International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 2158-2171www.ijprajournal.com ISSN: 2456-4494

Development and Optimization of Microemulsion Based Gel of Methylprednisolone

Tularam Barot*, Krutika Patel, Shruti Barot, Urja Patel, Khushboo Kapadia
Department of Pharmaceutics, ROFEL, Shri G. M. Bilakhia College of Pharmacy, Vapi.

Submitted: 05-06-2022 Revised: 18-06-2022 Accepted: 27-06-2022

ABSTRACT: The present study enlightens to enhance the solubility and permeability of Methylprednisolone, a poorly soluble drug, by preparing a Microemulsion and then incorporate this microemulsion in to the gel. Methylpredinisolone is steroid drug and used in treatment of dishydrosis dermatities. Methylpredinisolone loaded microemulsion were prepared by using Capmul MCM C8 EP as oil, Cremophore RH 40 as surfactant and polyethylene glycol 600 as co-surfactant.Different Smix ratio (Surfactant and co-surfactant ratio) were used to prepare the ternary phase diagram. The S mix ratios used were- 1:1, 2:1, 3:1, 4:1. The Pseudo Ternary phase diagram (Chemix software 4.1) were used to identify the efficient Microemulsion region. After the selection of Smix ratio, preliminary batches were prepared & evaluated for selecting the levels. From the results of the preliminary batches, the levels of Oil, Surfactant and co-surfactant were selected. Design Expert 10.0.1 software was used for designing various batches for optimization. Mixture Optimal Design was used to optimize the microemulsion. The batches were evaluated for % transmittance and Globule size.The prepared Microemulsion were Evaluated for % Transmittance, Globule size.The data were statistically analysed using ANOVA and was found to be statistically significant ($P < 0.05$). The microemulsion was incorporated into gel & the prepared gel was evaluated diffusion study, viscosity, drug content & spreadability & stability study.

KEYWORDS: Ternary phase diagram, Mixture optimal design, Solubility, Steroid drug.

I. INTRODUCTION:

The exact cause of dyshidrotic eczema is unknown. Experts believe that the condition may be related to seasonal allergies, such as hay fever, so blisters may erupt more frequently during the spring allergy season.Atopic Dermatitis (eczema) is likely related to a mix of factors, including dry skin, a gene variation, an immune system dysfunction, bacteria on the skin and environmental conditions.Contact Dermatitis results from direct contact with one of many irritants or allergens such as poisonivy, jewelry containing nickel, cleaning products, perfumes,cosmetics and even the preservatives in many creams and lotions. Seborrheic Dermatitis may be caused by a yeast (fungus) that is in the oil secretion on the skin. People with seborrheic Dermatitis may notice their condition tends to come and go depending on the season.[1,8] Methylprednisolone is a steroidal drug used to prevent inflammation and used in the treatment of DishydrosisDermatities.[1]**.**in the treatment of DishydrosisDermatities.[1]The targeted application of the drug in gel form will avoid systemic side effects of the drug.[2]The half-life of Methylprednisolone is 1-3 hours. [3-4]So, external application in the gel formulation will release the drug for longer time.[5]Microemulsion based gel formulations are used to improve the solubility & skin permeability of the drug. [5-6] The Transderml route of administration is potential route for local and Transdermal delivery of drug. This route provides a controlled diffusion of drugs & improves the patient compliance. [7]

II. MATERIAL & METHODS:

2.1 Materials:

MethylPrednisolone was procured from Apex Pharma, Vapi. Other excipients - Capmul MCM C8EP, Capmul MCM EP, Captex 200 P(Abitech Corporation JANESVILLE,USA),Maisine35-1 (Gattefosse, France), Olive Oil, Sunflower Oil (Loba Chemie Pvt Ltd, Mumbai), Labrafac PG, Labrafil-M-2125(Gattefosse, France), Tween 20, Tween 80 (Loba Chemie Pvt Ltd, Mumbai), Cremophore-RH40(BASF, Mumbai) PG, PEG-200 , PEG-400, PEG-600, Carbopol (Astron chemicals, Naroda Ahmedabad), Methyl Paraben(Gayatri lab pvt.ltd), Methanol (Thomas Baker pvt led, Mumbai). All the materials were of Analytical grade.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 2158-2171www.ijprajournal.com ISSN: 2456-4494

2.2 Method of preparation & optimization:

2.2.1 Solubility determination:

The solubility of Methylprednisolone was carried out in various oils, surfactant and co-surfactant by dissolving an excess quantity of drug in 1 g of respective media. Shaking was performed on a Rotatory shaker for 72 hours with agitation of 150 rpm at 37°C. After attaining equilibrium stage, the sample mixture were subjected to centrifugation at 3000 rpm for 15 min, then supernatants are collected, diluted and drug concentration in each media were determined by UV-Spectrophotometer.[8]

2.2.2 Drug Excipients compatibility study:

The compatibility study of the drugs and excipients was checked out using the FTIR spectrophotometer. Sample compartment was purged with nitrogen gas before runs, and filled with dry desiccant to absorb any moisture present. Samples were prepared by physically mixing drug and different excipients separately in the ratio of 1:1 and were kept for a month at 40°C/75% relative humidity. Then the mixture was mixed thoroughly with dry KBr (IR grade) in ratio of 1:5 (mixture + KBr) and triturated in a small size mortar and pestle until the powder is fine and uniform. Then pellets of mixture was prepared by compressing the powder in a hydraulic pressure of 20,000 psi. The sample was placed in a sample holder which is placed in compartment. Sample were scanned in region of 4000-4500 cm^{-1} by using pure KBrpowder for baseline correction.[9-10]

1. Methylprednisolone + Capmul MCM C8 EP
2. Methylprednisolone + Cremophor RH 40
3. Methylprednisolone + PEG 600
4. Methylprednisolone + Triethanolamine
5. Methylprednisolone + Carbopol 934

2.2.3 Development of Pseudo Ternary Phase Diagram:

After screening the suitable oils, surfactant and co-surfactant, Pseudo-ternary phase Diagrams were constructed to know the extent and nature of micro emulsion region. Phase titration method was used for construction of Pseudo ternary phase diagram. The different weight ratios of surfactant to co-surfactant were varied. Then water and Surfactant / co-surfactant mixture was mixed in different weight ratio and oil was added drop by drop to the mixture of water and surfactant /co-surfactant under magnetic stirring at 37°C until the mixture become turbid. The data obtained were used to prepare phase diagram using Chemix school software and then micro emulsion formulation were selected at desired component ratios. The effect of drug addiction on micro emulsion region was also noted. Different Smix ratio (Surfactant and co-surfactant ratio) were used to prepare the ternary phase diagram. The Smix ratios used were- 1:1, 2:1, 3:1, 4:1.[11]

2.2.4 Preparation of Optimized Methylprednisolone Microemulsion

The optimized formula for the microemulsion was obtained from the Design Expert Software. This formula was further used for preparing microemulsion based gel. Methylprednisolone microemulsion was prepared by dissolving drug into surfactant and co-surfactant in glass vials and oil was accurately weighed and added in to glass vial. All the components were mixed at room temperature to form a transparent microemulsion.

2.2.5 Formulation Optimization by using Mixture Optimal Design

Microemulsion is a mixture of the components – Oil, Water &Smix. Therefore, the Mixture Optimal Design was used for further optimization of the microemulsion. Design Expert 10.0.1.0 software was used for designing various batches for optimization. Independent variables selected were - Amount ofwater (%w/w) (X_1), Amount of Smix (%w/w) (X_2) and Amount of oil (%w/w) (X_3). The dependent variables (responses) were % T (%Transmittance) (Y_1) and globule size (nm) (Y_2). The batch size was - 4 g of microemulsion for all batches. The levels selected for independent variables are given in Table 1. The formula of design batches is given in Table 2. The responses were analyzed for significance using ANOVA. The optimized microemulsion as suggested by the software was used further.[11]

Table1: Level for Factor

Independent Variables	Low Level	High Level
Amount of Oil (%)	6	24
Amount of Oil Water (%)	40.5	49.5
Amount of Oil S mix (%)	35.5	44.5

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 2158-2171www.ijprajournal.com ISSN: 2456-4494

Table 2: Formula for Microemulsion of design batches

Formula for Microemulsion Batches in Percentage			
Batch No.	**Water (%w/w)**	**S mix (%w/w)**	**Oil (%w/w)**
F1	49.5	39.1101	11.3899
F2	40.8673	39.686	19.4467
F3	49.5	44.5	6
F4	47.7	35.5	16.8
F5	40.5	44.5	15
F6	44.7614	40.8065	14.4321
F7	43.902	44.5	11.598
F8	47.6876	42.6606	9.65182
F9	40.5	35.5	24
Actual Formula of Microemulsion (4g)			
Batch No.	**Water (g)**	**S mix (g)**	**Oil (g)**
F1	1.98	1.56	0.46
F2	1.63	1.59	0.78
F3	1.98	1.78	0.24
F4	1.91	1.42	0.67
F5	1.62	1.78	0.6
F6	1.79	1.63	0.58
F7	1.76	1.78	0.46
F8	1.91	1.71	0.38
F9	1.62	1.42	0.96

2.3 Evaluation of Optimize Methylprednisolone Microemulsion.[11-13]

2.3.1 Globule size (nm):

The globule size of microemulsion was determined by Zetasizer instrument by Malvern Instruments Ltd.

2.3.2 % Transmittance (%T):

% Transmittance was performed by changing the mode of UV - 1800 spectrophotometer to yield a reading of % Transmittance. %T indicates the transmittance of the mixture.

2.3.3 Zeta potential:

Zeta potential was determined by using Zetasizerby Malvern Instruments Ltd. Zeta potential is useful for assessing flocculation since electrical charges on particles influence the rate of flocculation**.**

2.3.4 Robustness to dilution:

Robustness to dilution was used to check the effect of dilution on the stability of the microemulsion. The optimized microemulsion was diluted up to 10 & 100 times & the %T was measured to check the stability of the microemulsion.

2.3.5Poly dispersityindex:

Polydispersibility was determined by using Zetasizerby Malvern Instruments Ltd. It indicates the homogeneity of the microemulsion.

2.3.6 pH:

pH of microemulsion was measured by using calibrated Digital pH meter.

2.3.7 Centrifugation

The microemulsion system was centrifuged at 3000 rpm for 15 minutes to determine whether the system shows signs of creaming or phase separation.

2.3.8 Drug Content:

1 g microemulsion was dissolved in suitable amount of methanol. The drug content in the microemulsion was found by the UV Spectrophotometer.

2.4 Preparation of Gel:

Take required amount of water in three beakers. Add 0.5 %, 1%, 1.5% carbopol in the water respectively. Allow it to hydrate for 24 hours. Then mix well & adjust the pH with

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 2158-2171www.ijprajournal.com ISSN: 2456-4494

Triethanolamine until the gel is prepared. Then mix well & adjust the pH with Triethanolamine until the gel is prepared. The prepared gel was measured for viscosity &consistency.The viscosity was measured by using Brookfield viscometer at room temperature.For evaluating consistency in blank gel, the blank gel was applied on top of the palm. The consistency was given the points from 1 to 5, where 1 is poorest consistency & 5 is the best consistency. Based on the viscosity & consistency, amount of carbopol was chosen.[12]

2.4.1 Incorporation of Optimized Microemulsion in to Gel

The optimized microemulsion has 20 mg Drug in 4g microemulsion. To make 0.1% Methylprednisolone gel, this 4gmicreemulsion was mixed well to make 20 g total gel. (That means, 4 g microemulsion + 16 g Gel) 0.1 % Methyl Paraben & 0.1 % Propyl Paraben[53] were added as preservatives to the gel to avoid any fungal growth during storage.[12]

2.5 Evaluation of OptimizedMicroemulsion basedGel: [11,14,15]

2.5.1 Appearance:

Microemulsion based gel was visually cheaked for its colour, Homoginicity, Consistancy and phase sepration.

2.5.2 pH:

pH of microemulsion were measured by calibrated Digital pH meter.

2.5.3 Viscosity Measurements:

Rheological behaviour of the formulation was evaluated using a Brookfieldviscometer at room temperature.

2.5.4 Spreadability:

Spreadability was measured on the basis of 'Slip' and 'Drag' characteristics of gels. A ground glass slide is fixed on the block. 3 gm of Microemulsion based gel was placed on this ground slide. Then it was sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 Kg weight was placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the microemulsion based gel between the slides. Excess of the gel was scrapped off from the edges. The top plate was then subjected to be pulled by applying the weight with the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 2 cm be noted.

$S = (m \times l) / t$

S = spreadability, m= weight tied to the upper slide, l= length of glass slide, t= time in second.

2.5.5 Drug Content:

1 gm of Methylprednisolone gel was dissolved in 50 ml of Methanol. The absorbance was measured after suitable dilution at 243 nm against the corresponding blank solution by using UV-Visible Spectrophotometer (UV-1800, Shimadzu).

2.5.6 In-vitro Diffusion Study (Permeation Study)[7,16]

Franz diffusion cell with an effective diffusion area of 3.79 $cm^2$was used for in vitro permeation studies. The Egg-shell membrane was mounted carefully on diffusion cells. The receiver compartment was filled with 22 ml Phosphate Buffer pH 5.5 to ensure sink condition. Its temperature was maintained at 32 ± 0.5°C with magnetic stirring at 600 rpm throughoutthe experiment. For each sampling, 1 ml sample of the receivermedium was withdrawn at predetermined time and then the volume was made up with the equal volume of fresh receiver medium. All samples were filtered through a 0.45 m pore size cellulose membrane filter and then were measure the absorbance by UV Spectrophotometer.

2.5.7 FTIR Study:

FTIR spectrum of formulation after 30 days was performed to check the All the major peaks of drug was present or absent.

2.5.8 Stability study:

The stability study was performed to check physical and chemical integrity of the formulation. The optimized microemulsion based gel was subjected for stability study.Storage conditions were kept as per ICH (International Conference of Harmonization) guidelines. For accelerated stability study, 40 ± 2 °C and 75 ± 5 % RH and for real time study 25±2°C and 60 ± 5 % RH were used.

Time period: One Month (30 days).

Packing material: Optimized microemulsion batch was kept in bottle and covered with triple laminated aluminum pouch and sealed. The sealed bottle was kept in a stability chamber for 1 month. Samples were withdrawn after one month and evaluated.

III. RESULTS & DISCUSSION:

3.1 Solubility determination:

Solubility of Mecthylprednisolone was shown in Table3,4,5. It was observed that the drug has maximum solubility in Capmul MCM C8 EP oil(148.44 mg/gm), Cremophore RH 40surfactant –(376.68mg/gm), PEG 600co-surfactant –(164.33 mg/gm).Therefore these ingredients were selected further.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 2158-2171www.ijprajournal.com ISSN: 2456-4494

Table 3: Solubility study of Methylprednisolone in different oils.

Oil	Solubility (mg/gm)
Oleic Acid	60.54 ±0.424
Castor Oil	30.75 ± 0.734
Olive Oil	33.74 ± 0.155
Sunflower Oil	18.65 ± 0.243
Capmul MCM C8 EP	148.44 ± 1.647
Capmul MCM C10	59.12 ± 0.745
Captex 200	61.35 ± 0.562
Maisine 35	119.14 ± 1.544

***All values are ± SD which are mean of 3 determinations**

Table 4: Solubility of Methylprednisolone indifferent surfactants.

Surfactant	Solubility
Labrafil	18.45 ± 0.226
Labrafac	176.23 ±1.737
Tween 80	173.57 ± 1.553
Cremophore RH 40	376.68 ± 2.424
Tween 20	152.84 ± 1.645

***All values are ± SD which are mean of 3 determinations**

Table 5:Solubility of Methylprednisolone in different co-surfactants.

Co-Surfactants	Solubility
PG	71.35 ± 0.727
PEG 200	147.36 ± 0.843
PEG 400	150.46 ± 1.842
PEG 600	164.33 ± 1.355

***All values are ± SD which are mean of 3 determinations.**

3.2 Drug-excipients compatibility study: The FTIR study showed that all the characteristic peaks of the drug Mecthylprednisolone were present in the drug-excipients mixture which indicates absence of any interaction between drug & excipients.

3.3 Pseudo Ternary Phase Diagram:

The pseudo ternary phase diagrams having Smix ratios - 1:1, 2:1, 3:1, 4:1 are shown in Figures 1(a), 1(b), 1 (c), 1(d) respectively. The pseudo ternary phase diagram of 3:1 Smix ratio showed largest microemulsion region. Therefore 3:1 Smix ratio was selected further shown in Figure 2.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 2158-2171www.ijprajournal.com ISSN: 2456-4494

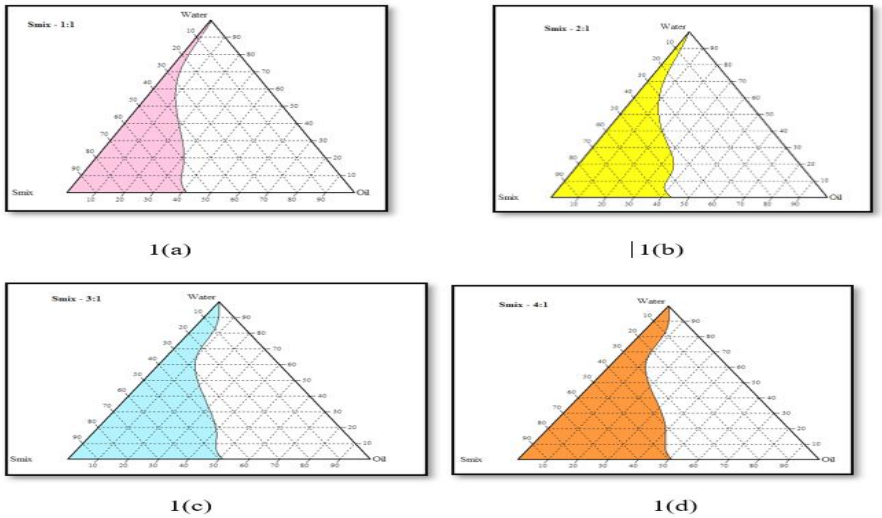


Figure 1: 1(a) Phase Diagram Using Smix 1:1, 1(b) Phase Diagram Using Smix 2:1, 1(c) Phase Diagram Using Smix 3:11(d), Figure4: Phase Diagram Using Smix 4:1

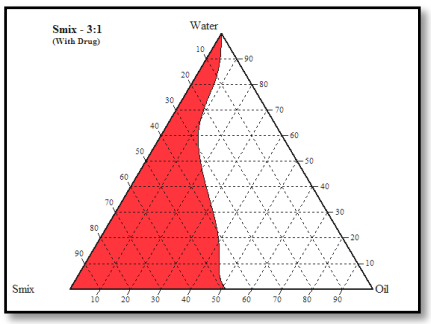


Figure 2: Phase Diagram of Smix 3:1 (with Drug)

3.4 Evaluation of design batches:

Results of % T (%Transmittance) (Y_1) and globule size (nm) (Y_2) of the design batches are shown in Table 6. ANOVA analysis results for responses Y_1&Y_2 are given in Table 7 & Table 8 respectively. p values for both the responses were found to be < 0.05 which shows that independent variables have significant effect on both the responses Y_1&Y_2. The contour plots & 3D surface plot diagrams of responses Y_1 are given in Figures 3 (a) &3 (b) respectively. The same for Y_2 are given in Figures 4 (a) &4 (b) respectively. The polynomial equations for the responses are as below:

For response % T:

$Y1(\%\ T) = 14.63X1 - 14.02\ X2 - 6.50X3 + 1177.66X1X2 - 222.29\ X1X3 + 587.77X2X3 - 486.35X1^2 - 772.64X2^2 - 450.25X3^2 + 99.59$

From the contour plot and 3D surface plot, it was observed that as concentration of oil increase the %Transmittance decreases and as concentration of water increase the % Transmittance increases. From the polynomial equation it was found that the interaction between the factors plays significant effect on the response, where interaction between water &Smix quantity plays significant effect on the response.

For response globule size:

$Y2(\text{Globule Size (nm)}) = -121.48X1 + 10.49X2 + 336.46X3 - 10047.60X1X2 + 2711.14X1X3 - 7498.64X2X3 + 4013.74X1^2 + 7057.77X2^2 + 5931.46X3^2 + 101.04$

From the contour plot, 3D surfaces plot & the polynomial equation it was observed that the interaction between the factors plays significant effect on the response. The interaction between amount of water & surfactant significantly decreases the globule size, while the interaction between water & oil results in increased globule size of the microemulsion.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 2158-2171www.ijprajournal.com ISSN: 2456-4494

Table 6: Responses of Mixture optimal Design batches.

Formulation No	%T	Globule size(nm)
F1	98.47	108.8
F2	97.93	121.1
F3	95.23	127.6
F4	96.82	133.1
F5	93.45	151.2
F6	99.42	102.3
F7	94.83	136.8
F8	98.25	105.1
F9	93.38	214.1

Table 7: Result of Analysis of Variance for %Transmittance.

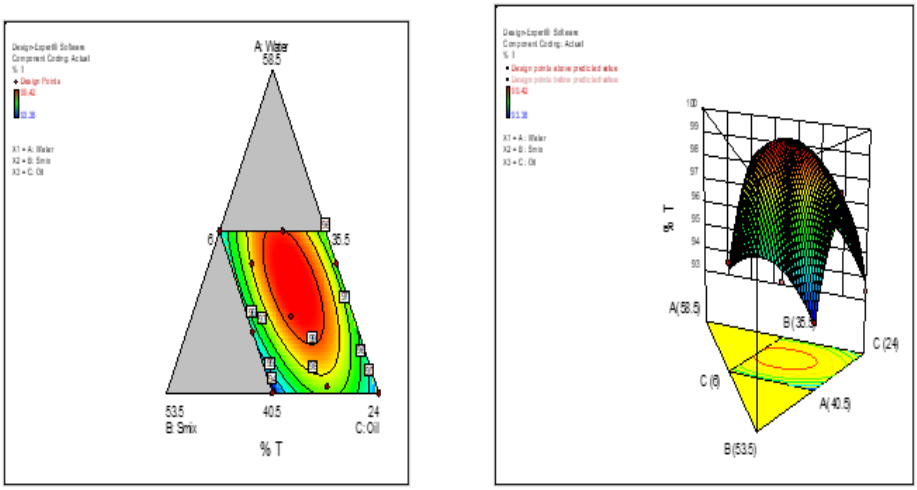
Analysis of variance table						
Source	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	
Model	39.84	5	7.97	20.73	0.0156	Significant
[1]Linear Mixture	10.01	2	5.00	13.01	0.0332	
AB	14.05	1	14.05	36.54	0.0091	
AC	2.77	1	2.77	7.21	0.0748	
BC	23.93	1	23.93	62.24	0.0042	
Residual	1.15	3	0.38			
Cor Total	41.00	8				

Table 8: Result of Analysis of Variance for Globule Size:

Here, p value is < 0.05. Therefore, the co-relation is significant.

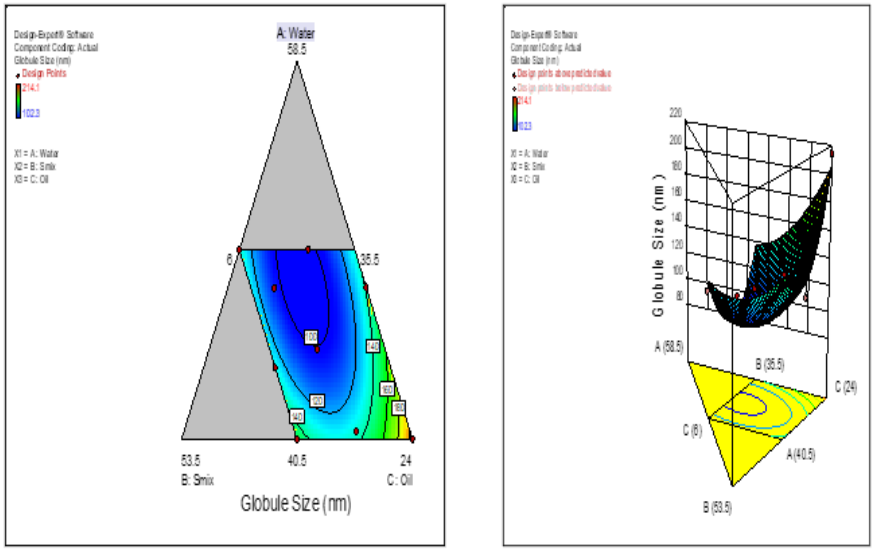
Analysis of variance table						
Source	Sum of Squares	df	Mean Square	F Value	p-value Prob> F	
Model	8829.35	5	1765.87	9.30	0.0479	significant
[1]Linear Mixture	4213.89	2	2106.95	11.09	0.0411	
AB	1055.42	1	1055.42	5.56	0.0996	
AC	284.18	1	284.18	1.50	0.3086	
BC	3063.68	1	3063.68	16.13	0.0277	
Residual	569.79	3	189.93			
Cor Total	9399.14	8				

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 2158-2171www.ijprajournal.com ISSN: 2456-4494



3(a) 3(b)

Figure 3: Contour plots & 3D surface plot diagrams of responses Y_1



4(a) 4(b)

Figure 4: Contour plots & 3D surface plot diagrams of responses Y_2

3.5 Validation and Optimization:

The optimized batch was found from the Design Expert 10.0.5. The design was validated by generating one formulation point. For the generated formulation point, the predicted responses are compared with the actual responses shown in Table 10. It was decided to select optimized batch Microemulsion based upon the criteria 99 to 99.9 for % Transmittance and for Globule size 1 to 100 nm. The optimized batch was prepared as per Figure 5 in which yellow region is the optimized region. The formula for optimized batch was shown in Table 9.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 2158-2171www.ijprajournal.com ISSN: 2456-4494

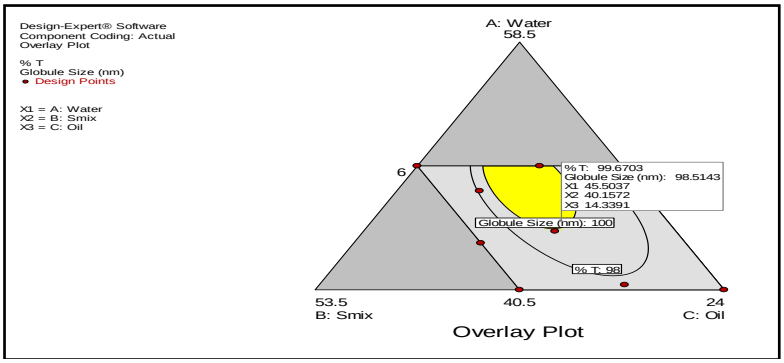


Figure 5: Overlay plot of Optimize Batch.

Table 9: Formula for Optimized Microemulsion batch.

Ingredients	Percentage Formula (%w/w)	Quantity (g)
Methylprednisolone (Dissolved in oil phase)	--	20 mg
Oil (Capmul MCM C8EP)	14.34	0.57 g
S mix	40.16	1.61g
Water	45.50	1.82g

Table 10: Validation of Design

Sr.No	Parameter	Predicted value	Experimental Value
1.	% Transmittance	99.67 %	99.48 ± 0.37 %
2.	Globule size	98.51 nm	98.19 nm

3.6 Evaluation parameter of optimized batch of Microemulsion.

3.6.1Globule size:

Globule size of the optimized microemulsion is shown in Figure 6. Globule size of the optimized microemulsion was found to be 98.19 nm.

3.6.2PDI:

Polydispersibility Index was found to be 0.349 is shown in Figure 6. The PDI value is < 0.5, therefore it can be concluded that the particle size distribution is good.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 2158-2171www.ijprajournal.com ISSN: 2456-4494

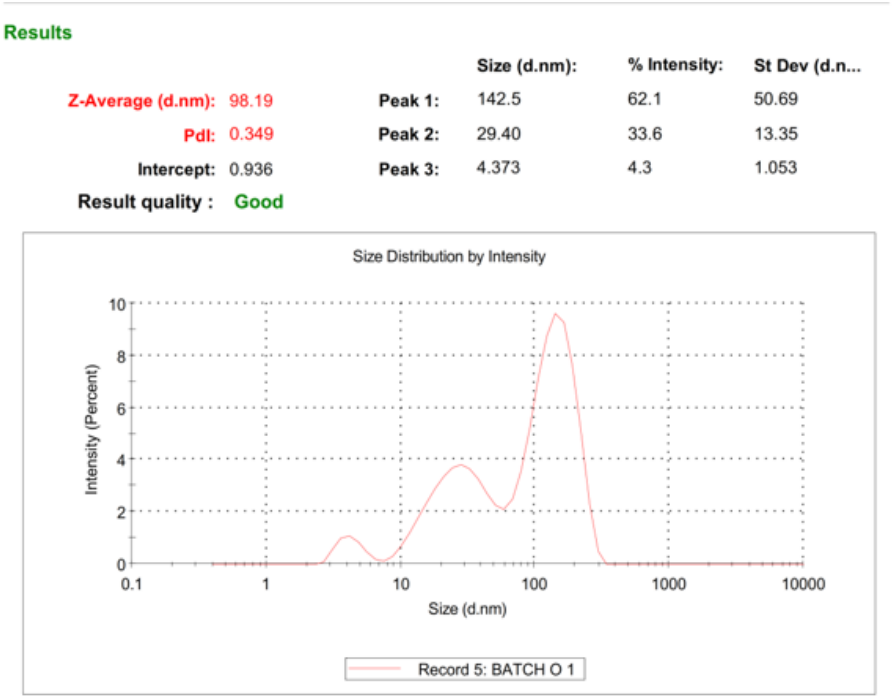


Figure 6: Globule size of the optimized microemulsion

3.6.3 Zeta potential:

The zeta potential was found to be -32.7 mV is shown in Figure 7, which is < -30 mV. Therefore, it suggests that the microemulsion globules have enough repulsive forces amongst them. So, the prepared microemulsion is stable.

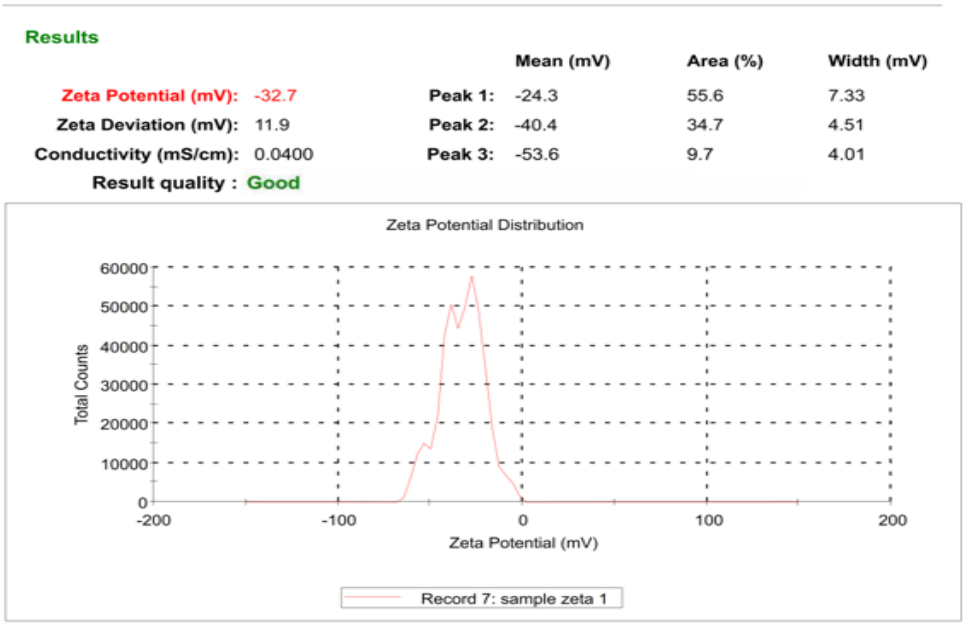


Figure 7: Zeta potential of the optimized microemulsion

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 2158-2171www.ijprajournal.com ISSN: 2456-4494

3.6.4Visual Appearance:
The microemulsion was transperant liquid. Microemulsions have the globule size less than the wavelength of the light (400-800 nm). Therefore, microemulsion globules cannot refract the light wave. And therefore, they look transparent.

3.6.5 pH
pH of the microemulsion was found to be 6.2 ±0.2.

3.6.6 Centrifugation:
No phase separation was observed after centrifugation. Thus, optimized formulation was found to be physically stable.

3.6.7 Drug content
Drug content of the microemulsion was found to be 99.27 ± 0.21.

3.7 Selection of gel.
Three gel formulations with 0.5%, 1% & 1.5% w/w carbopol were evaluated.Viscosity& consistency of three gel formulations is given in table. For consistency, 1 is poorest & 5 is highest consistency.1% carbopol was selected for preparation of gel for further study is shown in Table 11.

Table 11: Viscosity & consistency

Sr. No.	% Concentration of Carbopol 934	Viscosity (cps)	Consistency
1	0.5%	31,658 ±57.63	3
2	1%	53,272±63.31	5
3	1.5%	67,729±32.52	2.5

Table 12: Final Formula for Microemulsion Based Gel

Ingredients	Quantity (20g)
Optimized batch of Microemulsion	4 g
Carbopol Gel	16 g
Methyl Paraben	0.1 % w/w
Propyl Paraben	0.1 % w/w

Methylprednisolone (Dissolved in oil phase)	20 mg
Oil (Capmul MCM C8 EP)	0.57 g
S mix	1.61g
Water	1.82g

3.8 Evaluation parameters of optimized batch of Microemulsion based gel.

3.8.1Appearance:
The prepared microemulsion based gel was transperant to transclusant in appearance.

3.8.2 pH:
pH of the microemulsion based gel was found to be 6.5 ± 0.2 by using calibrated digital pH meter.

3.8.3 viscosity:
The viscosity of optimized microemulsion based gel was found to be 53,272 ± 72.55

3.8.4 Spreadability:
Spreadability of the optimized microemulsion based gel was found to be 16.66 ± 0.38 gm.cm/sec

3.8.5 Drug content:
Drug content of the optimized microemulsion based gel was found to be 99.16 ± 0.43 %.

3.8.6 in-vitro diffusion study:
Results of in-vitro diffusion study from the optimized microemulsion based gel and marketed cream from the egg-shell membrane is

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 2158-2171www.ijprajournal.com ISSN: 2456-4494

given in the table 13. The study shows the drug released in 8 hrs from microemulsion based gel and marketed cream respectively. The drug released from microemulsion based gel was higher compared to marketed cream. This may be due the nano sized globules of microemulsion. The microemulsion based gel contains the oil globules with very small size, which results in higher diffusion of drug in the media.

Table 13: In-vitro Drug Diffusion Study :

Time (hour)	% Drug Released	
	Optimized Microemulsion Based Gel	Marketed Cream
0	0	0
0.5	18.11 ± 0.55	12.99 ± 0.33
1	34.50 ± 0.37	22.34 ± 0.47
2	57.06 ± 0.43	37.54 ± 0.56
4	69.58 ± 1.13	51.31 ± 0.87
6	83.06 ± 1.36	60.25 ± 0.85
8	96.62 ± 0.52	69.82 ± 1.32

3.8.7 FTIR:

FTIR spectrum of formulation after 30 days was shown in Figure 8 All the major peaks of drug were present, indicating there is no extensive degradation of drug in formulation.

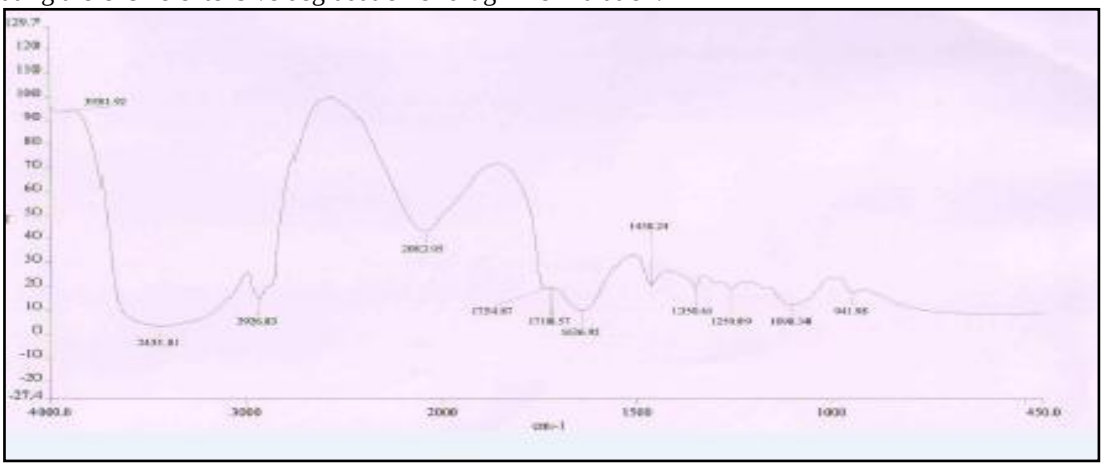


Figure 8: FTIR spectra of final formulation after 30 days.

3.8.8 Stability study:

The stability study was carried out at 25 ± 2°C, 60 ± 5 %RH &40 ± 2°C, 75 ± 5 %RH. After 30 days pH, Viscosity, Drug Content & Drug diffusion study was performedshown in Table 14. No significance changes were observed in the properties of the Micro emulsion-based gel.

Table 14: Stability study data.

Evaluation Parameters	25 ± 2°C , 60 ± 5 %RH	40 ± 2°C , 75 ± 5 %RH
pH	6.6 ± 0.3	6.4± 0.2
Viscosity (cps)	52,272 ± 62.75	51,273± 84.39

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 2158-2171www.ijprajournal.com ISSN: 2456-4494

Drug content (%)	98.86 ± 0.65 %.		98.79± 0.85 %.	
Diffusion Study	Time (Hours)	% Drug Released	Time (Hours)	% Drug Released
	0	0	0	0
	0.5	17.32 ± 0.84	0.5	17.68 ± 0.27
	1	33.86 ± 0.57	1	32.93 ± 0.25
	2	59.3 ± 0.38	2	56.63 ± 0.49
	4	68.73 ± 0.55	4	67.37 ± 0.85
	6	81.53 ± 1.12	6	80.73 ± 0.76
	8	95.74 ± 0.85	8	95.12 ± 0.73

IV. CONCLUSION:

Methylprednisolone is corticosteroid that is derivative of prednisolone and used to suppress the immune system and decrease inflammation. The mechanism is to inhibit the arachidonic acid from phospholipid there by inhibit release of various inflammatory mediator such as prostaglandins, leucotrins and decrease the inflammation. Saturation solubility of Methylprednisolone was carried out in different oils, surfactants and co-surfactants. The result revealed that solubility of drug in different oils decrease in order of Capmul MCM C8 EP >Maisine 35-1 >Captex200P> Oleic acid >capmal MCM C10> Olive oil > Castor Oil>Sunflower oil; in different surfactants decrease in order of CremophorRH40>Labrafac> Tween 80 > Tween 20 >LabrafilM2125> and in different co-surfactants decrease in order of Polyethylene glycol 600 > Propylene glycol 400l> Polyethylene glycol 200 > Polyethylene glycol. UV visible spectroscopic method was performed for estimation of Methylprednisolone which showed λmax at 243 nm in Methanol. FTIR studies confirmed the purity of drug. The preliminary and expansion of preliminary trial batches were carried out by varying the concentration of oil, surfactant and co-surfactant. The microemulsion formulation were prepared by dissolving drug into surfactant and co-surfactant in glass vials and oil was accurately weighed and added in to glass vial. All the components were mixed to form a Transparent homogenous mixture. The prepared Microemulsion was evaluated for % transmittance and Globule size study. For optimization Mixture Optimal design was employed to study the effect of independent variables i.e. amount of Water (X_1), amount of Smix (X_2) amount of Oil (X3) was selected for optimized formulation which showed % Transmittance 99.67% and Globule size 98.51 nm. The data were statistically analysed using ANOVA and was found to be statistically significant (P <0.05). The microemulsion was incorporated into gel & the prepared gel was evaluated diffusion study, viscosity, drug content & spreadability & stability study. It is concluded that the microemulsion based gel was successfully prepared.

REFERENCES:

[1]. DishydrosisDermatities**2022**, "https://www.verywell.com Skin Health Eczema Atopic and Contact Dermatitis".
[2]. Chudasma A, patel.V, Nivsarkar M, Vasu K, "Investigation ofmicroemulsion system for transdermal delivery of itraconazole'' J Adv PharmTechnol Res.**2011** 2 (1)30–38.
[3]. "Methylprednisolone", October 2022, https://pubchem.ncbi.nlm.nih.gov.
[4]. "Methylprednisolone", October2022, https://www.drugbank.ca/drugs/DB00959.
[5]. Madikattu1 K, Naidu K.V.S, Srisailam K, "Microemulsion based TransdermalGels of Isradipine to Enhance Bioavailability: In vitro and In vivoEvaluation",Asi.J.Pharm.**2016**, 9(5).
[6]. Okura N, Apaydınb E, YavasN,Gluc O, Yavas A, "Evaluation of skinpermeation and anti-inflammatory and analgesic effects of new naproxenmicroemulsion formulations'' Int.J. of Pharm.**2011**,136– 144.
[7]. Mahdy M, Hafez.S, Ibrahim M, "Organogels, hydrogels and bigels as transdermal delivery system for diltiazem hydrochloride" A. Jou. of Pharma Sci. **2013,** 48(57).
[8]. Zhua W, YuaA,Wanga W, Dongb R, Wuc J, Zhaia G, "Formulation designof microemulsion for dermal delivery of penciclovir'', Int.J. of Pharma.**2008,** (360),184–190.
[9]. Lachman L**;** Liberman H; and Kanig.The theory and practice of industrial pharmacy

third Edn;Varghese Publishing House 1987, 297-300.

[10]. Gupta K, "Drug excipient compatability study using thermal and non-thermal method of analysis." Int.J.chem Appl. **2006** , 2(2), 23-49.

[11]. Dhingani A, Garala K, "Quality by Design Approach for Development of w/o type BarotB,Gohel M, Shelat P, "Microemulsion-Based Gel of Terbinafine for the Treatment of Onychomycosis: Optimization of Formulation Using D-Optimal Design"AAPS Pharm. Sci.Tech. **2012** Mar; 13(1) 184–192.

[12]. Dhingani A, Garala K, "Quality by Design Approach for Development of w/o type Microemulsion based Transdermal systems for Atenolol."J.of Dispersion Sci. and Technology, **2013**35(5), 619-640.

[13]. Gomes A. D. M, Lima M. V. C, Ferreira L. M. A, "Topical Delivery of Fluconazole: In Vitro Skin Penetration and Permeation Using Emulsions as Dosage Forms Drug."Dev. Ind. Pharm.**2007**, 33, 273-280.

[14]. Singh N, Arora S, "Emulgel: insight" European Jou. of Pharma and medical Reserch"**2015**, (2)4,1186-1168.

[15]. Cartensen J, "ICH guideline in drug stability principleandpractices."1995, 2, 541-546.

[16]. Upadhyay K, Jain S,Bohidar H,"Sorbitan Ester Organogels for Trasdermal delivery of Sumatriptan "Drug Development and Industrial Pharmacy.33.617-625,2007