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Research Article

FORMULATION DESIGN AND EVALUATION OF HERBAL ANTI PSORIATIC EMULGEL

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ABSTRACT
Psoriasis is an inflammatory condition associated with painful, itchy, scaly skin and disfiguring skin lesions. The lack of possible cure and associated disadvantages in allopathic medicines has led to extensive research in natural products with anti psoriatic activity. *Commiphora mukul* (Gum guggul) and *Psoralea corilyfolia* (Babchi oil) were found to be efficacious and cheap anti-inflammatory drugs with least side effects as compared to the synthetic drugs used in the treatment of Psoriasis. Therefore these two drugs were selected for the present study. Considering the above justification an attempt was made to design and develop herbal anti psoriatic topical drug delivery system wherein biphasic drug delivery system of combined herbal drugs in the form of emulgel was formulated and their effect was compared to marketed preparation widely used for treatment of Psoriasis. In the study, topical emulgels of powdered extract of *Commiphora mukul* and Babchi Oil were formulated. The factorial and optimized batches were evaluated for %EE and %DR followed by in vivo studies. From the in vitro studies, formulation M3 showed maximum release of 79.72%, 94.34% in 6hrs respectively. The formulation M3 was comparable with marketed tacrolimus ointment. The results indicated that the optimized batch containing both the drugs *Commiphora mukul* (Gum guggul) and *Psoralea corilyfolia* (Babchi oil) exhibited good results. Thus, the results indicate that an effective herbal formulation containing *Commiphora mukul* and Babchi oil can be prepared overcoming the side effects posed by synthetic drugs.
Keywords: Psoriasis, *Commiphora mukul*, Babchi oil, Emulgel.

INTRODUCTION

Psoriasis is a skin disease that causes scaling and inflammation (pain, swelling, heat, and redness) causing patches of thick, red skin with silvery scales. These patches can itch or feel sore. The immune system plays a key role in psoriasis. The immune system makes white blood cells that protect the body from infection. In psoriasis, the T cells (a type of white blood cell) abnormally trigger inflammation in the skin. They also cause skin cells to grow faster than normal and to pile up in raised patches on the outer surface of the skin[1]. Normally, skin cells that are formed in the deepest layers of human skin make their way to the surface. This process is called cell turnover. They mature, are sloughed off the body's surface, and are replaced with new skin cells from below. This cycle takes approximately a month. In people with psoriasis; however, the immune system activates a faster-than-normal skin cell cycle. The body does not shed these excess skin cells, leading to the cells pile up on the surface of the skin and lesions form. The lack of possible cure and associated disadvantages in allopathic medicines has led to an extensive research in natural products with anti psoriatic activity. The literature survey reveals that although extensive work has been reported on the treatment of psoriasis[2-10], a limited research has been carried out on the herbal drugs in the area of psoriasis. *Commiphora mukul* (Gum guggul) and *Psoralea corilyfolia* (Babchi oil) were found to be efficacious and cheap anti-inflammatory drugs with least side effects as compared to the synthetic drugs used in the treatment of Psoriasis. Work has been reported on Gum guggul topical anti inflammatory gel[11] and Babchi oil anti psoriatic topical emulgel[12], but no work has been reported on combined effect of both the drugs as anti psoriatic emulgel. It is noteworthy that anti psoriatic creams, ointments and topical solutions have been formulated, but no work has been initiated on herbal anti psoriatic emugel systems. Emulgels have emerged as one of the most interesting topical delivery system as it has dual release control system i.e. gel and emulsion [13,14]. The aim of the present investigation was to explore the possibilities of using anti psoriatic herbal drugs in the topical dosage form and to design and develop biphasic drug delivery system of combined herbal anti psoriatic drugs in the form of emulgel.

MATERIALS AND METHODS

Babchi oil and *Commiphora mukul*, were generously gifted by Pukhraj Herbals and Kuber Impex Ltd, Indore (M.P) respectively. Captex 355 and Capmul MCM C8 were obtained as gift samples by Abitec Corporation, Mumbai. Cremophor RH 40 was gifted by SigNET AC Limited, UK. Rest of the chemicals used was procured from Loba Chem. Pvt. Ltd., Mumbai, India. 12 wistar albino rats were procured from Yash Farms, Pune, India

Methods

Characterization of powdered extract of *Commiphora mukul* and Babchi oil

Organoleptic Properties

Powdered extract of *Commiphora mukul* and Babchi oil were analyzed for the organoleptic properties like colour, odour and appearance[15].

Solubility Profile

Solubility of powdered extract of *Commiphora mukul* and Babchi oil was checked in distilled water, methanol, ethanol, chloroform, acetone, DMSO and phosphate buffer (pH 5.4). Accurately weighed one gm of drug was transferred in a clean and dry test tube followed by addition of the solvents individually and shaken vigorously and the solubility of drug was checked visually.

Determination of solubility in mixture of DMSO and phosphate buffer pH 5.4 for determination of ratio

Accurately weighed 20mg of powdered extract of *Commiphora mukul* and Babchi oil was added to ten clean

and dried volumetric flasks each of 10ml capacity individually. DMSO and phosphate buffer pH 5.4 solvent system was added in the ratio 1:9, 2:8, 3:7, 4:6, 5:5, 6:3, 7:3, 8:2, 9:1 and the samples were shaken for 1hour on linear motion shaker (Model no. REMI RQ 123, Spectra Whirlmatic Lab, India). The solutions were checked visually for their clarity.

Analytical Methodology

The ultraviolet absorption spectrum of a solution of powdered extract of *Commiphora mukul* and Babchi oil in DMSO and (8:2) mixture of DMSO and Phosphate buffer pH 5.4 was obtained using UV/VIS spectrophotometer (V-630, Jasco Corporation Tokyo, Japan) over a wavelength range of 200 to 400nm. Maximum absorption (λmax) values were determined and further used for plotting calibration curve[16].

Characterization of Oil, Surfactant and Co-Surfactant for Micro emulsion

Solubility Determination in Various Oil, Surfactant and Co-surfactant

The solubility of drug in various oils, surfactants and co-surfactants was measured and the solvents for the study were selected based on the good solubilising capacity for drug. An excess amount of drug was added into each vehicle followed by vortex mixing for 30sec (Remi mixer, Mumbai). Mixtures were shaken for 48h at 30^0C, followed by equilibrium for 24hr. The equilibrated samples were then centrifuged at 1000rpm for 10min to remove the insoluble drug and clear supernatant liquid was decanted. An aliquot of the supernatant was diluted with DMSO and solubility of drug was estimated by UV spectroscopy at 301 and 328nm[17].

Pseudo-Ternary Phase Diagram

The micro emulsion existence region was determined by constructing pseudo-ternary phase diagrams. On the basis of the solubility study of drugs; oils, surfactants, co-surfactants and aqueous phase were used for construction of phase diagram. Surfactant and co-surfactant (Smix) in each group were mixed in different weight ratio of (1:0, 1:1, 1:2, 2:1, 1:3, 3:1, 1:4, 4:1). For each phase diagram oil and specific Smix ratio were mixed thoroughly in different weight ratio from 1:9 to 9:1 (1:9, 2:8, 3:7, 4:6, 5.0:5.0, 6:4, 7:3, 8:2, 9:1) in different glass vials. Pseudo-ternary phase diagram was developed using aqueous titration method. Water was added drop wise with constant stirring on 6 Station magnetic stirrers (Spectralab, Whirlmatic, India) until homogeneous dispersion or solution was obtained. After each addition the system was examined for appearance and flow property. The end point of the titration was the point in which the solution becomes cloudy or turbid. The quantity of aqueous phase required to achieve turbidity point was noted. Slow titration with aqueous phase is performed to each weight ratio of oil and Smix. The physical state of the micro emulsion was marked on a pseudo-three-component phase diagram with one axis representing aqueous phase, the other representing oil and the third representing a mixture of surfactant and co-surfactant at fixed weight ratios (Smix ratio)[18,19].

Formulation Study

Formulation of Emulgel

The factorial Batches of micro emulsion that contained both *Commiphora mukul* and Babchi oil were formulated by mixing oil, surfactant and co-surfactant with varying component ratio. Accurately measured 0.15 (%w/v) of *Commiphora mukul* was mixed with 0.18 (%v/v) Babchi oil and dissolved in the mixture of oil, surfactant and co-surfactant and then an appropriate amount of water was added to the mixture drop wise with constant stirring on 6 station magnetic stirrer (Spectralab, Whirlmatic, India). Micro emulsion of *Commiphora mukul* and Babchi oil was obtained spontaneously on stirring the mixtures at ambient temperature. Various gelling agents namely, Sodium CMC, Hydroxypropyl methylcellulose (Methocel K4000M), HPMC CR, Carbopol 934 and Carbopol 940 were evaluated for their ability to gel medicated micro emulsion. Gelling agent was dispersed slowly in the medicated micro emulsion with the help of overhead stirrer. In case of Carbopol 940 and 934, the dispersion was neutralized by using triethanolamine to obtain the gel.

Factorial Formulations

The effect of formulation variables on the responses were statically evaluated by applying one-way ANOVA, using the commercially available software package Design-Expert® version 8.0. 2^3 factorial design was implemented for optimization of micro emulsion that contained three independent variables (X1= Captex, X2= Cremophore, X3= Capmul MCM at two levels +1 and -1.

Evaluation of the Factorial Batches of Micro emulsion Based Gel containing Both *Commiphora mukul* and Babchi Oil

% EE

Accurately weighed 1mg of gel was mixed in 10ml calibrated volumetric flasks containing 9ml DMSO; it was diluted appropriately and drug content was determined spectrophotometrically. % EE was calculated as per the formula[20].

$$\text{Percent EE} = \frac{\text{Actual drug content} - \text{Free drug content}}{\text{Actual drug content}} \times 100$$

% DR

The in vitro drug release studies were carried out using a modified Franz diffusion (FD) cell. Accurately weighed 1gm of sample was applied on cellophane membrane which was placed between donor and receptor compartment of the FD cell. 8:2 mixture of DMSO and Phosphate buffer pH 5.4 was used as a dissolution media. This whole assembly was kept on a magnetic stirrer and the solution was stirred continuously using a magnetic bead. Accurately weighed 1gm of drug containing gel was placed in the donor compartment. Samples (0.5ml) were withdrawn from the receptor fluid at 1hr interval for up to 6hrs after the application. An equal volume of the fresh phosphate buffer was immediately replenished after each sampling maintaining sink conditions. Samples were analyzed by UV-visible spectrophotometer (Jasco, V630) at 301nm and 328nm respectively with suitable dilutions and the cumulative % drug release was calculated[20].

Formulation of the Optimised Batch

The optimised batch was formulated using the predicted values of the %EE and %DR from the software.

Table 1: 2^3 Factorial design of *Commiphora mukul* and Babchi Oil Micro emulsion in Coded and Actual form

Levels (Code Value)	Actual values			Response	
	X_1 (% w/v) (Captex)	X_2 (% w/v) (Cremophor)	X_3 (% w/v) (Capmul MCM)	Y_1	Y_2
-1	0.25	0.25	0.25	% Entrapment Efficiency	% Drug Release
+1	0.5	0.5	0.5		

Table 2: Factorial batches of *Commiphora mukul* and Babchi Oil Micro emulsion Based Gel with HPMC CR as Gelling Agent

Sr. No.	Formulation Code	Ingredients					
		Commiphora mukul (%) (w/v)	Babchi Oil (%) (v/v)	Captex (%) (v/v)	Cremophor RH 40 (%) (v/v)	Cap MCM (%) (v/v)	Water (%) (v/v)
1	M1	0.15	0.16	0.25	0.25	0.25	Upto 100
2	M2	0.15	0.16	0.5	0.25	0.25	Upto 100
3	M3	0.15	0.16	0.25	0.5	0.25	Upto 100
4	M4	0.15	0.16	0.25	0.25	0.5	Upto 100
5	M5	0.15	0.16	0.5	0.5	0.25	Upto 100
6	M6	0.15	0.16	0.25	0.5	0.5	Upto 100
7	M7	0.15	0.16	0.5	0.25	0.5	Upto 100
8	M8	0.15	0.16	0.5	0.5	0.5	Upto 100

Table 3: Organoleptic Properties of *Commiphora mukul* and Babchi oil

Parameters	*Commiphora mukul*		Babchi oil	
	Experimental	Theoritical	Experimental	Theoritical
Colour	Slight yellow	Slight yellow	Brownish yellow colour	Brownish yellow colour
Odour	Acrid	Acrid	pungent	pungent
Taste	Bitter	Bitter	Bitter	Bitter

Table 4: Solubility Profile of *Commiphora mukul* and Babchi oil

Solvent	Solubility	
	Commiphora mukul	Babchi oil
Distilled Water	Insoluble	Insoluble
Methanol	Sparingly Soluble	Soluble
Ethanol	Sparingly Soluble	Freely Soluble
Chloroform	Sparingly Soluble	Sparingly Soluble
Acetone	Sparingly Soluble	Freely Soluble
DMSO	Soluble	Soluble
Phosphate Buffer (5.4 pH)	Sparingly Soluble	Sparingly Soluble

Table 5: Solubility Determination of Drugs *Commiphora mukul* and Babchi Oil in Various Oil, Surfactant and Co-surfactant

Solvent		Solubility (µg/ml) In	
		Babchi Oil	*Commiphora mukul*
Oil	Captex	66.7	62.2
	Wheatgerm Oil	18.5	25.5
	Olive Oil	21.9	24.2
	Capryol 90	62.5	65.6
	Soyabean Oil	14.1	32.8
	IPM	Insoluble	3.7
Surfactant	Cremophor RH-40	5.2	70.5
	Tween 80	5.2	139.4
	Acconon MC8-2	3.7	45.7
Co-surfactant	Ethylene Glycol	Insoluble	50.2
	Propylene Glycol	Insoluble	56.2
	PEG 400	27.8	38.9
	Capmul MCM C-10	4.9	55.7
	Capmul PG8	4.0	49.2

Table 6: Factorial batches that Contained both *Commiphora mukul* and Babchi Oil Micro emulsion with HPMC CR as Gelling Agent

Batch Code	% EE*		Cumulative % DR*	
	Babchi Oil	*Commiphora mukul*	Babchi Oil	*Commiphora mukul*
M1	79.26±1.45	81.28±0.41	92.425±0.16	77.029±0.31
M2	81.01±0.62	87.85±0.07	93.998±0.05	79.156±0.01
M3	**85.31±2.12**	**88.79±0.18**	**94.342±0.01**	**79.721±0.48**
M4	81.04±2.05	81.39±2.03	92.929±0.35	76.210±0.01
M5	82.65±0.15	85.92±0.11	88.038±0.46	78.826±0.01
M6	83.89±1.56	88.62±2.81	91.284±0.01	75.100±0.17
M7	80.23±0.15	82.53±2.81	93.084±0.06	77.540±0.26
M8	82.52±1.25	84.58±0.43	92.440±0.01	79.615±0.04

Table 7: Formulation of optimised batch that Contained Both *Commiphora mukul* and Babchi Oil Micro emulsion Based Gel

Formulation Code	Ingredients					
	Commiphora mukul (%) (w/v)	Babchi Oil (%) (v/v)	Captex (%) (v/v)	Cremophor RH 40 (%) (v/v)	Cap MCM (%) (v/v)	Water (%) (v/v)
M3	0.15	0.16	0.25	0.5	0.25	Up to 100

Table 8: Comparison between the Experimented and Predicted Values for Most Probable Optimal Formulation

Dependent variables	Optimized formulation M3			
	Commiphora mukul		Babchi oil	
	Experimented value	Predicted value	Experimented value	Predicted value
% Drug Release	79.721 ±0.48	79.712	94.342 ±0.01	94.342
% Entrapment Efficiency	88.79±0.18	87.88	85.31±2.12	86.86

Table 9: Mean Paw Oedema Volume and Percentage Inhibition of the Oedema in the Albino Rats

Time (in hrs)	Mean Paw Oedema Volume			Percentage Inhibition of the Oedema		
	Control	Test	Standard	Control	Test	Standard
0	0.224	0.216	0.225	-	22.51	21.37
1	0.258	0.192	0.193	-	25.71	25.55
2	0.279	0.115	0.113	-	60.90	59.85
3	0.332	0.108	0.107	-	67.07	68.06
4	0.364	0.102	0.098	-	71.58	72.66
5	0.392	0.092	0.102	-	74.88	73.70
6	0.428	0.105	0.108	-	75.64	74.51

Table 10: Stability Study of Optimised Batch

Parameters		Formulation code M3			
		Initial	1month	2months	3months
	Visual appearance	No Change	No Change	No Change	No Change
	pH	5.04	5.04	5.02	5.01
C. mukul	%EE	88.79±0.18	88.65±0.42	86.93±1.11	88.03±2.84
	Cumulative% DR	79.721±0.48	79.552±1.59	79.453±2.13	79.034±0.81
Babchi oil	%EE	85.31±2.12	85.15±0.43	84.95±0.21	84.03±1.26
	Cumulative% DR	94.342±0.01	94.152±0.42	93.953±0.11	93.934±0.82

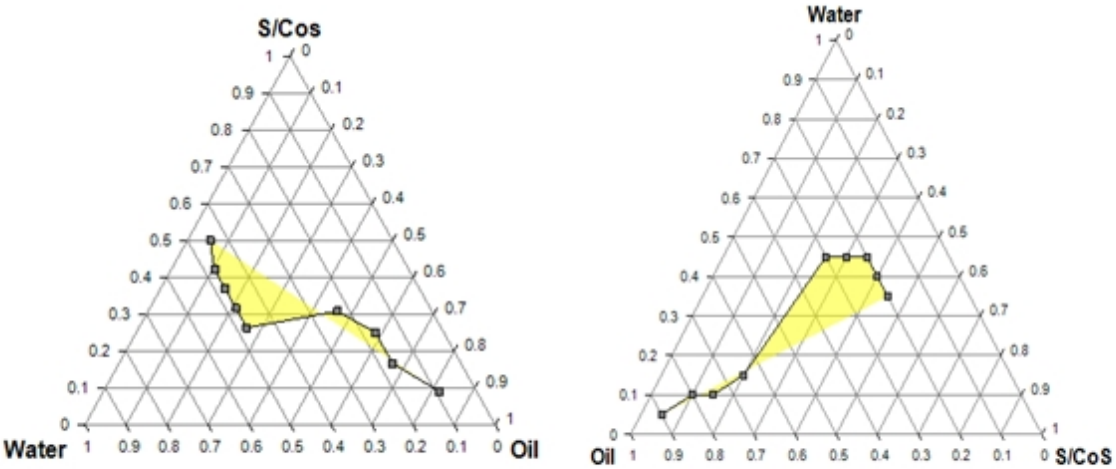


Fig. 1. Ternary Diagram of Ratio of Oil (Captex) to Smix (Cremophor : Capmul MCM (2:1))

Fig. i

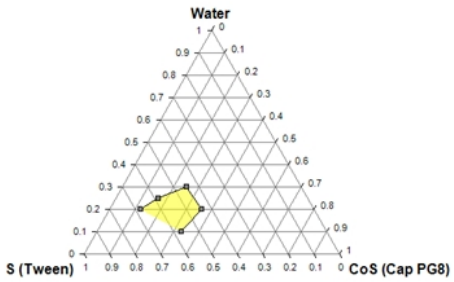


Fig. ii

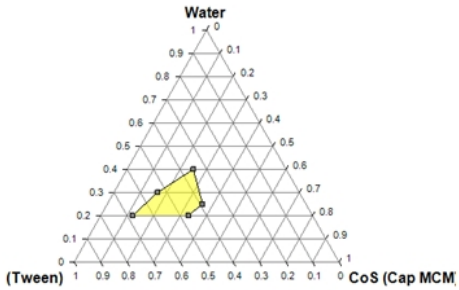


Fig. iii

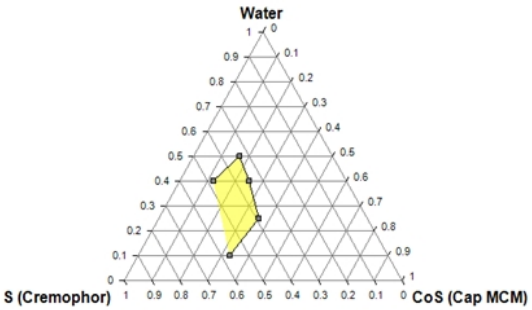


Fig. iv

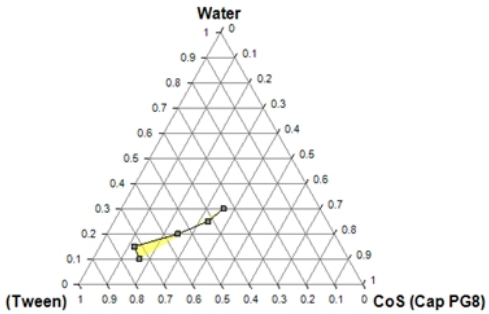


Fig. 2. Ternary Diagram of (i) Oil Captex Surfactant Tween and Co-Surfactant Capmul PG 8 (ii) Oil Captex Surfactant Tween and Co-Surfactant Capmul MCM (iii) Oil Captex Surfactant Cremophor and Co-Surfactant Capmul MCM (iv) Oil Olive oil Surfactant Tween and Co-Surfactant Capmul PG 8

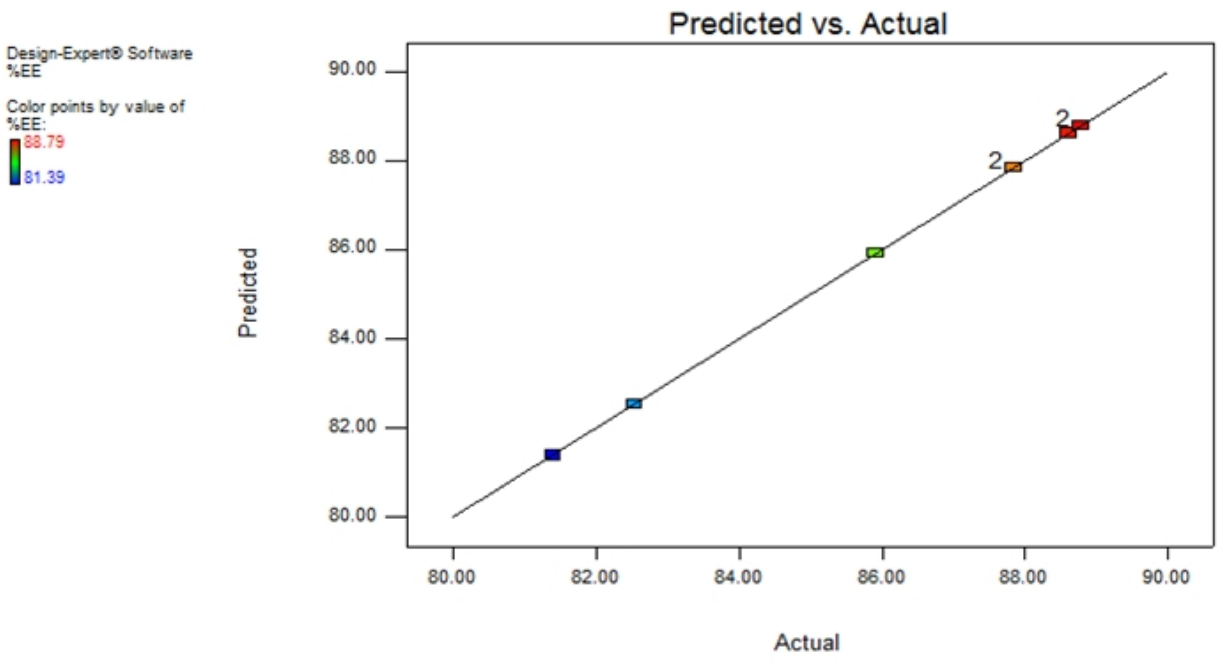


Fig. 3: Linear Correlation Plot between Actual and Predicted values for % EE (Y_1)

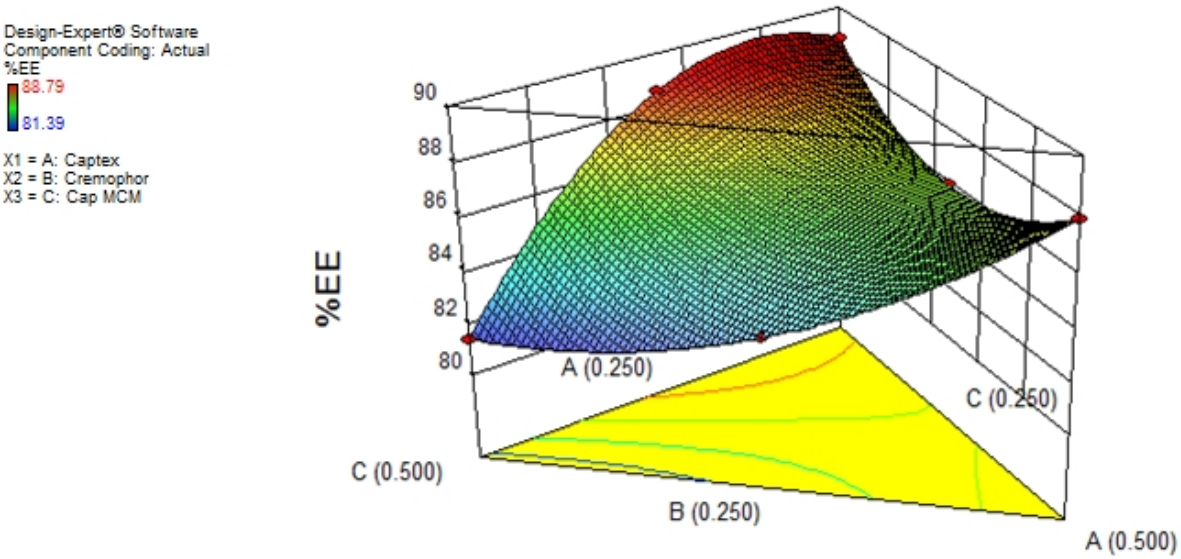


Fig. 4: Response surface plot showing effect of formulation variables on % EE (Y_1)

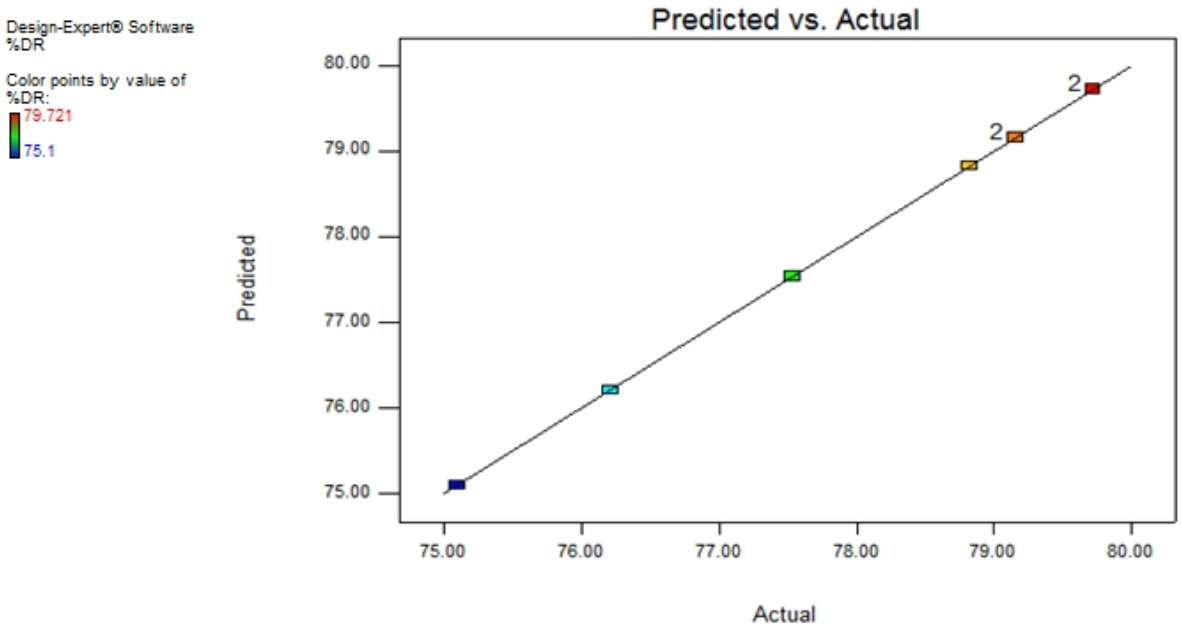


Fig. 5: Linear Correlation Plot between Actual and Predicted values for % DR (Y_2)

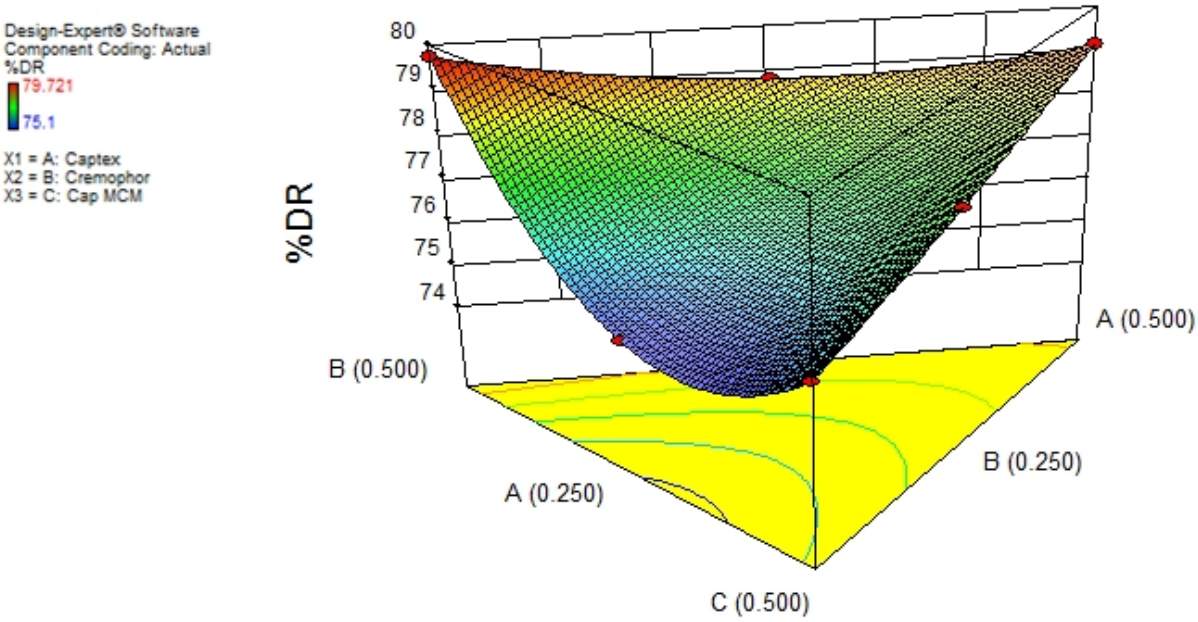


Fig. 6: Response surface plot showing effect of formulation variables on % DR (Y_2)

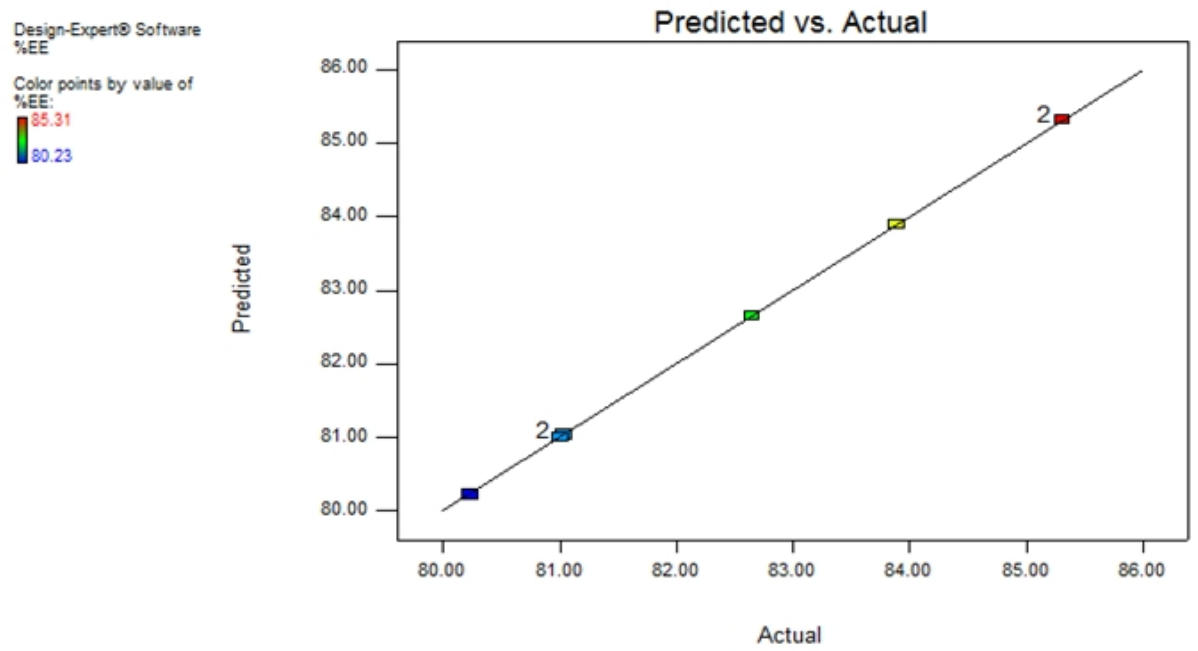


Fig. 7: Linear Correlation plot between actual and predicted values for % EE (Y_1)

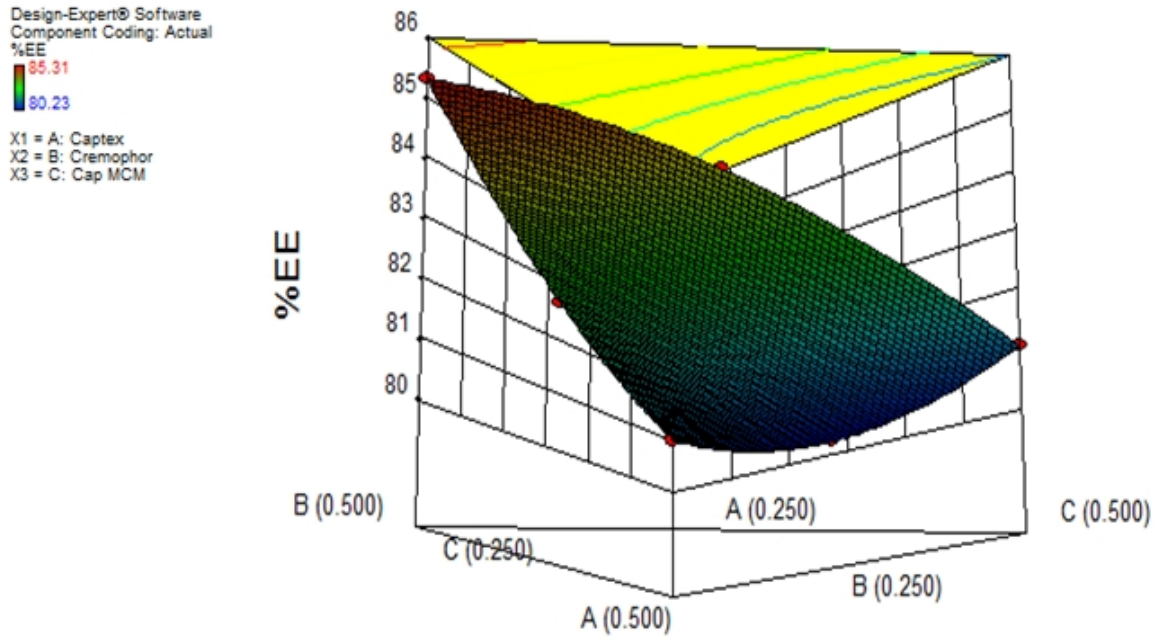


Fig. 8: Response surface plot showing effect of formulation variables on % EE (Y_1)

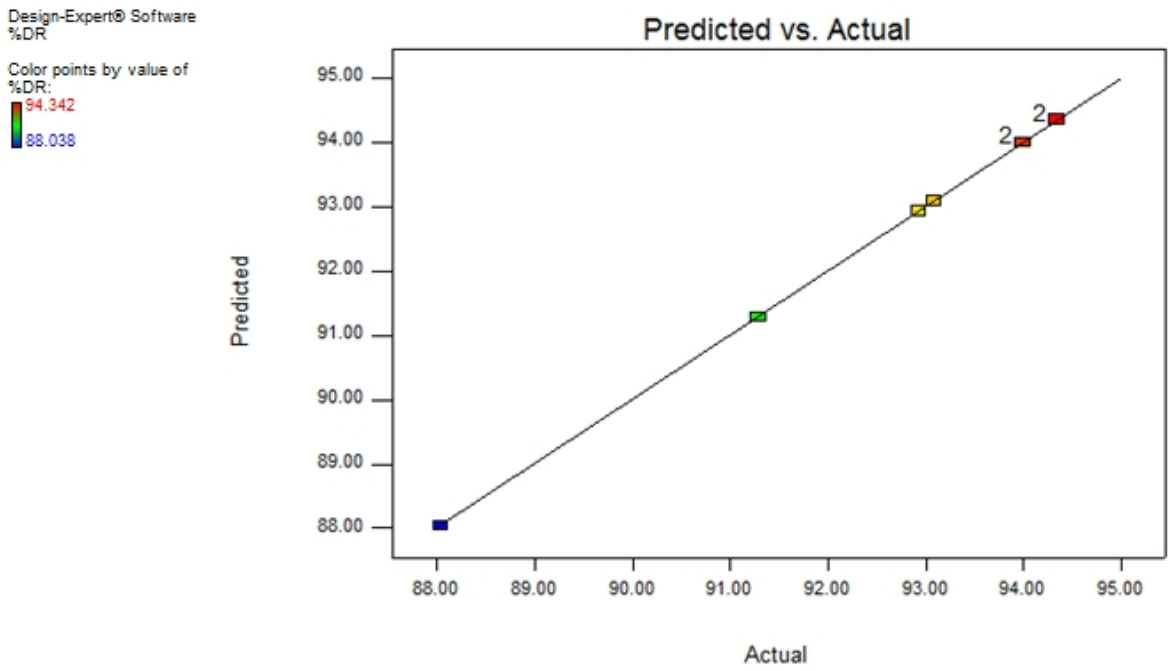


Fig. 9: Linear Correlation Plot between Actual and Predicted values for % DR (Y_2)

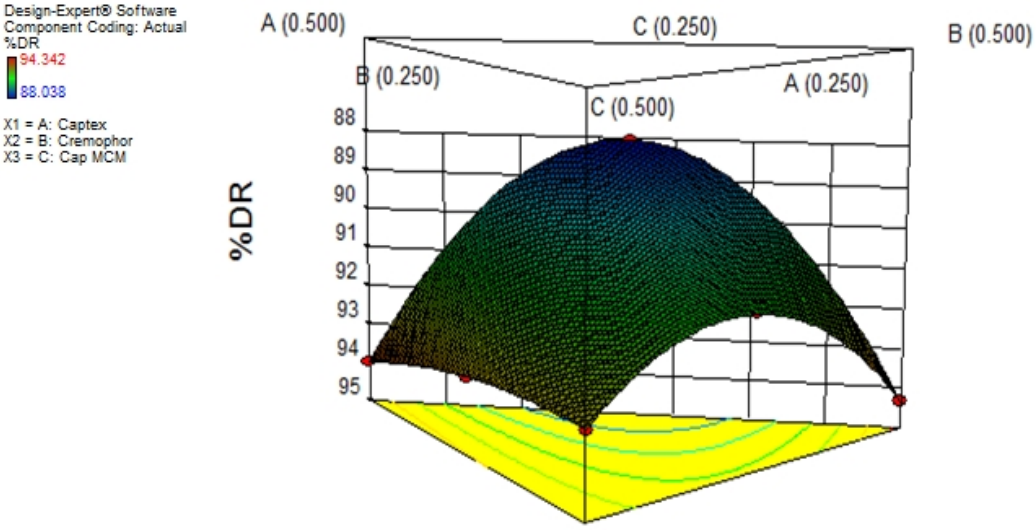
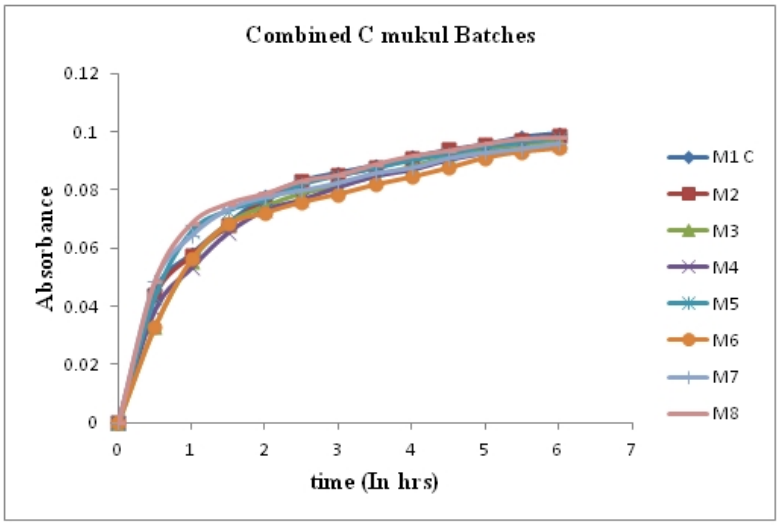


Fig. 10: Response surface plot showing effect of formulation variables on % DR (Y_2)



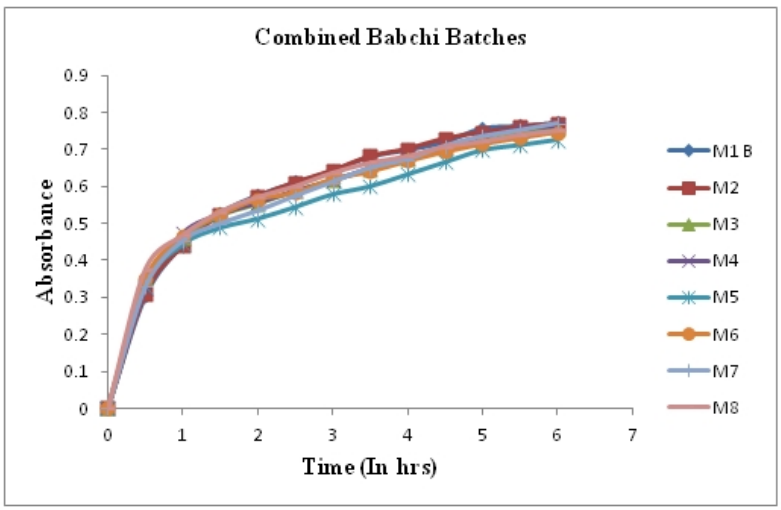


Fig. 11 Diffusion Graphs of Factorial Batches that Contained Both Commiphora mukul and Babchi Oil

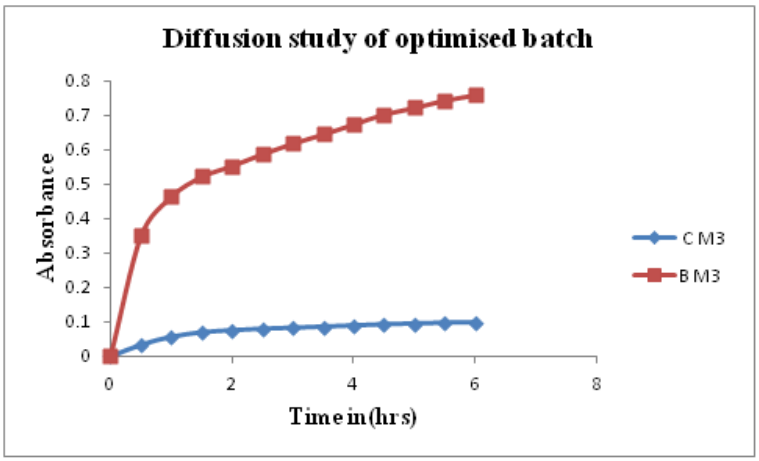
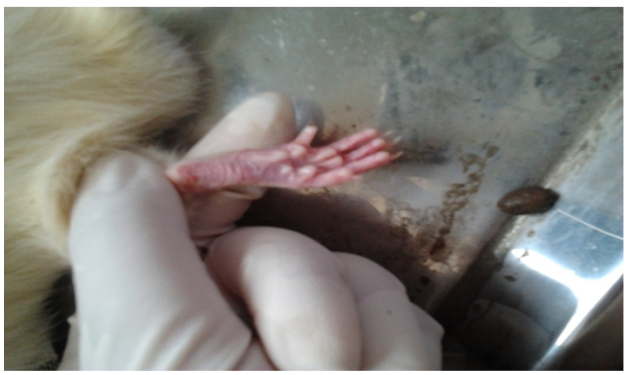
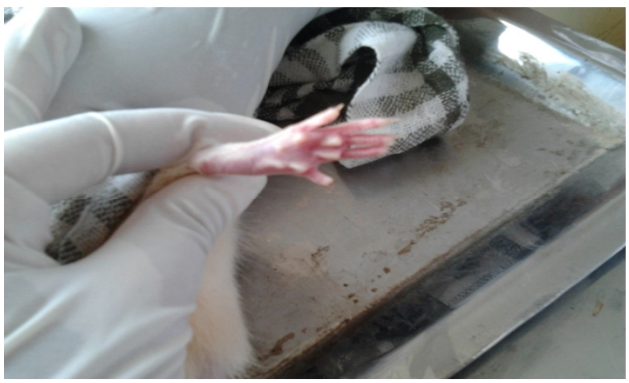


Fig. 12: Diffusion Graphs of Optimised batches



a

b



c

d

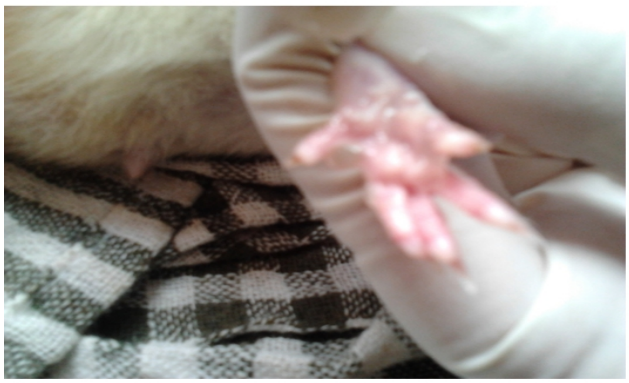


Figure No. 13: Rat Paw Edema Test, results after 6hrs

a) **Inhibitory Effect of Optimised Batch S3 of Commiphora mukul MBG**
b) **Inhibitory Effect of Optimised Batch P8 of Babchi oil MBG**
c) **Inhibitory Effect of Optimised Batch M3 of Combined Drugs MBG**
d) **Inhibitory Effect of Marketed formulation (Tacrolimus Ointment)**
e) **Carrageenan Induced Inflammation**

Evaluation of Optimised Batch Containing both *Commiphora mukul* and Babchi Oil Micro emulsion Based Gel

The optimized gels were evaluated for %EE and %DR.

Skin irritation test (patch test)

A set of 3 rats was used in the study. The emulgel was applied on the properly shaven skin of rat. Undesirable skin changes, i.e., change in colour, change in skin morphology were checked for a period of 24hr.

In Vivo Anti-Inflammatory Activity for Optimised Batches of *Commiphora mukul* and Babchi Oil Combined Micro emulsion Based Gel

Wistar albino rats of either sex, weighing 150-210gm were used for the experiment. All experiments were performed after an overnight fast. All studies were conducted in accordance with protocols, reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of Allana College of Pharmacy, Pune, Maharashtra, India. The serial number of the approval protocol was Ref/ ACP/ IAEC/11-12/29-02 for in vivo anti inflammatory studies. In order to establish anti inflammatory activity oedema was induced on the left hind paw of the rats by sub plantar injection of 1% (w/v) carrageenan. Formulation, i.e., M3 and standard (tacrolimus ointment) were applied 30min before carrageenan administration. The paw volume was measured by mercury displacement method using plethysmometer[21]

Group 1 (Control group): Carrageenan (1%)
Group 2 (Standard group): Topical marketed Tacrolimus gel+ Carrageenan.
Group 3 (Test): Formulations M3 +Carrageenan

The % inhibition of paw oedema in drug treated group was compared with carrageenan control group and calculated according to the formula.

$$\text{Percent Inhibition} = \frac{\text{Control paw volume} - \text{Test paw volume}}{\text{Control paw volume}} \times 100$$

Accelerated Stability Studies

The stability studies were carried out according to the ICH guidelines to assess the drug and formulation stability. The optimized formulation was sealed in aluminium packaging material. Sample was kept in a stability chamber (Thermolab) maintained at 45ºC and 75% RH for 3months. The sample was withdrawn at 0, 1, 2 and 3months[22].

Evaluation

The optimized formulation was evaluated over a period of 3months for the following parameters: Appearance, pH, %EE, %DR.

RESULTS AND DISCUSSION

Characterization of *Commiphora mukul* and Babchi oil

Physical appearance

The drugs were subjected to organoleptic evaluation. The results obtained are shown in Table 3. Organoleptic properties obtained practically matches the properties given in the literature. Thus it confirms the identity of the drug.

Solubility Profile and Saturation Solubility

Solubility and saturation solubility of *Commiphora mukul* and Babchi oil are depicted in Table 4. It can be depicted from the Table 4 that *Commiphora mukul* is soluble in DMSO and Babchi Oil is soluble in Ethanol, Methanol and DMSO, but DMSO being the common solvent for dissolving both the drugs was selected for further studies. Solubility of *Commiphora mukul* and Babchi oil in DMSO and phosphate buffer pH 5.4 mixtures was determined for determination of ratio and 8:2 was selected as the best ratio.

Analytical Methodology

The λ_{max} of *Commiphora mukul* and Babchi Oil in DMSO and (8:2) mixture of DMSO: Phosphate buffer pH 5.4 was found to be 328, 329nm; 301nm, 315nm respectively.

Characterization of Oil, Surfactant and Co-Surfactant Selection of Excipients

The oils and surfactants were selected on the basis of their tendency for instant emulsification. The excipients selected needed to be pharmaceutically acceptable, non irritating and non sensitizing to the skin and to fall into the GRAS (generally regarded as safe) category. Higher solubility of the drug in the oil phase was another important criterion, as it would help the micro emulsion to maintain the drug in solubilised form. Safety is a major determining factor in choosing a surfactant, as a large amount of surfactants may cause skin irritation. Non-ionic surfactants are less toxic than ionic surfactants. An important criterion for selection of the surfactants is that the required hydrophilic lipophilic balance (HLB) value to form the o/w micro emulsion be greater than 10. The right blend of low and high HLB surfactants leads to the formation of a stable micro emulsion formulation. In this study, we selected Cremophor RH 40 as a surfactant with an HLB value of 15. The presence of co surfactant decreases the bending stress of interface and allows the interfacial film sufficient flexibility to take up different curvatures required to form micro emulsions over a wide range of composition. Thus, the co surfactant selected for the study was Capmul MCM, which has an HLB value of 5-6. Babchi Oil is a highly lipophilic drug, and its pharmacological properties suggest that it has good potential for topical drug delivery, whereas *Commiphora mukul* is a hydrophilic drug. It can be depicted from the Table 5 that in oils, Captex; in surfactants Cremophor RH 40 and in Co-Surfactants Capmul MCM has better solubility with the drugs as compared to others. Therefore on the basis of solubility data polymers were selected for formulations.

Pseudo-Ternary Phase Diagram

Ternary diagram of Ratio of Oil to Smix

Oil = Captex
Smix = Cremophor: Capmul MCM (2:1)

Thus from the ternary diagram it can be concluded that best ratios of Oil: Smix that gives maximum micro emulsion region are 5:5, 4:6.

Selection of Surfactant and Co Surfactant

Ternary diagram of different concentration of surfactant and co-surfactant is given in Figure 2. It can be depicted that Cremophor (surfactant) and Capmul MCM (co-surfactant) with Captex as oil gives the maximum micro emulsion region. Phase behaviour investigation of this system demonstrated the suitable approach to determine the water phase, oil phase, surfactant concentration, and co surfactant concentration with which the transparent, 1-phase low-

viscous micro emulsion system was formed. The phase study revealed that the maximum proportion of oil was incorporated in micro emulsion systems when the surfactant-to-co surfactant ratio was 5:5. From pseudoternary phase diagrams, the formulation in which the amounts of oil phase completely solubilised the drug and which could accommodate the optimum quantity of Smix and distilled water was selected for the study.

Formulation Study

Factorial Batches of *Commiphora mukul* and Babchi Oil Micro emulsion Formulated with HPMC CR as Gelling Agent

Commiphora mukul

Figure 4 showed the response surface plot, which displayed the effect of X_1, X_2 and X_3 on the %EE Y_1. From the Figure, at maximum level of X_2 (0.5), and minimum levels of X_1, X_3 (0.25) results in increasing the %EE of the formulation to the maximum 88. On the other hand, increasing X_1, X_3 up to (0.5) and decreasing X_2 to (0.25) results in decreasing the %EE to the minimum 82. Also, it was found that, high level of X_1 and X_2 (0.5) and low levels of X_3 (0.25) resulted in high value of %EE. The %EE of the formulation will be maximized either at low 0.25 or high 0.5 of X_1, where %EE of the formulation was 88 and 86. Figure 3 showed the linear correlation plot of predicted and actual values of %EE and these values are near by each other indicating the correctness of the model.

Figure 6 showed the response surface plot, which displayed the effect of X_1, X_2 and X_3 on the %DR Y_2. From the figure, at maximum level of X_2 (0.5), and minimum levels of X_1, X_3 (0.25) results in increasing the %DR of the formulation to the maximum 79. On the other hand, decreasing X_1, X_2 to (0.25) and increasing X_3 up to (0.5) results in decreasing the %DR to the minimum 75. Also, it was found that, high level of X_1 and X_2 (0.5) and low levels of X_3 (0.25) resulted in high values of %DR. The %DR of the formulation will be maximized either at low 0.25 or high 0.5 of X_1, where %DR of the formulation was 79 and 78. Figure 5 showed the linear correlation plot of predicted and actual values of %DR and these values are near by each other indicating the correctness of the model.

Babchi oil

Figure 8 showed the response surface plot, which displayed the effect of X_1, X_2 and X_3 on the % EE Y_1. From the Figure, at maximum level of X_2 (0.5), and minimum levels of X_1, X_3 (0.25) results in increasing the %EE of the formulation to the maximum 85. On the other hand, decreasing the X_2 to (0.25) and increasing X_1, X_3 up to (0.5) results in decreasing the %EE to the minimum 81. Figure 7 showed the linear correlation plot of predicted and actual values of %EE and these values are near by each other indicating the correctness of the model. Figure 10 showed the response surface plot, which displayed the effect of X_1, X_2 and X_3 on the %DR Y_2. From the Figure, at maximum level of X_2 (0.5), and minimum levels of X_1, X_3 (0.25) results in increasing the %DR of the formulation to the maximum 94. On the other hand, increasing X_1, X_2 to (0.5) and decreasing X_3 to (0.25) results in decreasing the %DR to the minimum 89. Figure 9 showed the linear correlation plot of predicted and actual values of %DR and these values are near by each other indicating the correctness of the model.

Evaluation of the Factorial Batches that contained both *Commiphora mukul* and Babchi oil Micro emulsion Based Gel

Batch M3 showed good drug release as compared to other batches thus it was selected as an optimized batch.

Formulation of the Optimised Batch

The optimised batch was formulated using the predicted values of the %EE and %DR from the software.

Evaluation of Optimised Batch Containing *Commiphora mukul* and Babchi Oil Combined Micro emulsion Based Gel

Since the experimental and predicted results obtained were found to be nearly same for batches with above mentioned composition, it was subjected to stability study as per ICH guidelines. The optimized batches showed similar release profile compared to factorial batches. Release shown was 79.721±0.48, 94.342±0.01 for *Commiphora mukul* and Babchi oil combined batches respectively in 6hrs.

Skin irritation test (patch test)

No allergic symptoms like inflammation, redness, irritation appeared on rats up to 24h. The results indicated that the control preparation (which did not contain any drug), test gel and marketed products did not cause any skin reaction. It can be assured that drug and the excipients did not cause any skin irritation and can be used in the gel formulation.

In Vivo Anti-Inflammatory Activity for Optimised Batches of *Commiphora mukul* and Babchi Oil Combined Micro emulsion Based Gel

Percentage increase in paw volume (inflammation) and percentage inhibition of inflammation in control group and groups treated with test and marketed products and the results are given in the Table 9 and Figure 13. In control group which received carrageenan alone, a rapid and continuous increase in paw volume (i.e. inflammation) was observed and the inflammation was sustained during the entire period of 6hrs of study. In the groups which received test products, the percentage increase in paw volume was low when compared to the control group, indicating that the test and marketed product possess good anti-inflammatory activity. The inflammation due to carrageenan was markedly inhibited by the test and marketed products. A comparison of the percentage inhibition of inflammation (i.e., anti-inflammatory activity) of test and marketed products is made in Table 9. The % inhibition of Tacrolimus (marketed preparation) and Test formulations were found to be 74.51% and 75.64% respectively. The pharmacological activity (anti-inflammatory) of optimized batch containing both the drugs *Commiphora mukul* and Babchi oil was comparable to the marketed preparation; these results indicated the rapid onset of action and higher activity during the initial periods due to their enhanced dissolution and absorption rates.

Accelerated Stability Study

All the prepared emulgel formulations were found to be stable upon storage for 3months is depicted in Table 10.

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Abbreviation

DMSO- Di Methyl Sulphoxide
HLB- Hydrophilic Lipophilic Balance
%DR- Percent Drug Release
%EE- Percent Entrapment Efficiency
Smix- Surfactant and Co-surfactant Mixture

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