr. Dinesh Prabhakar Patil, Research Scholar, Shri Jagdishprasad Jhabarmal Tibrewala University, Jhunjhunu, Rajasthan-333001, India

Email: patil.dinesh344@gmail.com

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Abstract

Background: More than 50000 pathogenic fungal species are prevalent in recent times. Despite of current antifungal treatments available there is a need for exploration of a molecule to treat superficial fungal disorder for topical, localized delivery due to resistance of present medications and adverse events related to them.

Aim: The aim of present work is to develop the Posaconazole microemulsion based system using gel as a secondary carrier system to treat superficial and deep tissue fungal infections.

Methods: The microemulsion containing Posaconazole, labrasol as surfactant, PEG 400 as co-surfactant was prepared using phase titration method and optimized using a D-optimal design. Microemulsion was characterized for organoleptic characteristics, zeta potential, globule size, PDI value, etc. The posaconazole microemulsion based gel (PMBG) was prepared by adding babool gum into microemulsion. The microemulsion based gel was characterized for drug content, in-vitro drug release, skin permeation study, skin irritation study and stability study.

Results: The clear transparent microemulsion was having globule size of 86 ± 3 nm. The zeta potential of microemulsion was 16 ±0.4 mV along with PDI value of 0.0013 indicating the stability of microemulsion. The microemulsion based gel was having a drug content of 102.69 ± 0.58%. The drug release from the microemulsion was and the 98.50 ± 0.37%, drug permeation of PMBG was 87.27 ± 0.17% and was non-irritant to skin.

Conclusion: From the above results, it can be said that Posaconazole microemulsion based gel is safe, effective, and efficient for treatment of fungal infections via topical route of application.

INTRODUCTION

Although there are various ailments available in the market for treatment of superficial fungal infections, still the fungal infections have been an unaddressed issue pertaining in present times. More than 50000 fungal species have been in to existence which is pathogenic to humans.(1) With the evolution in the fungal species genera there is evolution in the resistance of the fungal species too. The current antifungal therapy in the market is ketoconazole, fluconazole, clotrimazole, etc. Variety of the fungal species has gained a resistance to the present medications.(2) The resistance in the phenomenon is due to the change in the genetic sequencing of the microbial flora. The other reason can be the longer duration of therapy that can lead to gain of resistant strain and thus reduced patient compliance. Also, the adverse events faced by the patients like, rash, pruritus, numbness of hands, unusual bleeding, bruising, inflammation, hypersensitivity, etc. make the available therapy undesirable to treat fungal infections. Hence there is a need for exploration of a molecule to treat fungal disorders.(3)

Posaconazole chemically named 4-[4-[4-[4-[[(3R,5R)-5-(2,4-difluorophenyl)-5-(1,2,4-triazol-1-ylmethyl)oxolan-3-yl]methoxy]phenyl]piperazin-1-yl]phenyl]-2-[(2S,3S)-2-hydroxypentan-3-yl]-1,2,4-triazol-3-one is a potent triazole antifungal agent used for the treatment of the invasive fungal infections in adults therapeutically administered for Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant to either of these two antifungal products.(4) Posaconazole formulations are also indicated in the prophylaxis of Patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high-risk of developing invasive fungal infections and hematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high-risk of developing invasive fungal infections.(5)Mechanism of action of posaconazole is similar other triazole agents i.e. posaconazole inhibits the enzyme lanosterol 14α-demethylase and consequently inhibits the biosynthesis of ergosterol, which is an essential component of fungal cell membrane.(6) This results in an accumulation of methylated sterol precursors and depletion of ergosterol within the cell membrane, thereby weakening the structure and function of the fungal cell membrane, which is considered to be responsible for the antifungal activity of posaconazole as shown figure1.(7)

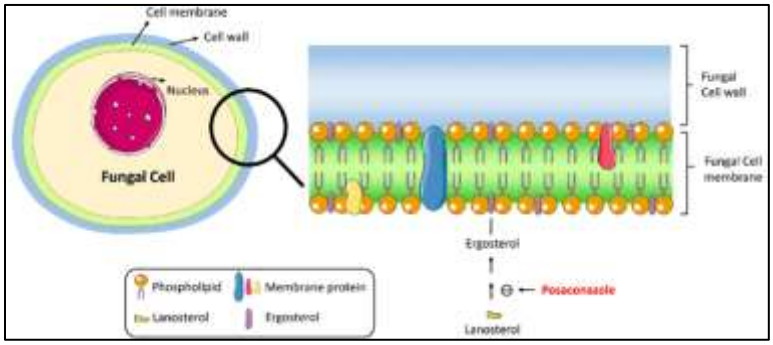


Figure1: Mechanism of action of Posaconazole

Micro-emulsion is a novel drug delivery system which is believed to be thermodynamically stable, singular optically isotropic systems and clear to translucent solutions with droplet size in the submission ranging from 100nm to few microns.(8) Micro-emulsions contain a constant oil phase, a surfactant a co-surfactant and aqueous phase systems which are combined to form clear thermodynamically stable solution.(9) Micro-emulsions are reported to increase the rate and extent of absorption of lipophilic drugs.

In topical route of administration, transdermal drug delivery system has seen a light in a few years that has overshadowed the disadvantages of delivering a drug from oral route.(10) Since years, skin has been used as a route of drug delivery for treating superficial infections and other local effects leading to high patient compliance and adherence to therapy along with achieving maximum therapeutic benefits with least side effects.(11) Transdermal drug delivery system is defined as a painless method of drug delivering drugs by applying formulations onto a healthy and intact skin.(12)

Thus, taking the advantages of the transdermal drug delivery systems and the advantage of posaconazole as a powerful and broad antifungal spectrum, the aim of present work is to develop the posaconazole microemulsion based system using gel as a secondary carrier system to treat superficial and deep fungal infections.(13)

MATERIALS AND METHODS

Posaconazole was obtained as a gift sample from BDR Pharmaceuticals private limited, Vadodara. Tween 80 was purchased from Sulab chemicals, Vadodara. Isopropyl alcohol was obtained from Finar chemicals private limited, Ahmedabad. Babool bark gum was procured from Neeraj traders, Mumbai, India. Sodium methyl paraben and sodium propyl paraben were procured from Merck International, Mumbai, India.

Methods

Preformulation of posaconazole API(14)

The organoleptic characterization includes the physical aspects like physical state, melting point, colour, odour, texture, crystallinity or solid-state form. Melting point was measured using ptheils tube. 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. Drug excipient compatibility study was conducted by preparing a physical mixture of drug and excipients in 1:1 ratio and subjecting them to 40ºC / 75% RH for one month and Fourier transformation infra-red spectrophotometer was used to confirm the compatibility of the drug and formulation samples.

Preparation of microemulsion and microemulsion based gel

Posaconazole drug was solubilized in oil phase and the Smix ratio was added to the same while continues stirring. The drug, oil – Smix mixture was stirred till clear homogenous mixture is obtained. The specified quantity of water is added homogenously under continues stirring to obtain a homogenous clear microemulsion. Sodium methyl paraben and sodium propyl paraben was dissolved in microemulsion. Babool gum was slowly dispersed with posaconazole loaded microemulsion to obtain a clear microemulsion based gel.

Characterization of microemulsion

Microemulsion was visually evaluated for Organoleptic characteristics like general appearance, odour and phase separation. % Transmittance of a posaconazole loaded microemulsion were measured using UV visible spectrophotometer (UV series 1800 schimadzu, Kyoto, Japan) at 650 nm keeping distilled water as blank. pH of microemulsion was performed using a digital pH meter (Electro quip, India). Refractive index of a microemulsion was performed using a Abbe's refractometer by placing the sample in the sample cell and noting the reading of the refractometer. The conductivity of the microemulsion was measured using a conductometer (Electro quip, India). Viscosity of the posaconazole loaded microemulsion was measured by using Brookfield viscometer using the spindle number LV DV ++ PRO (Spindle no. LV 62) at 30 rpm and viscosity along with % torque was measured. Zeta potential and PDI of microemulsions were measured using a Malvern zeta sizer ZS90 (Zetatrac software 10.6.2 by microtrac.inc, India). The samples of microemulsions were diluted 10 folds with water and was placed in the sample cell for analysing the globule size and zeta potential of microemulsion. The globule size of a microemulsion and morphological characterization of microemulsion globules was done using transmission electron microscopy at IIT Bombay.

Characterization of posaconazole microemulsion based gel (PMBG)

Physical characterization of posaconazole microemulsion based gel (PMBG)

Organoleptic characterization was done for appearance, smell, phase separation and texture of PMBG. pH of 10% solution of microemulsion based gel was observed using a digital pH meter. Viscosity of microemulsion based gel was performed using a Brookfield RST cone plate rheometer (Brookfield, USA) where 2.0 g of gel was placed on the plate and the cone was then fixed on the sample which rotates axially from 10 RPM to 100 RPM and the sensor notes the viscosity of the sample.

Texture analysis of PMBG (spreadability)(15)

Texture properties of the MBG were studied using a Brookfield texture analyser (CTS T3, Brookfield, USA). Before testing, the upper cone probe was calibrated against the lower cone so that the starting point was at the same height for each test, e.g., 25mm above the lower cone. During testing, the upper cone probe approached and then penetrated into the sample and continued to a depth of 2mm above the sample holder surfaces, i.e., the probe moved a distance of 23mm from its start point (with test speed of 3 mms-1). The Brookfield texture analyzer (QTS 3) was used to test the texture properties of posaconazole loaded microemulsion based gel which was compared with marketed aloe-vera gel base. The Extrudability i.e., peak load indicates that force required to extrude the formulation was studied with comparison to aloe vera gel base. The Spreadability was indicated by deformation point or surface spreading of the formulation on the surface of the probe which is detected by the sensor.

Drug Content

The drug content of posaconazole microemulsion based gel was evaluated using a UV Visible spectrophotometer (UV 1800, M/s Shimadzu, Kyoto, Japan) at 260 nm, where the content of posaconazole in the formulation was calculated using the as standard by the equation given below.

Cu/Cs = Au/As

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

In-vitro drug release

In-vitro drug release study was carried out using a Franz diffusion cell. Cellulose acetate membrane (pore size 0.22 microns) was soaked in pH 5.5 buffer to enhance the permeability and was placed in the sample compartment (cross sectional area = 3.14 cm2) between donor and receptor membrane and the receptor membrane was filled with acetate buffer pH 5.5 up to volume 25ml.The diffusion medium was stirred continuously using magnetic stirrer. Aliquots of 1mL were collected periodically at the predetermined time points and replenished with the fresh diffusion medium. The drug release in receiver compartment was analyzed using UV Visible spectrophotometer (UV 1800, M/s Shimadzu, Kyoto, Japan).

In-vitro skin permeation study

Skin preparation

Wistar rats weighing 150–200 g were sacrificed using cervical dislocation and the full thickness skin was removed from the abdominal region. The hair of test animals was carefully removed with surgical blade and freed from any adhering fat material. The excised skin was washed with normal saline twice and was previously submerged in acetate buffer pH 5.5 for 24 hours and then was used for ex vivo skin permeability studies.

In-vitro skin permeation study

Franz diffusion cells (cross-sectional area of 3.142 cm2) were used to study ex-vivo permeation of formulation. The rat skin was mounted between the donor and receptor compartment, where receptor compartment was filled with phosphate buffer pH 7.4. The mounted skin was marked with marker on which 1 gram of posaconazole gel was applied. The assembly was maintained at 32℃± 1℃ with the help of a thermo-regulated outer water jacket, while the diffusion medium was stirred continuously using a magnetic stirrer. Aliquots of 1mL were collected periodically at the predetermined time points and replenished with the fresh diffusion medium. Drug concentration in receptor compartment was recorded using UV visible spectrophotometer and cumulative amount of drug permeated through the skin was calculated through the equation.

$$Q_n = C_n \times V_0 + \sum_{i=1}^{n-1} C_i \times V_i$$

Where Cn is the drug concentration in receptor medium at each sampling time , Vo is the volume of receptor compartment, Ci is the drug concentration at ith sampling and Vi is the volume of the sample. The flux values were calculated from slope of the linear graph between the amounts of drug released per unit surface area versus time. The flux was calculated from the slope of linear portion of curve (on versus Time). The permeability coefficient was calculated as equation described below.

J= P X Cd

Where, J is the flux (mcg/cm-2 h-1) of the formulation across the skin, P (cm-2 h-1) is the permeability coefficient and Cd is the concentration of the formulation in the donor compartment. After completion of permeation studies, skin mounted on the diffusion cell was carefully taken off. The adhered formulation on the skin was cautiously removed and analysed for drug content. The cleaned skin tissue was washed thrice with ultrapure water and dried on lint-free cotton swab. The skin tissue was chopped into small pieces and macerated in ethanol (5 mL) for 24 h for complete drug

extraction to take place. After filtering the solution through a membrane (0.45 mm), the filtrate was analysed using a UV Visible spectrophotometer (UV 1800, M/s Shimadzu, Kyoto, Japan).

Skin irritation study

Skin irritation study was performed on wistar rats weighing 150-250 g whose hairs on the dorsal side of abdomen were removed using a suitable hair remover clip. The skin surface was cleaned using saline solution via cotton piece for 3-4 times and was allowed to dry. 500 mg of microemulsion based gel was topically applied for 24 hours. Post 24 hours the topically applied formulation was removed carefully and then animal was sacrificed with cervical dislocation; area of skin samples where the formulation was applied were then harvested and stained with haematoxylin and eosin, which were then observed microscopically under 10X power in an optical microscope.

Stability study

For the stability test, Posaconazole MBG formulation was examined at 25±2℃/60± 5%, 30±2℃/65± 5% and 40±2℃/75± 5% RH as per ICH. The Formulation was analysed for discoloration, pH changes, liquefaction, phase separation and drug content. However, the best storage temperature for all formulations was found to be at 25± 2℃, followed by 30℃ ± 2℃. The physical stability of MBG formulation was also maintained throughout the testing period, as only negligible changes were observed in the appearance, pH changes, liquefaction, phase separation, drug content and zone of inhibition.

RESULTS AND DISCUSSION

Posaconazole is a white to off white crystalline drug, with no odour, characteristic taste, smooth texture and had a melting point of 170-174°C. The bulk density of posaconazole was 0.248 g/ml. Posaconazole was practically insoluble in water. As per the FTIR of the drug excipients and the mixture, the drug and excipients were compatible as shown in the figure 2.

Primary focus of developing a microemulsion of Posaconazole was to determine a suitable surfactant co-surfactant system for posaconazole microemulsion. Surfactant's co-surfactants were screened as per solubility of posaconazole in oil phase, surfactants and co-surfactants as shown in Figure 3. Posaconazole was highest soluble in oleic acid hence posaconazole solubilized in oleic acid was used as oil phase, labrasol was chosen as surfactant and polyethylene glycol 400 (PEG 400) was chosen as co-surfactant. As the required HLB value for emulsifying any microemulsion ideally should be within 10-18, Labrasol and PEG 400 had an RHLB of 16 and hence were found suitable surfactants and so surfactants for preparing posaconazole topical microemulsion.

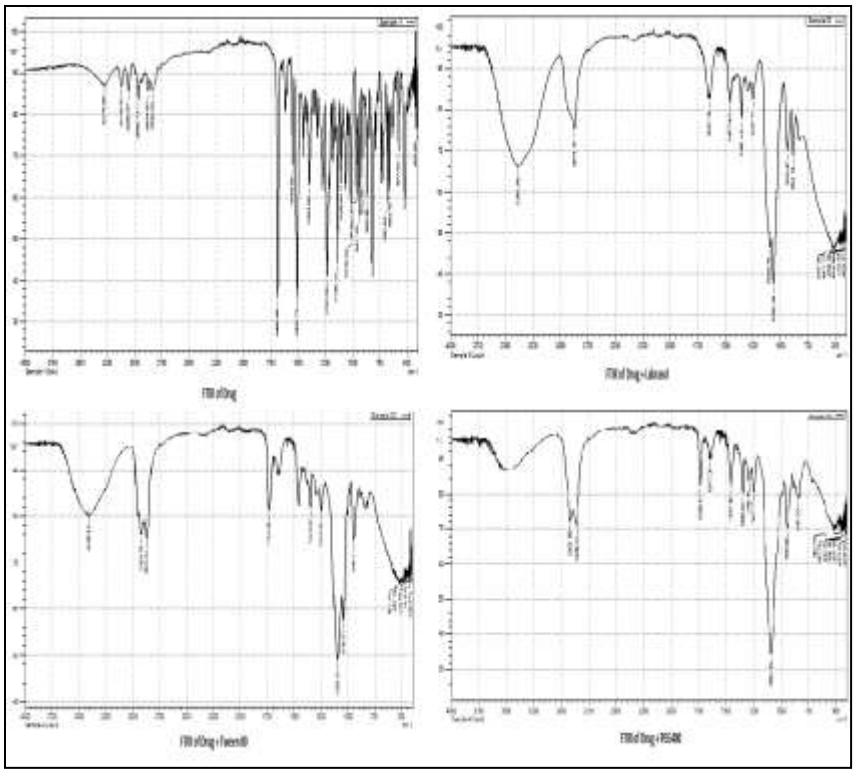


Figure 2: Results of Drug excipient compatibility study.

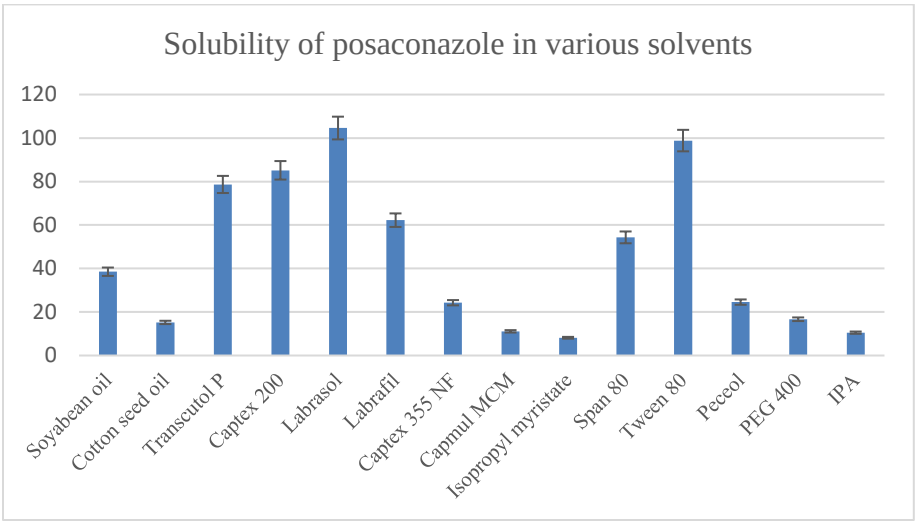


Figure3: Solubility of posaconazole in oils, surfactants and co-surfactants

Surfactant co-surfactant ratio was optimized using phase titration method using pseudo ternary phase diagram. For the construction of pseudo-ternary phase diagram at each Smix ratio, the mixtures containing water and Smix were prepared with volume ratios ranging between 1:9 and 9:1, and titrated drop by drop with oily phase under magnetic stirring at ambient temperature till the appearance of turbidity. The ME area of the ternary system was mapped as a triangular phase diagram using computer software (Chemix 7.0, India) shown in the figure below. From the pseudo ternary phase diagrams, it was observed that the largest microemulsion region obtained with the ratio of Labrasol: Polyethylene glycol 400 (Smix) was 2:1. Hence ratio 2:1 was considered for further optimization of posaconazole microemulsion

formulation.

Optimization of PLME and PLMBG

A D-optimal design was performed to optimize the posaconazole loaded microemulsion based gel (PLMBG). Table describes the set of 12 experiment runs suggested by the design expert software (D-optimal design). The responses selected for the optimization via design of experiment were Globule size in nm (Y1), Zeta potential (Y2) and % Drug loading (Y3) and the effect on the factors on the responses were determined after formation of microemulsion based gel. The table 1 below describes the factors and the values of responses after the experiments were conducted as per the runs suggested by design of experiment.

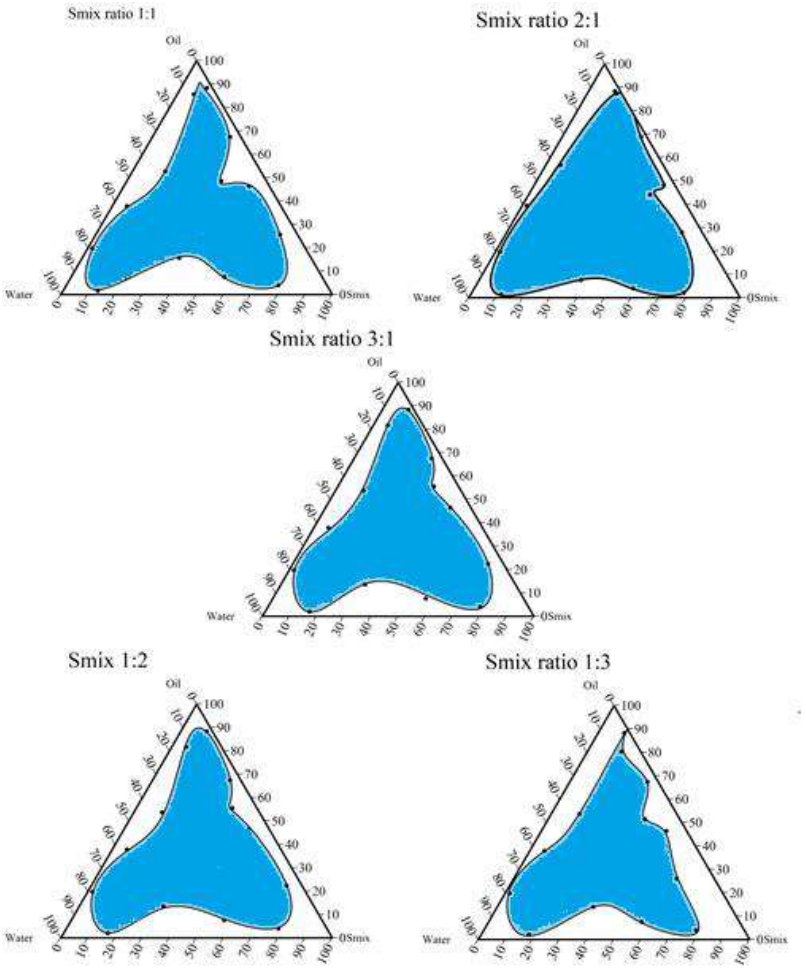


Figure 4: Pseudo-ternary phase diagrams for screening of PLME Smix

Table 1: Experimental results of responses as per runs suggested by DOE

Trial	Oil	Smix	Water	Globule size	Zeta potential	% Drug loading
1	0.33	0.34	0.33	73 ± 0.36	9.0 ± 0.8	78.0 ± 0.8
2	0.00	0.50	0.50	99 ± 0.71	16.0 ± 3.2	99.6 ± 0.75
3	0.00	1.00	0.00	153 ± 0.39	12.0 ± 0.87	95.0 ± 0.47
4	0.00	0.00	1.00	88 ± 0.63	16.0 ± 0.95	99.9 ± 0.3
5	0.67	0.16	0.16	79 ± 0.41	8.0 ± 0.5	72.0 ± 1.8
6	0.50	0.00	0.50	73 ± 0.44	10.0 ± 0.64	76.0 ± 2.76

7	0.16	0.17	0.67	193 ± 0.87	6.0 ± 0.89	92.0 ± 0.87
8	0.50	0.50	0.00	64 ± 0.21	13.0 ± 0.63	97.0 ± 0.91
9	0.17	0.67	0.16	61 ± 0.91	9.0 ± 0.97	93.0 ± 0.57
10	0.00	0.00	1.00	48 ± 0.73	8.0 ± 0.89	80.0 ± 2.18
11	1.00	0.00	0.00	184 ± 0.86	26.0 ± 0.75	97.0 ± 1.37
12	0.83	0.17	0.00	201 ± 0.17	19.0 ± 0.7	91.0 ± 0.36
13	1	0	0	196 ± 0.28	10.0 ± 0.92	76.0 ± 0.63

The responses globule size (Y1) % zeta potential (Y2) and % drug loading (Y3) was determined as per the method described in material and method section. As shown in table lowest globule size was achieved with highest amount of surfactant and lowest amount of oil. This behaviour indicates that microemulsion globules tend to constrict and get stabilized with higher amount of Smix when proportion of oil decreases significantly. The wide range of globule size in the design space implies the effect of selected independent variables on the globule size.

The relationship between responses (dependent variables) and factors (independent variables) was established using polynomial equation generated through statistical analysis by the software to determine the composition that yields microemulsion formulation with ideal attributes. The polynomial mathematical model comprising of coefficients was postulated with the intercept where the coefficients represent the interaction terms. The equation derived for each of the variables are given below. The polynomial equation that fitted to the data is expressed as below:

$$Y= \beta1X1 + \beta2X2 + \beta3X3 + \beta4X1X2 + \beta5X1X3 + \beta6X2X3 + \beta7X1X2X3 + \beta8X1X2(X1-X2) + \beta9X1X3(X1-X3) + \beta10X2X3(X2-X3)$$

The polynomial equation described above depicts interactions of each of the variables on the response based on the coefficient values. β1 to β10 are the coefficients obtained using DoE by the input of results achieved of independent variables performed practically. Model summary statistics for each factors and response interactions is shown in the table 2 below.

Table 2: Model summary statistics

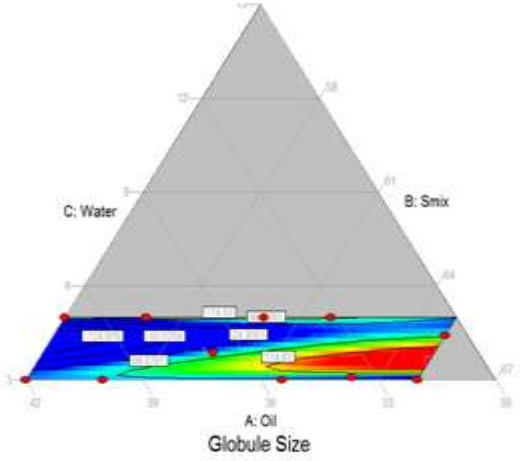
Coefficient code	**Y1**	**Y2**	**Y3**
Model suggested	Cubic	Cubic	Cubic
β1	0.0037	-22.48	71.40
β2	68.69	7.43	76.31
β3	27.30	6.19	-80.70
β4	-0.068	61.36	1694.84
β5	-0.005	64.25	1687.90
β6	129.89	5.91	-15.60
β7	-0.00438	-60.76	51.42
β8	-0.00204	-85.03	0
β9	-0.00258	148.38	0
β10	-21.27	-125.57	0
R square	0.9994	0.8958	0.8781
Mean	90.89	18.58	95.68
SD	0.21	0.58	0.41
PRESS	31.50	124.25	372.54

Coefficients with each independent variable in the equation indicate the effect of the particular factor, while the coefficients with more than one factor represent the synergistic effect within those factors. A positive sign denoted to the terms indicates synergistic effects, while the negative sign represents the antagonistic effect of the factors.

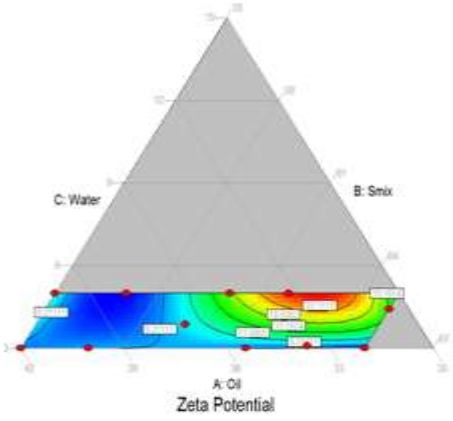
X1 (oil) has a significant effect on globule size, zeta potential and % drug loading on the skin i.e. with increase in oil concentration increases the globule size, the loading of drug increases and the zeta potential decreases which is owing

to the fact of lipophilic nature of drug. This relation is reflected in the polynomial equation that shows positive interaction of oil on all the three dependent variables. The independent variable X2 (Smix)has a positive correlation with all the three responses owing to direct effect of the concentration of Smix on all the dependent variables and similar are the observation noted with factor X3 on all the independent variables. As the concentration of oil increases and Smix and water decreases the zeta potential increases and vice-versa. The oil and Smix have a positive impact on zeta potential due to the interaction of oil and Smix reduces the globule size and reduces the surface free energy to overcome the surface charge barrier, there by stabilizes the system. The water and oil have a positive interaction due to their opposite nature as well as the concentration of oil phase is less than the concentration of Smix which would reduce the electrostatic barrier. As the concentration of oil increases and Smix and water decreases, the % drug loading increases and vice-versa.

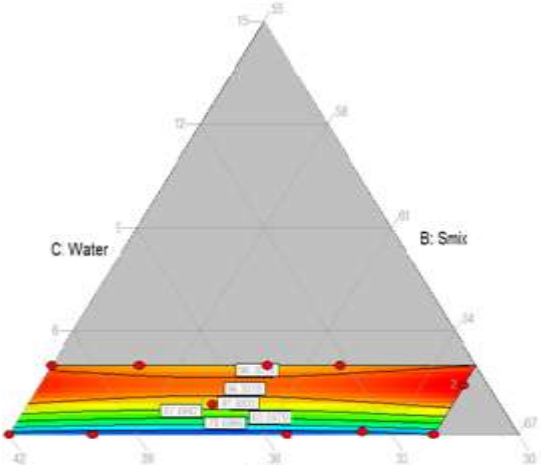
The drug loading is desire to achieve the complete loading of drug in oil phase such that drug crosses the stratum corneum i.e., the region underlying infection. Higher the drug loading till the desired therapeutic concentration is desirable to achieve the therapeutic action. The individual effect and the interaction effect of the factors and responses are backed by the counter plots of each factors and its impact on the responses. The counterplots of all the factors and responses are shown in the figure below. The overlay plot of suggested by the DOE is also shown in the figure 5. As per the design space suggested by the design of experiment final formulation of posaconazole loaded microemulsion has 1.0% of posaconazole, 3.42% of oelic acid, 20.38% of labrasol, 10.20% of polyethylene glycol 400 and 65.0% of water. To obtain PLMBG complete microemulsion was loaded into along with 1.0% of babool gum and 1.0% of propylene glycol as emollient.



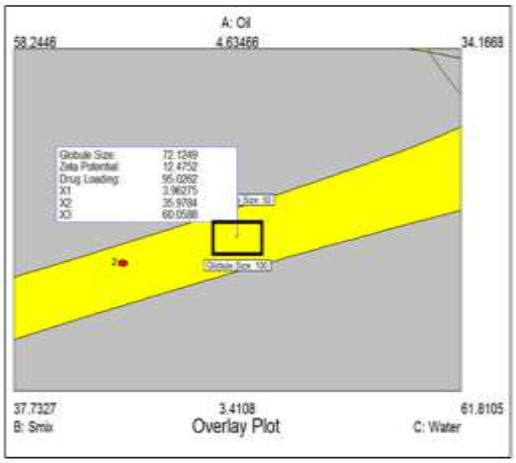
Globule Size



Zeta Potential



Drug Loading



Overlay Plot

Figure 5: Counter plots and overlay plots suggested by DoE for optimization of PLMBG

Posaconazole microemulsion was a clear transparent microemulsion. The pH of the PLME was found to be 6.14 which was isotonic with skin pH. The % transmittance of PLME was 99.40% indicating a clear and transparent

microemulsion. The conductivity of microemulsion was 143 ± 12 µs/cm confirming oil in water nature of microemulsion. The zeta potential and PDI value of microemulsion was 16 ±0.4 mV and 0.0013 indicating stable nature of microemulsion. The viscosity of microemulsion was 0.742 cps. The globule size of microemulsion was 86 ± 3 nm indicating stable nature of microemulsion. The globule size distribution of droplets of microemulsion of was confirmed by TEM image as shown in the figure 6 below.

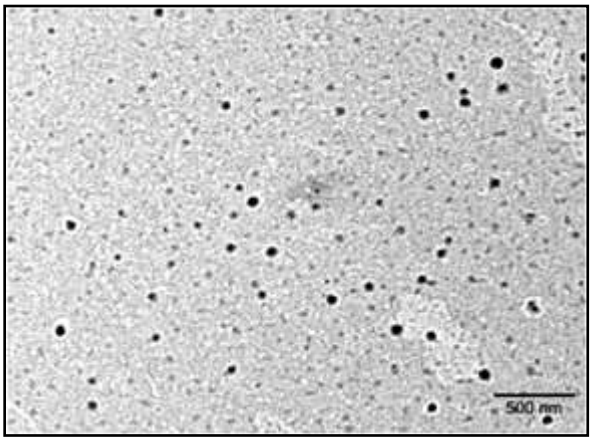


Figure 6: TEM of posaconazole loaded microemulsion

The optimized posaconazole microemulsion based gel was a clear transparent gel with no odour and smooth texture. The viscosity of the gel was found to be 12.87 m.pas/cm. sec. The pH of PLMBG was found to be 6.29, which was isotonic to skin pH and hence was non-irritant to the skin. The drug content of the PLMBG was found to be 102.69 ± 0.58%. The Brookfield texture analyzer (QTS 3) was used to test the texture properties of posaconazole loaded microemulsion based gel which was compared with marketed aloe-vera gel base and the results obtained are shown in figure below. The extrudability i.e. peak load was found to be 3.1 g that indicates that force required to extrude the formulation is less than the aloe-vera gel base which was found to be 44.24g. The spreadability was indicated by deformation point or surface spreading of both Posaconazole MBG and marketed formulation was found to be 9.10 mm and 9.72mm respectively indicating equivalent surface of spreading of both the formulations as shown in Figure 7 below. Thus, it can be said that Posaconazole MBG formulation has similar texture properties as marketed formulation.

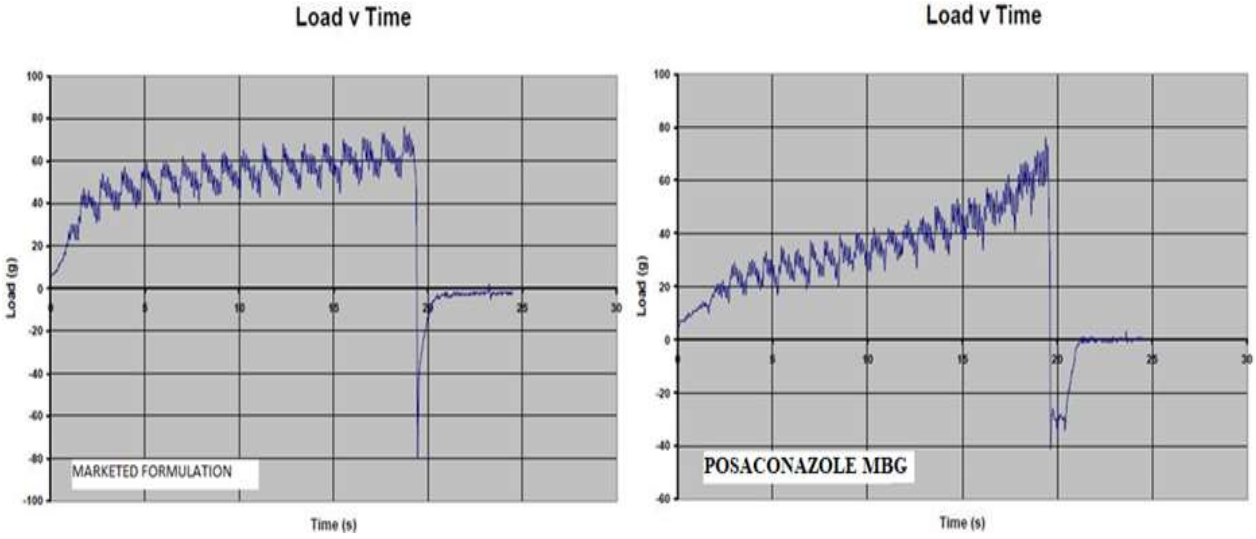


Figure 7: Spreadability and extrudability of Posaconazole MBG and marketed formulation

The in-vitro drug release study of Posaconazole MBG was performed in Franz diffusion cell using acetate buffer pH 5.5 of was found to be 98.50 ± 0.37%, ensuring the complete release of drug substance from the secondary drug carrier as shown in Figure 8. Also, the onset of action can be seen after 10-25 minutes of application.

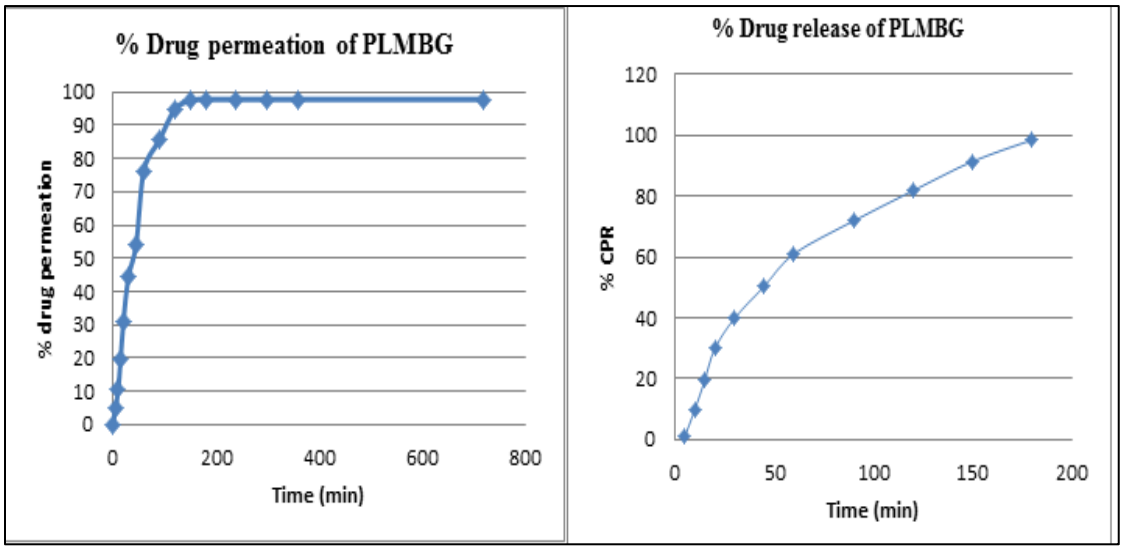


Figure 8: In-vitro release and permeation of PLMBG

The in-vitro skin drug permeation study performed on hairless rat skin using phosphate buffer pH 7.4 showed that 3.29 ± 0.16% drug retained on the skin surface while 7.59 ± 0.31% drug was found within the skin layers and 87.27 ± 0.17% drug was permeated through the skin layers to the receptor compartment as shown in Figure 8. The flux was found to be 0.0133 mg.cm-2sec-1, indicating fast release of the microemulsion based gel into the skin layers and the permeation coefficient was found to be 0.03878mg.cm-2.sec-1. This indicates the permeation of drug in the systemic circulation to give fast onset of action and cure infection. Thus, Babool gum was a suitable delivery carrier for the microemulsion based formulation.

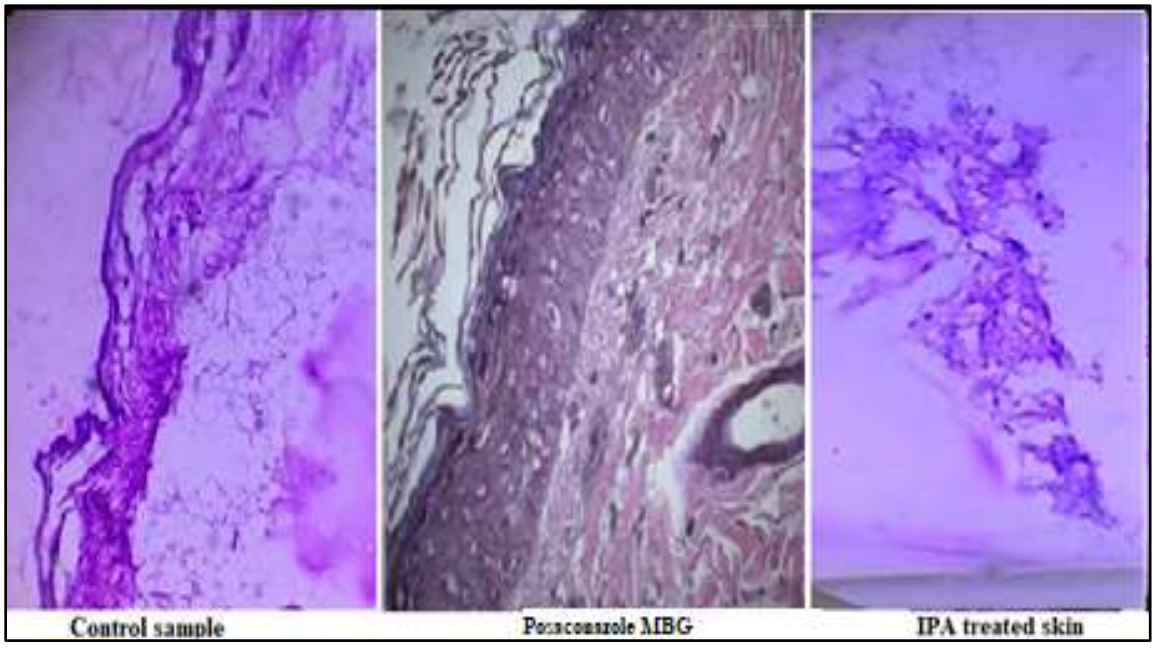


Figure 9: skin irritation study of posaconazole MBG

The comparison between the control sample, IPA treated sample and posaconazole microemulsion based gel is shown in the Figure 9. The skin applied on the skin showed no signs of irritation even after 72 hours. While the IPA completely disrupted the skin surface. Hence it can be said that posaconazole microemulsion based gel is safe formulation for human application. The posaconazole loaded microemulsion based gel was found stable for 6 months at 40°C/75% RH as shown in Table above. The microemulsion based gel was found stable at 25°C/60% RH. The ideal storage condition for storage of microemulsion based gel can be suggested as "Store at room temperature not exceeding 25°C".

CONCLUSION

The posaconazole microemulsion based gel formulated using oelic acid as oil phase, labrasol and PEG 400 as Smix system and water as aqueous phase had a pH isotonic to skin, smooth texture, drug content was more than 100%, had a good spreadability and extrudability and the gel easily penetrable through the skin layers. The gel showed complete drug release within 30 minutes of application. The gel was non-irritant to the skin and was stable at 40°C/75% RH for six months. Hence, it can be said that posaconazole microemulsion based gel is safe, effective and efficient for treatment of fungal infections via topical route of application.

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