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Formulation and Development of Luliconazole loaded Microemulgel using QBD Approach

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ABSTRACT: Point of the current examination is to diminish the molecule size, increment the surface area with increment saturation of medication and change frequency of medication at explicit site. Accordingly getting more noteworthy remedial viability. Present examination has been included to plan microemulsion of an ineffectively water-dissolvable medication, Luliconazole. Prior to the plan of Luliconazole microemulsion, the preformulation study would be performed. Most extreme solvency of Luliconazole in oils, surfactants and co-surfactants was assessed to recognize potential excipients. Microemulsion region was chosen through the development of the pseudo ternary phase diagram by phase titration technique. A 3^2 full factorial design was applied to analyze the joined impact of two detailing factors, each at 3 levels and the conceivable 9 blends of Luliconazole microemulsion were readied. Improved microemulsion was arranged and fused into Carbopol 934P which was added as gel network to change over microemulsion into microemulgel. Microemulsion and microemulgel were assessed by %transmittance, thickness, pH, conductivity, molecule size, Zeta potential, surface strain, refractive index, In-vitro dissolution study, Physical appearance, consistency, spreadability, extrudability measurement, examination with marketed item, antifungal activity and stability study. From FTIR and DSC study it was discovered that there is no interaction among drug and excipient. Based on pseudo ternary phase diagram it was tracked down that the framework comprising of Capryol 90, tween 80 and PEG 400 showed great emulsifying property at S_{mix} proportion 4:1. Microemulsion formulation F10 was optimized based on %Transmittance, consistency, %CDR (3 hrs.). Based on actual assessment, consistency, pH and spreadability result Diffusion Study, and Kinetic Model Study of gel, formulation LMEG1 was optimized batch that contains 1% Carbopol as gelling specialist. These above outcomes show Luliconazole stacked microemulgel drug conveyance framework might be promising vehicle for skin administration of Luliconazole.

Key words: Luliconazole, Microemulsion, Microemulgel, Quality by Design, Design of Experiment

I. INTRODUCTION[1]

The concept of micro-emulsions was first introduced by Hoar and Schulman during 1940s. It is defined as a system of water, oil and amphiphile, which is an optically isotropic and thermodynamically stable liquid micro- solution, and have a low viscosity or interfacial film consisting of surfactant/co-surfactant. It is the vehicle for improving the delivery, efficacy and bioavailability of several drugs.

As the name suggest they are the combination of emulsion and gel. Emulgel is the one of the recent technologies in NDDS used for Dual action of emulsion and gel for topical drug delivery system. Emulgel is emulsions, either of the oil-in-water or water-in-oil type, which are gelled by mixing with a gelling agent.Emulgel is one such a unique feature of topical system for drug makes the localized administration and direct acceptability of the drug anywhere in the body through ophthalmic, vaginal, skin& rectal routes. The main objective behind emulgel is delivery of hydro phobic drug via skin so that hydrophobic moiety can enjoy the unique properties of gels. The clinical evidence indicates that topical emulgel is a safe and effective treatment.

Ideal Properties of Drug Candidate to Formulate as Emulgel:[2]

- Drug dose should be low i.e., less than 10 mg.
- Molecular weight of drug should be 400 Dalton or less.
- Partition coefficient i.e., Log p (Octanol-

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water) between 0.4-0.8.
- Half life of drug 10 hr or less.
- Oral bioavailability and therapeutic index should be low.
- Drug should be non irritating and non-sensitizer having a less polarity.

Emulgels have proven as most convenient, better and effective delivery system. It provides gel like property due to its non-greasy nature and lacks oily bases therefore it provides better release of drugs as compared to other topical drug delivery system. Incorporation of emulsion into gel makes it a dual control release system and solves the further problem such as phase separation, creaming associated with emulsion gets resolved and its stability improves. Emulgel loaded with specific drugs has been found effective in some topical disorders and it is emerging as potential drug delivery system in area of dermatology. In future Emulgel will provide a solution for topical delivery of hydrophobic drugs. Many of drugs that have utility in treatment of skin disorders are hydrophobic in nature. Such drugs can be delivered in the form of Emulgel where they can be incorporated in oil phase of emulsion and combined with gel.[3]

II. MATERIALS AND METHODOLOGY

Method of Preparation of Luliconazole Microemulsion

Microemulsions is prepared by the spontaneous emulsification method (phase titration method) and can be express with the help of phase diagrams. Construction of phase diagram is a useful approach to study the complex series of interactions that can occur when different components are mixed. The understanding of their phase equilibria and demarcation of the phase boundaries are essential aspects of the study.[4]

Formulation and Development of Luliconazole Microemulgel by Design of Experiment (DoE) Using QbD Approach

A design space may signify formulation and process understanding viz. attributes which are related to drug substance, materials, equipment, IP and finished product quality. For this purpose, risk assessment was done based on the understanding process and formulation related parameters on Microemulgel quality. Preliminary studies and later Design of Experimentation (DoE) were carried out for high-risk parameters. Based on effect of Critical Quality Attributes (CQAs) of Targeted Quality Product Profile (TQPP), a design space was proposed for obtaining robust formulations. Characterization of Microemulgel was done for various parameters viz. Particle size analysis, micromeritic properties, encapsulation efficiency, percentage yield, in vitro drug releases shape and surface topography (SEM).[5]

Preparation and Characterization of Luliconazole Microemulgel [6-9]

Characterization of Luliconazole Microemulsion

Percentage Yield

It was calculated by the following formula: -

% Yield = (Weight of Microemulsion obtained practically / Total weight of Drug + Polymer theoretically) X 100

Drug Content:

25 mg of Microemulsion was weighed accurately and mixed in 25 mL Methanol with shaking. The solution was filtered using Whatman filter paper and 1 mL was withdrawn from this solution to volumetric flask with 10 ml dilution. The quantitative determination of Luliconazole in Microemulsion was carried out using a linear model UV absorbance detector at 296 nm against blank (methanol).

Mean Particle Size Analysis:

Particle size analysis of drug and Microemulsion was done using Optical Microscope and Malvern Instrument.

In Vitro Drug Release Study of Microemulsion

The dissolution test was done in 900 mL Phosphate buffer (PH 7.4) at the 37.0 ± 0.5°C, 150 RPM in USP-II Type dissolution apparatus. Aliquots were withdrawn every hour up to 8 hrs and replaced immediately with fresh solvent. The sample was estimated by absorbance of the solution at λ_{max} 296nm using UV- Visible spectrophotometer and % CDR was calculated.

Kinetics of Drug Release

The kinetic release study was performed to find drug release mechanism from dissolution parameter by using different kinetic model equations.

Zero Order Release Kinetics: -

Qt = Q0 + K0t

Where,

Qt = amount of the drug dissolved in time t,

Q0 = initial amount of drug in the solution (most of the times, Q0 = 0) and

K0 = zero order release constant expressed in units of concentration/time.

Plot: Cumulative amount of drug remaining vs time.

First Order Kinetics: -

Log C = Log C0 - Kt / 2.303

Where,

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C0 = initial concentration of drug,
K = first order rate constant, and
t = time.

Plot: log cumulative percentage of drug remaining vs. time.

Higuchi Model: -

$Q = KH \times t1/2$

Where,
KH = Higuchi dissolution constant.

Plot: cumulative percentage drug release vs Square root of time.

Hixson-Crowell Model: -

$W_O^{1/3} - W_t^{1/3} = \kappa t$

Where,
W_0 = initial amount of drug in the pharmaceutical dosage form,

Plot: cube root of drug percentage remaining in matrix vs time.

Korsmeyer- Peppas Model: -

$Mt / M_\infty = k t^n$

Where,
Mt / M∞ = fraction of drug released at time t,
k = release rate constant and
n = release exponent.

Plot: log cumulative percentage drug release vs log time.

Method of Preparation Luliconazole Microemulgel [10]

Carbopol 934-P was weighed accurately and liquefied in 100 mL of water for 2 hours soaking with 600 RPM agitation, then penetration enhancer was added to the formulated gel which will prevent drying of gel. Triethanolamine was added with slow agitation with continuous stirring. The Luliconazole Loaded Microemulsion was added in the gel.

Characterization of Topical Gel [11-

Physical evaluation

It was done to evaluate organoleptic property, Occlusiveness and washability of gel.

Measurement of pH of gel

The pH was checked of formulated gel by a digital pH meter.

Viscosity study of gel

50 gm of prepared gel was kept in 50 mL suitable beaker and spindle Groove was dipped at specific RPM in Brookfield Viscometer. This was done three times and from the recorded observation mean was calculated.

Spreadability of gel

1 g of gel was accurately weighed and was pushed among two slides and left as such for about 5 minutes. Diameters of speed circles were measured in cm and were taken as comparative values for Spreadability when no further spreading was observed.

Homogeneity and grittiness

The consistency of prepared gel was determined by pressing between the thumb and the index finger. Minor quantity gel was applied on skin on back of hand to check the homogeneity and grittiness.

Drug content

1 gm of each gel formulation was dissolved in 20 mL of alcohol in volumetric flask with 30 min stirring. Finally, it was diluted and filtered. Further dilution was made up to 10 mL alcohol and again 1 mL was withdrawn from above and diluted to 10 mL alcohol. The absorbance was measured at 296 nm in UV.

Comparison of optimized Luliconazole Microemulgel with Marketed Luliconazole conventional topical formulation

The optimized formulation Luliconazole Microemulgel topical gel will be compared with Marketed conventional Luliconazole topical formulation for in-vivo performance.

III. RESULTS AND DISCUSSION

Preliminary TrialBatches

The preliminary batches were taken after screening and construction of pseudo ternary phase diagram to optimize various types and levels of variables for DoE study.

Table 1. Preliminary Trial Batches Based on Pseudo ternary Phase Diagram

Batch code	Composition of microemulsion					
	Oil (%w/w)	Smix (%w/w)	Water (%w/w)	Oil(ml)	Smix(ml)	Water(ml)
LMG1	5.00	70.00	25.00	0.5	7.00	2.50
LMG2	12.90	51.61	35.49	1.29	5.16	3.54
LMG3	20	46.67	33.33	2	4.66	3.33

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Table 2. Characterization of Batch LMG1 to LMG3

Batch code	**Viscosity(cps)**	**%Transmittance**	**%CDR**		
			Time (hr.)		
			1	2	3
LMG1	165	98.8	10.76	14.28	27.31
LMG2	221	97.1	5.26	11.35	21.74
LMG3	286	95.6	2.81	9.66	18.27

Risk assessment to identify variables affecting drug product quality

Dependent variables(Y)	**Critical Quality Attributes (Independent variables- X)**	
	Oil concentration	**S_{mix} concentration**
%Transmittance		
Viscosity		
%CDR		

High Severity	Low severity

Formulation and Development of Luliconazole Microemulsion by using Design of Experiment [DoE] Approach

Table 3. 3^2 Factorial Design

Independent variables offormulations			
Independent variables	Low (-1)	Medium (0)	High (1)
Oil concentration (%) (X_1)	5%	10%	15%
Smix concentration (%) (X_2)	50%	55%	60%
Dependent variables			
Y_1= %Transmittance			
Y_2 = Viscosity			
Y_3 = %Drug release			

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Table 4. Compositions of Factorial Batches in Coded Form

LMG Microemulsion 3^2 = 9 Batches		
Batch No	**Variable level in coded form**	
	Oil Concentration (X1)	**Smix Concentration (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

Table 5. Compositions of Factorial Batches in Actual Form

Batch No	**LMG Microemulsion 3^2 = 9 Batches**			
	Actual value			
	Oil Concentration (%) (X1)	**Smix Concentration (%) (X2)**	**Amount of Oil (ml) (X1)**	**Amount of Smix (ml) (X2)**
F1	5	50	0.5	5
F2	5	55	0.5	5.5
F3	5	60	0.5	6
F4	10	50	1	5
F5	10	55	1	5.5
F6	10	60	1	6

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F7	15	50	1.5	5
F8	15	55	1.5	5.5
F9	15	60	1.5	6

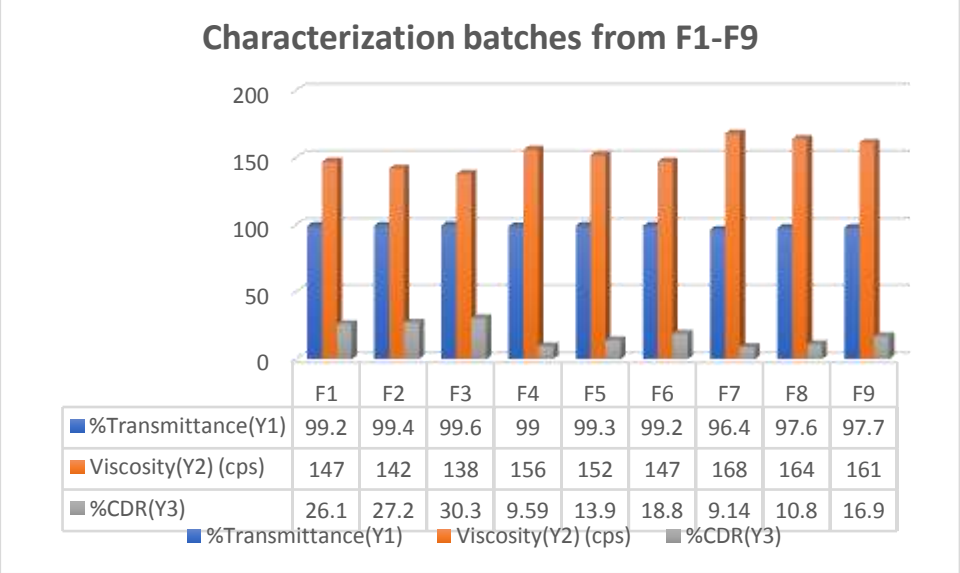

Fig. 1 Characterization Of batches from F1 to F9

Statistical Analysis:

Design expert software version 10.0 was used for Statistical analysis. From preliminary results, a 3^2 full factorial design was utilized in which two factors were evaluated, separately at three levels and possible nine combinations were formulated. Three level factorial studies were carried out using two different variables. In factorial design, amount of oil concentration (X1) and S_{mix} concentration (X2) were taken as independent variables while %Transmittance (Y1), Viscosity (Y2) and %CDR (Y3) were selected as dependent variables for both factorial designs.

Effect on %Transmittance(Y1) - Surface Response Study

The Negative value for coefficient of X1 indicates decrease in response of Y1i.e., %transmittance. Positive value of coefficient X2, Smix concentration indicates increase in %transmittance. It indicates linearity of surface response and contour plot as shown in figure 5.27 and 5.28. Full model was significant and detailed ANOVA, Response Surface Counter Plot and 3 D plots are asfollows:**%transmittance= +98.74-1.25* X1+0.42* X2**

Table 6. ANOVA Table for Response Y1

ANOVA for Response Surface Linear model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		**Mean**	**F**	**p-value**	
Source	**Squares**	df	**Square**	**Value**	**Prob > F**	
Model	**10.42**	2	**5.21**	**13.79**	**0.0057**	significant
A-concentration of oil	**9.38**	1	**9.38**	**24.83**	**0.0025**	
B-concentration of Smix	**1.04**	1	**1.04**	**2.76**	**0.1478**	
Residual	**2.27**	6	**0.38**			
Cor Total	**12.68**	8				

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Effect on viscosity (Y2) - Surface Response Study

The positive value for coefficient of X1 oil concentration indicates increase in response of Y2 i.e., Viscosity. Negative value of coefficient X2, concentration of Smix indicates decrease in response of Y2 i.e., viscosity. It indicates linearity of surface response and contour plot as shown in Fig. 5-14 and 5-15. Full model was significant and detailed ANOVA, Response Surface Counter Plot and 3 D plots are asfollows:**Viscosity = +153.11+9.33* X1-3.67* X2**

Table 7. ANOVA Table for Response Y2

ANOVA for Response Surface Linear model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob > F**	
Model	603.33	2	301.67	239.56	< 0.0001	Significant
A-concentration of oil	522.67	1	522.67	415.06	< 0.0001	
B-concentration of Smix	80.67	1	80.67	64.06	0.0002	
Residual	7.56	6	1.26			
Cor Total	610.89	8				

Effect on %CDR(Y3) - Surface Response Study:

The negative value for the coefficient of X1 indicates decrease in response of Y3 i.e.,%CDR. The positive value of coefficient of X2 concentration indicates increase in response of Y3 i.e., %CDR. It indicates the linearity of the surface response and contour plot as shown in figure 5.31 and 5.32. Full model was significant and detailed ANOVA, Response Surface Counter Plot and 3 D plots are as follows:**%CDR= +18.68-7.79* X1+4.02* X2**

Table 8. **ANOVA Table for Response Y3**

ANOVA for Response Surface Linear model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		**Mean**	**F**	**p-value**	
Source	**Squares**	**df**	**Square**	**Value**	**Prob > F**	
Model	460.99	2	230.49	20.93	0.0020	Significant
A-concentration of oil	364.10	1	364.10	33.06	0.0012	
B-concentration of Smix	96.88	1	96.88	8.80	0.0251	
Residual	66.09	6	11.01			
Cor Total	527.07	8				

Establishing Design Space and Control Strategy:

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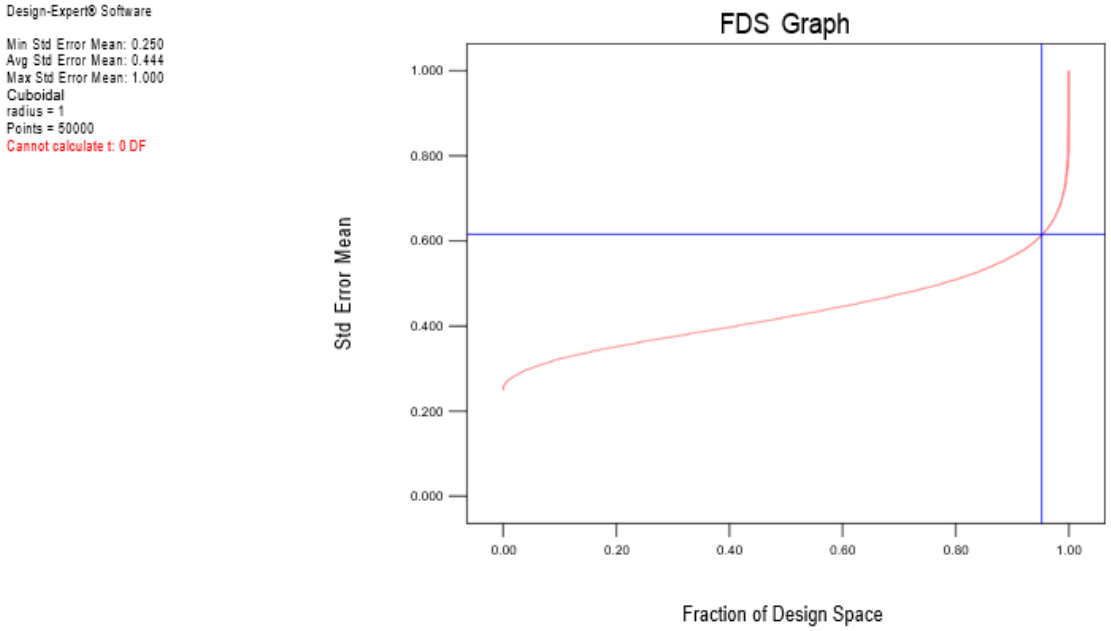

Fig. 2 FDS Graph

FDSgraph ofgood design will havea flatter and lower curve than apoor design as shown inFig. 2. Flatter means the overall prediction error will be constant. Lower means the overallprediction error will be smaller. FDS should be at least 0.8 or 80% for exploration, and 100% forrobustnesstesting.

Validation:

From polynomial equations generated for response, intensive grid and integrated study was performed over experimental field using Design Expert Software (10). During independent variable characterization study, impact of parameters oil concentration and S_{mix} concentration were assessed. Criteria consideredof %Transmittance(Y1), Viscosity(Y2), and %CDR(Y3) is between 96.4-99.6%, 138- 168 and 9.14% - 30.31% respectively. Design space shown in Fig. 5-18 also called as overlay plot which is shaded region with yellow colour indicates that region of successful operating ranges.

Table 9. Validation of Batches F10 & F11: Predicted Response

Batch No	**Oil Concentration (%) (X1)**	**S_{mix}concentration (%) (X2)**	**% Transmittance (Y1) (%)**	**Viscosity (cps) (Y2)**	**%CDR (Y3)**
F10	6.03	55.9	99.76	145.35	26.25%
F11	6.7	51.12	99.18	148.68	21.40%

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Table 10. Validation Batches F10 & F11: Actual Response

Batch No	Oil Concentration (%) (X1)	S_{mix} Concentration (%) (X2)	% Transmittance (Y1) (%)	Viscosity (cps) (Y2)	%CDR (Y3)
F10	6.03	55.9	99.23	145.12	25.91%
F11	6.7	51.12	98.30	150.20	20.22%

Table 11. Composition Formula of Microemulsion

Ingredients	Concentration (%)	Actual value for 10 ml microemulsion
Oil	6.03%	0.6
S_{mix}	55.9%	5.59
Water	49.87%	4.9

Selection of optimizedformulation

F10 was selected as validated optimized batch and further considered for formulating in to gel which was having %transmittance 99.23%, Viscosity 145.12cps and %CDR 25.91%.

Discussion:

A total 11 formulations were prepared as per the experimental design and characterized for various responses like %Transmittance, Viscosity and %CDR within 3 hr.

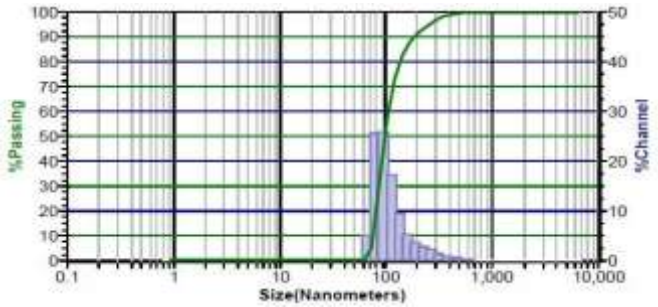

Fig 3. Zetapotential of optimized batch

Response surfaceanalysis was carried out to understand the effect of selected independent variables on the observed response.

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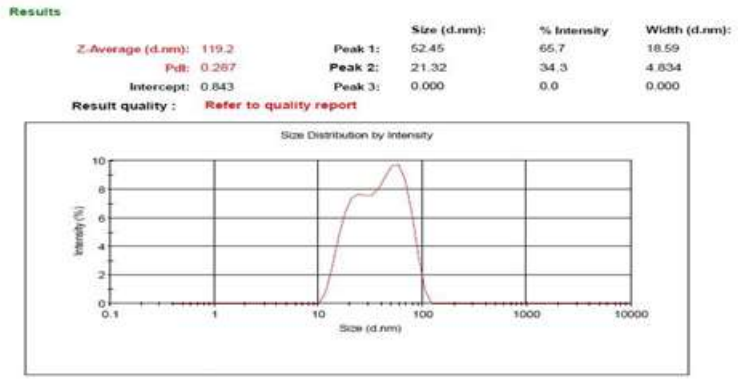

Fig. 4 Particle size analysis

Result of Optimized Gel

Table 12 Result of Optimized Gel

Parameter	**MarketedLuliconazoleFormulation**	**Optimized Luliconazole(LMEG1) Gel**
Dose	1%	**200mg**
Strength	20gm	**20gm**
Clarity	Transparent	**Transparent**
Odour	Odourless	**Odourless**
pH(Mean±S.D.)(n= 3)	6.96±0.02	**6.72±0.09**
Spreadability(Mean± S.D.)(n=3)	11.28±1.03	**21.36±0.75**
Viscosity(Mean±S.D.) (n=3)	9896±43cps	**9641±0.0028cps**
%Drugcontent(Mean ± S.D.) (n =3)	92.59±1.57%	**83.73±1.58%**
Anti-FungalActivity (Zone of Inhibition-mm)	3.3	5.6
Ex-vivo permeability study	**69.16**	**75.94%**

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Table 13. Release Kinetic study of Luliconazole microemulsion and microemulgel

Model	Parameter	Optimized microemulsion	Optimized Microemulgel
Zero Order	**R2**	0.979	0.990
	Slope	11.99	9.306
	Intercept	-5.290	-1.342
First Order	**R2**	0.942	0.970
	Slope	-0.081	-0.059
	Intercept	2.062	2.025
Higuchi Model	**R2**	0.993	0.997
	Slope	3.526	3.527
	Intercept	9.018	9.022
Hixon Crowell	**R2**	0.960	0.978
	Slope	3.534	0.180
	Intercept	-0.157	-0.059
Kors-Meyer Peppas	**R2**	0.924	0.947
	Slope	79.15	61.40
	Intercept	-1.623	1.501

According to result it indicates that in-vitro release of Luliconazole microemulsion and microemulgel formulation followed Higuchi model have R^2 value 0.993 and 0.997.

Ex-vivo permeability study

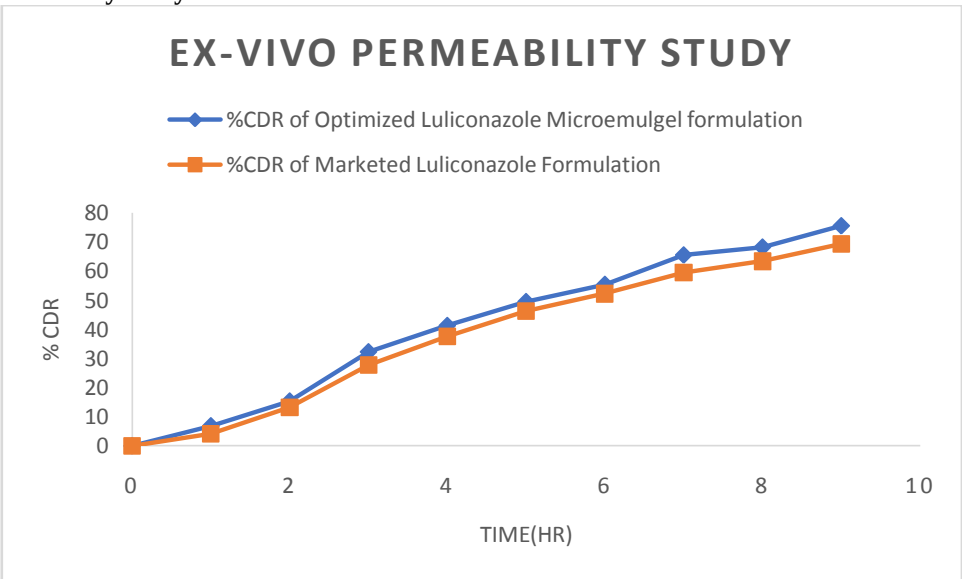

Fig 5. Ex-vivo permeability study

Table 14. Stability Analysis of optimized batch at Room Temperature for 1 Month

Parameter	Optimized Luliconazole microemulgel			
	Room Temperature			
	0 Day	**10 Day**	**20 Day**	**30 Day**
Clarity	Opaque	Opaque	Opaque	Opaque

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Odour	Odourless	Odourless	Odourless	Odourless
pH	6.96	6.88	6.81	6.76
Spreadability	20gm.cm/sec	20.1gm.cm/sec	20.2gm.cm/sec	20.2gm.cm/sec
Viscosity(cps)	9641	9649	9655	9659
%Drug Content	98.08%	97.44%	96.89%	95.87%

From the above study, we have concluded that Optimized Luliconazole microemulgel formulation prepared by using Carbopol 934P having good spreadability and viscosity. So, the Optimized Luliconazole microemulgel formulation prepared from the Carbopol 934P would be a good candidate in making an ideal topical preparation. From the Ex – vivo drug diffusion study, we have concluded that the Optimized Luliconazole microemulgel formulation prepared by the Carbopol 934P which provide modify drug release and also reduces the cost oftherapy.

IV. SUMMARY AND CONCLUSION

Briefly explains the discussion of the all parameters like preformulation study of drug like organoleptic properties, melting point solubility study, partition co efficient, calibration curve etc. Identification of drug purity by the FTIR and DSC study. Drug particle size is significantly important parameter for topical preparation that is also studied. Solubility of Luliconazole was determined in different oils, surfactants and co-surfactants. From the solubility study the pseudo ternary phase diagram was constructed. From the basis of the broad microemulsion region of the phase diagram the preliminary trial batches were taken of that S_{mix}ratio and evaluated. From the preliminary trial batches Preliminary selection of formulation and process variable, TQPP, CQAs for DoE was done. Optimized batch was selected on the base of check pointanalysis. After that 3^2 full factorial design was applied and evaluated their independent variables like%Transmittance(Y1),Viscosity(Y2)and%CDRat9hrs.(Y3). Results of a 3^2 full factorial design shown that independent variables like Oil concentration (X1) and S_{mix} concentration(X2) has significant affect on the dependent variables. Further Characterized of optimized microemulsion for, particle size, %Transmittance, Viscosity, drug content, In–vitro diffusion study. Further the chapter describes the preparation of Luliconazole microemulgel and its evaluation for spreadability, extrudability, In-vitro diffusion study, comparison with marketed product, drug content, Anti-Fungal Study, stability study. From the extrudability study it was understood that emulgel would require a lesser amount of weight to extrude out from the collapsible aluminium tube. Luliconazole microemulgel had highest zone of inhibition compare to marketed formulation so it clearly indicated that the present Luliconazole microemulgel had excellent antifungal activity. Results of stability study shown that Luliconazole microemulgel formulation was acceptably found to be stable for one month.

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