Research Article

Design and Development of Emulgel Containing *Pongamia pinnata* Extract

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ABSTRACT

Emulgel is an emerging topical drug delivery system. The present work aimed at design, preparation and statistically optimization of *Pongamia pinnata* extract emulgel for enhanced transdermal delivery using 3^2 factorial designs. The independent variables selected were Carbopol and Emulsified agent ratio (Span: tween) and the dependent variables were Viscosity (cp) (Y1) and spredability (Y2). The prepared *Pongamia Pinnata* extract emulgel were evaluated for their physical appearance, rheological behavior, in vitro drug release and ex vivo permeability study. From % drug diffusion study it was observed that, the prepared topical PPE emulgel formulation released a maximum of 59.15% ± 0.512 over a period of 6 hours. The studies of the prepared emulgel were carried out for 90 days by keeping at 40° C ± 2°C and 75% ± 5% relative humidity (RH). The results indicated that there was no phase separation and no significant changes in physical appearance, % viscosity, % spredability, and drug content observed when compared with the initial formulation.

Keywords: Emulgel, Pongamia Pinnata, In vitro dissolution, Psoriasis, Topical delivery

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INTRODUCTION

Various novel topical carriers have been evaluated for enhancing skin penetration of drug by microemulsion, nanogel, niosomes, and liposomes.[1, 2] The delivery of synthetic drugs for psoriasis is hindered by the inherent side effects of drug moiety or the problems associated with the conventional delivery systems.[3, 4]

Emulgels are emulsions, either of the oil-in-water or water-in-oil type, which are gelled by mixing with a gelling agent. The presence of a gelling agent in water phase converts an emulsion into emulgel.[5] Emulgels are a combination of both emulsion and gels and act as a dual control release system for hydrophobic drugs.[6] Emulgels for Topical use have several merits such as thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water-soluble, greater shelf life, bio-friendly. [7]

Pongamia pinnata traditionally has been utilized as medicine against many inflammatory disorders. Seed of this plant is consumed in tribal medicine and its oil is used in Ayurveda to treat psoriasis and arthritis. [8-10] As a novel approach, in our investigation, the topical emulgel was considered as a great potential product for an effective and safe way to administer *Pongamia Pinnata* for the treatment of skin diseases such as psoriasis. The aim of this research work was to develop an emulgel composed of *Pongamia pinnata* hydroalcohlic extract (PPE). Design of Experiments (DoE) was used in the optimization of PPE emulgel.

MATERIALS AND METHODS

Imiquimod was obtained from Glenmark Pharmaceutical. Carbapol 934 was obtained from Loba chemie LTD, Mumbai. Spans 80, Tween 80, Liquid Paraffin were obtained from Sigma Aldrich, Mumbai. Triethanolamine, Polyethylene glycol-400, Dimethyl sulfoxide was obtained from Merck chemical, Mumbai.

Experimental design (3^2 full factorial design)

Nine PPE emulgel formulations were prepared according to a 3^2 factorial design employing the qualitative factors and levels shown in Tables 1 and 2. Generation and evaluation of the experimental design was carried out using Design Expert software Expert® DX 10.0.7.0 (Stat-Ease Inc., MN). Two independent variables were evaluated: Amount of Carbapol (0.5, 1and 1.5 %w/w) (X1), amount of Emulsified agent ratio (Span: tween) 2 (0.9:1.1), 4(1.5:2.5) and 6(2:4) %w/w (X2). Viscosity (cp) (Y1) and spreadability (Y2) were selected as the dependent variables. Desirability was calculated for selection of the optimized formula which was subjected for further investigations.

Preparation of emulgel

The gel phase in the formulations was prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed using mechanical shaker, then the pH was adjusted to 6–6.5 using triethanolamine (TEA).[11] The oil phase of the emulsion was prepared by

dissolving span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving tween 20 in purified water. Methyl parabens were dissolved in propylene glycol whereas *pongamia pinnata* extract was dissolved in ethanol, and both solutions were mixed with the aqueous phase. DMSO was mixed in oil phase. Both the oily and aqueous phases were separately heated to 75^0 C, and then the oily phase was added to the aqueous phase with continuous stirring until it got cooled to room temperature. The obtained emulsion was mixed with the gel in 1:1 ratio with gentle stirring to obtain the emulgel. The composition of Herbal emulgel formulations is shown in table 1 and 2.

Table 1: 3^2 full factorial design: factors, factor levels and responses for Emulgel formulation

Factors (Independent variables)	Factor levels used		
	Low (-1)	Medium (0)	High (+1)
Amount of carbapol (X_1)	0.5	1	1.5
Amount of emulsified agent(X_2)(Span:Tween)	2	4	6
Responses (Dependent variable)			
Y_1 = Percent viscosity (% cp)			
Y_2 = Percent spreadability (% min/sec)			

Table 2: Preparation of Emulgel using following concentration (%W/W)

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carbapol 934	1	0.5	1.5	1.5	1.5	0.5	0.5	1	1
Emulsified Agent (Span:Tween)	6	4	2	6	4	2	6	4	2
Liquid paraffin	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Propylene glycol	5	5	5	5	5	5	5	5	5
DMSO	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Methyl Paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Triethanolamine	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100	Up to 100

Evaluation of Emulgel

Physical appreances

The prepared emulgel were visually checked for the color, appearance, homogeneity, phase separation and consistency. [12]

pH of emulgel

The pH of the emulgel was measured by a digital pH meter, at a working temperature of 25 ± 1°C. The measurements of pH of each system were replicated three times. [13]

Viscosity

The viscosity of the prepared formulations was determined at ambient temperature using Brookfield digital viscometer (DV-E) with spindle no. 63 at 12, 30 and 50 rpm. [14]

Determination of spread ability

The spreading coefficient of the formulations was determined using an apparatus consisting of two glass slides (7.5 × 2.5 cm), one of which was fixed onto the wooden board and the other was movable, tied to a thread which passed over a pulley, carrying a weight. Formulation (1 g) was placed between the two glass slides. Weight (100 g) was allowed to rest on the upper slide for 1 to 2 minutes to expel the entrapped air between the slides and to provide a uniform 1m of the formulation. The weight was removed, and the top slide was subjected to a pull obtained by attaching 30 g weight over the pulley. The time (sec) required for moving slide to travel a premarked distance (6.5 cm) was noted and expressed as spreadability. The spreadability was calculated by following formula. [15]

$$S=M.L/T$$

Where,

S= spredability,

M= weight tied to upper slide,

L= length of glass slides,

T= time taken to separate the slides completely from each other.

Determination of drug content

One gram of formulation was transferred to a 50 ml volumetric flask and was diluted with 50 ml Phosphate buffer. Five ml of this solution was further diluted to 25 ml and absorbance was measured at 210 nm using Shimadzu-1700 UV visible spectrophotometer. [16]

In vitro Diffusion studies

In vitro drug release studies were carried out by taking 1g of emulgel on the dialysis membrane, which was mounted on the Franz diffusion cell. The receptor medium with pH 7.4 phosphate buffer saline was maintained at constant temperature of 37°C by circulating water bath. The aliquots (1 mL)were collected at time intervals of 1 h up to 12 h. Samples were analyzed for drug content by UV-Vis spectrophotometer after appropriate dilutions. The release data were fitted into various mathematical models using PCP Disso-V2.08 software to know which mathematical model best fits the obtained release profile.

Ex Vivo permeation study:

Skin permeation study was carried out with rat dorsal skin using modified Franz diffusion cell by the same method as described above in the in- vitro drug releases study of emulgel. The abdominal skin of full thickness was excised from the rats weighing 105–120 g, free from any visible sign of disease. The emulgel was placed over it and the permeation study was carried out in a similar manner as described for dialysis through membrane. [17]

Stability study

The prepared emulgels were packed in aluminium collapsible tubes (5 g) and stability studies were carried out for 90 days by keeping at at 40° C ± 2°C and 75% ± 5% relative humidity (RH). Samples was withdrawn at 1month time intervals and evaluated for physical appearance, pH, drug content, spreadability, Bioadhesive strength and in vitro studies through dialysis membrane. [18]

RESULT AND DISCUSSION

Preparation of Emulgel

Experimental desing (3^2 full factorial design)

Full factorial design (3^2) was applied to optimize the emulgel formulation. All nine batches of Emulgel were prepared according to the formulation variables as shown in Table 2.RSM was exploited to estimate the influence of %w/w of Carbapol and Emulsified agent as independent variables and their interactions on the investigated responses (dependent variables; % viscosity and % Spreadability). This experiment was aimed to identify considerable factor effect influencing the formulation performance and to set up to their excellent levels for the desirability of responses shown in Table 3.

To evaluate the quantitative effects of factors (A and B) and their levels low (-1), middle (0), and high (+1) on the preferred responses, the experimental values of the flux were analyzed by Design Expert®DX210.0.7.0 license version software and mathematical models obtained for each response The mathematical relationship generated using multiple linear regression analysis (MLRA) for the studied response variables (% viscosity and % Spreadability) that were relating different response and independent variables are expressed as following polynomial equations (quadratic model).

$Y_1(cp) = 12839.22 + 3075.8A + 229.17B + 1597.75AB54.83A^2 + 2290.17B^2.$ (1)

Y_2 (SP) = 119.89 -7.17A – 12.17B – 4.45AB +2.17A^2 – 34.84B^2. (2)

The above equations expose the quantifiable effect of the independent variables,% w/w carbapol and Emulsified agent, on the responses such as % viscosity (Y_1) and in % spread ability (Y_2) as dependent variables. The correlation coefficient (r^2) of the quadratic model (0.9785) for response % viscosity (Y_1) and in % spread ability (Y_2) was found to be significant.

Table 3: Composition 3^2 full factorial design with measured responses of emulgel.

Batches	Variable level in coded form		Variable level in actual form		Response Variables	
	A	B	Carbapol %w/w (X_1, W)	Emulsified agent %w/w (X_2, W)	% Viscosity (cp)	% Spread ability (sec)
F1	-1	-1	0.5	2	12680	100
F2	0	-1	1	2	14001	55
F3	+1	-1	1.5	2	16110	141
F4	-1	0	0.5	4	8648	156
F5	0	0	1	4	14108	160
F6	+1	0	1.5	4	13852	48
F7	-1	+1	0.5	6	9678	62
F8	0	+1	1	6	14989	75
F9	+1	+1	1.5	6	19499	86

Regression analysis of above equation (1) of response Y_1 (%Viscosity) revealed that the coefficient of A was positive, and B was positive, this indicated that as Carbapol (A) increased the % viscosity increased and on increasing emulsifying agent (B) the % spread ability increases. The higher concentration of emulsified agent indications in decreases the viscosity which in turn decreased the % viscosity. The % viscosity of different emulgel batches was in a range of 8648 to 19499%. The minimum viscosity was observed in batch F4 with the composition of Carbapol: Emulsified agent (-1, 0).For estimation of the significance of the model, the analysis of variance (ANOVA) was executed, from the ANOVA data; the model F-value of response (B) (10.60) indicated that the model is significant. There is only a 4.01% chance that an F-value this large could occur due to noise. Values of "prob>F" less than 0.0500 indicate model terms are significant. In this case AB is significant model terms. Values greater than 0.1000 indicate that model terms are not significant.

The relationship between the dependent and independent variables was further elucidated using contour and response surface plots as shown in Figure 1. The contour and 3D response surface plots of % viscosity clearly indicated that A and B highly influenced the response 1(% viscosity). The change in % viscosity as a function of A and B was depicted in the form of contour and response surface plots based on full factorial design.

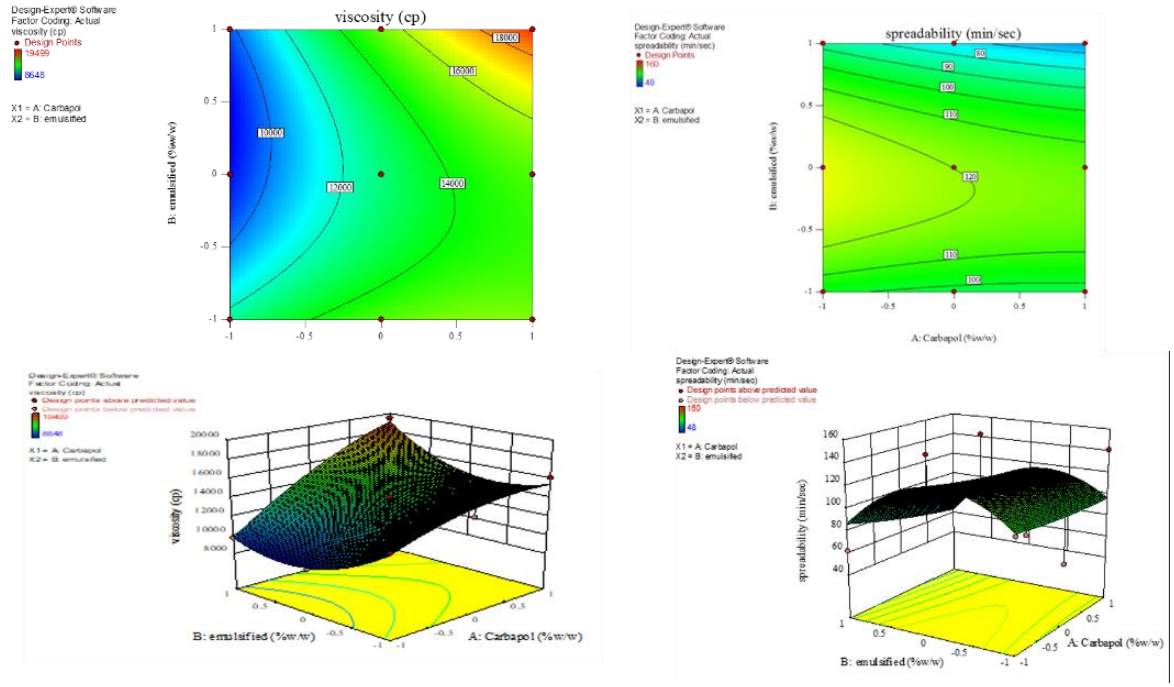

Figure 1: Contour plot and Response surface plot showing the effect of carbapol (X1) and emulsified agent (X_2) on % Viscosity and % spreadability (Y_2) of emulgel.

Percent Spread ability

Regression analysis of above equation (2) of response Y_2 (%Spreadability) revealed that the coefficient of A was negative, and B was negative, this indicated that as Carbapol (A) decreases the % spread ability increases and on decreases Emulsified agent (B) the % spreadability decreases. The % spread ability of different emulgel batches was in a range of 48 to 160.The maximum spread ability was observed in batch F4 with the composition of Carbapol: Emulsified agent (-1, 0).

Physical Appearance

The prepared PPE emulgel formulations were off white viscous with a smooth and homogeneous appearance. They were easily spreadable with acceptable bio adhesion.

PH Determination

The pH values of all developed formulae was in range 5.99 ± 0.04 to 6.82 ± 0.05which is considered acceptable as greater than this value may cause irritation upon application to the skin.

Drug Content

The drug content were found to be uniform throughout the formulated emulgel with the range from 95-100% and average value is assuring the process adopted to prepare the emulgel is capable of giving reproducible results. The drug content data showed good uniformity with low standard deviation which is shown in table 4.

The optimization parameter (Table 5) of desirability was determined by regulating the optimum input variables to obtain one or more optimal parameters. The desirability value ranged between 0 and 1, where a value of 1 is perfect, i.e., the ideal parameter value.

In-Vitro drug release

The in vitro release profiles of PPE from its various emulgel formulations are represented in Figure 2. From the data of % drug diffusion it was observed that, the prepared topical PPE emulgel formulation released a maximum of 59.15%±0.512 over a period of 6 hours. Thus, it may be concluded that the emulgel formulation can control the release of drug for a longer period of time, and thus reduces the cost of therapy.

Table 4: pH and drug content of all batches of Emulgel.

Formulation Code	pH of Emulgel	Drug Content
F1	6.32 ±0.09	97.3 ± 0.2
F2	6.23 ±0.07	98.7 ± 0.1
F3	6.01 ±0.09	97.3 ±0.2
F4	6.37 ±0.07	98.9 ±0.2
F5	6.82 ±0.05	98.4 ±0.4
F6	5.99 ±0.04	98.4 ±0.5
F7	6.12 ±0.10	98.3 ±.3
F8	6.45 ±0.03	97.4 ±0.2
F9	6.65 ±0.04	98.9 ±0.4

Standard Deviation mean n=3

Table 5: Characteristics of optimum formula

Object	Carbapol % w/w (X_1, W)	Emulsified agent %w/w (X_2, W)	% viscosity (Y_1, %)	Spreadability (Y_2, %)	Desire Ability	
Predicted	0.964	0.744	17499.9	83.636	0.925	Selected
Actual (F8)	1	6	14989	75		

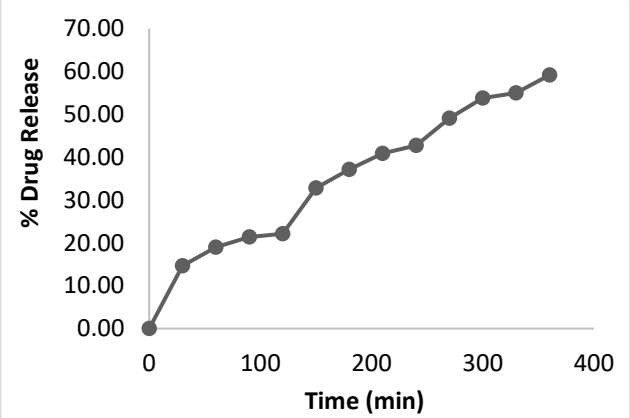

Figure 2: % Release of optimize emulgel

Ex Vivo Skin Permeation Study

The drug release through rat skin was carried out for optimized formulation shown in Figure 3 and showed 67.27 %±0.29 of drug permeated in 6 h. The amount of % drug permeated per square centimeter of the patches through the rat abdominal skin against time was plotted, showed that the permeation profiles of drug follow zero-order kinetics model as it was evident by correlation coefficients (R^2=0.9985), The release exponent value (n) was estimated to be 0.6517, thus indicating a non-Fickian super case II Diffusion release. Thus, emulgel was found to significantly enhance both the rate and the extent of drug permeation through rat Skin. The results of drug permeation from emulgel of through the rat abdominal skin confirmed that drug was released from the formulation and permeated through the rat skin and, hence, could possibly permeate through the human skin.[19]

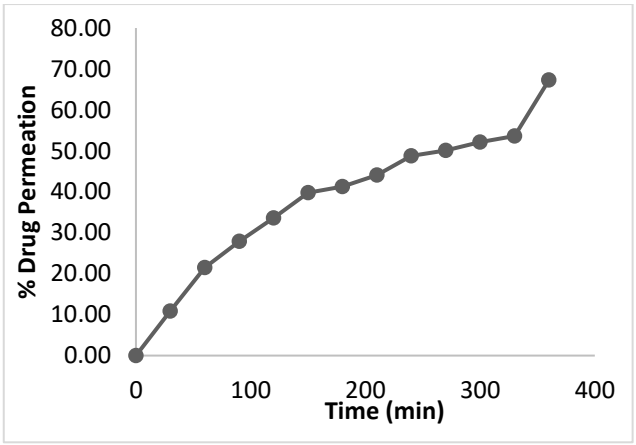

Figure 3: % Drug Permeation for emulgel

Stability Study of (Design Optimized) Emulgel

Optimized PPE Emulgel formulation was subjected to accelerated stability testing as per ICH guidelines. The emulgel were stored at a temperature of 40 ±2°C and 75 ± 5% RH for 90 days (3 months). The results indicated that there was no phase separation and no significant changes in physical appearance, % viscosity, % spredability, and drug content observed when compared with the initial formulation (table 6).

Table 6: Stability Study of (Design Optimize) Emulgel

Evaluation parameter	Time Period (Month)		
	1	2	3
% viscosity (cp)	17481	17501	17512
% spreadability (min)	1.02	1.10	1.12
Drug Content (mg)	91.65%	89.00%	91.45%

CONCLUSION

Emulgels are the one which combine gels and emulsions together. In this study, topical emulgel of pongamia pinnata were formulate and subjected to physicochemical studies i.e. rheological studies, spreadability, in- vitro, in-vivo and ex-vivo releases studies and showed prominent result. In vitro drug release of Pongamia pinnata from emulgel was performed to study the release behavior of drug from formulation. From the observed results it was concluded that there is increase in the drug release with respect to time.

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