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DESIGN, FORMULATION AND OPTIMIZATION OF RUTIN TRIHYDRATE EMULGEL BY RESPONSE SURFACE METHODOLOGY

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Keywords:

Rutin trihydrate emulgel, Design, formulation and optimization, Response surface methodology

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ABSTRACT: Rutin trihydrate a herbal drug having abundant medicinal properties, mainly used for topical treatment of inflammation, presents a hindrance and reduced anti-inflammatory activity. It is BCS class II drug having low oral bioavailability, poor water solubility (0.125 g/L), and low stability of rutin in aqueous alkaline medium, restricting its application in use. So, it is successfully formulated as an emulgel to improve its anti-inflammatory properties. The current study aims to design, formulate, and optimize Rutin trihydrate emulgel to enhance its efficacy and stability. Emulgel was designed, optimized by using a central composite design taking three independent variables and one dependent variable. Five responses were generated, and the optimized formulation was prepared using carbopol 934(0.8%), clove oil (12.5 ml), and span (2.32%). The emulsifying agent being Tween 20, Span 20, and the preservatives used are methyl and propyl parabens. The formulation (F2) with this combination gave emulgel of yellow color, homogeneous with good consistency, possessed pH of 6.51 ± 0.04 , drug content of 98.7%, the viscosity of 14, 980 cps, spreadability 13.5 gm.cm/sec and extrudability 36.2 and *in-vitro* drug release of 74.8% for 8 h. Since, F2 emulgel possesses an edge in terms of spreadability, viscosity, extrusion, *in-vitro* drug release it would become a solution for loading hydrophobic drugs in a water-soluble gel base.

INTRODUCTION: A drug delivery system *via* topical route has been used for local skin diseases because of its advantages of not undergoing first-pass metabolism and acid or enzymatic degradations¹. Emulgels, a biphasic semi-solid formulation² comprise of aqueous and non-aqueous phases, delivering both hydrophilic and lipophilic agents³. Emulgels, are emulsions prepared by mixing with gums⁴.

Lipophilic drugs can be easily formulated as emulgels, and these formulations are more stable compared with simple hydrogel base⁵. Rutin (2-(3,4-dihydroxyphenyl)-4, 5-dihydroxy-3-[3, 4, 5-trihydroxy-6-[(3,4,5-trihydroxy-6-methyl-oxan-2-yl)oxymethyl]oxan-2-yl]oxy-chromen-7-one) a plant pigment.

Also known as quercetin-3-Rutinosoid or sophorins known for its abundant medicinal properties. But the drug belongs to class II drug under BCS classification, with poor water solubility and poor bioavailability. Response surface methodology (central composite design (CCD)) is a tool for quality by design, which involves statistical and mathematical models building an experimental design model on the basis

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of polynomial equation with experimental data thus saving lots of time⁶. Various computer software applications are available for the processing of the experimental data, such as Design-Expert® and Minitab, while reducing the time and increasing the accuracy of experimental data⁷.

In the present investigation, emulgel based drug delivery system using Rutin trihydrate was designed and optimized using a central composite design taking three independent variables and one dependent variable. The formulated emulgel was evaluated for various parameters like drug content, spreadability, extrudability, viscosity, and *in-vitro* diffusion studies using diffusion membrane (dialysis membrane) and Franz diffusion cell apparatus, respectively.

Methodology:

Preparation of Rutin Trihydrate Emulgel:

Thirteen formulations were prepared using varying amount of gelling agent and penetration enhancers. The gel phase was prepared by mixing carbopol 934 in distilled water, pH was maintained to 6.5 using triethanolamine (TEA), and the oil phase was dispersed with span 20 in light liquid paraffin in which clove oil was added, the aqueous phase was prepared by dissolving tween 20 in purified water. Rutin trihydrate was solubilized in methanol, and it

was added to the aqueous phase. The oil and aqueous phases were separately heated to 70–80 °C; then, the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature⁸. The formulations were formulated and optimized using a central composite design. Thirteen confirmatory runs were formulated and evaluated for parameters.

Experimental Design: The formulation was optimized using a central composite design with three independent variables to estimate various parameters, interactions and also to evaluate the quadratic effects of ingredients on Rutin emulgel by constructing model using Design Expert (version 8.0.0, Stat-Ease Inc., Minneapolis, Minneta). The polynomial equation generated by this experimental design is given as:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{23}X_2X_3 + b_{13}X_1X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2$$

b_0 being regression coefficients from the observed experimental values of Y. The terms X_1 , X_2 , and X_1^2 , X_2^2 and X_3^2 indicates the interaction and quadratic terms. 13 runs were generated for the responses alphabetically labeled as F1 to F13, having a concentration of the factors ranging from minimum to maximum as given in **Table 1**.

TABLE 1: FULL FACTORIAL DESIGN LAYOUT

Factor	Name	Units	Type	Minimum	Maximum	Coded low	Coded high	Mean	Std. dev.
A	Carbapol	%	Numeric	0.8000	1.0000	-1 ↔ 0.80	+1 ↔ 1.00	0.9000	0.0816
B	Clove Oil	ml	Numeric	10.00	12.50	-1 ↔ 10.00	+1 ↔ 12.50	11.25	1.02
C	Span	ml	Numeric	2.32	2.40	-1 ↔ 2.32	+1 ↔ 2.40	2.36	0.0327

Evaluation of Emulgel:

Organoleptic Properties: All the formulated emulgels were visually inspected for colour, homogeneity, and phase separation after they have been settled in the container immediately as well as regularly for an interval of 15 days duration⁹.

Measurement of pH: The prepared emulgels were evaluated for pH in triplicate by taking 1 g of each emulgel in 10 mL beaker and measured the digital pH meter at room temperature.

Determination of Spreading Coefficient: A ground glass slide was fixed on the wooden block coated with an excess of emulgel under study. This slide is sandwiched with another second slide. The second slide is attached to a hook of the balance.

In order to expel the air, a weight of 250 - 500 mg was placed on the top of the two slides for 5 min. The required quantity of weight was placed in the other pan which is attached to the pulley through a hook. The time taken by the top slide to cover a distance of 5 cm was noted. A shorter interval indicates a better spreading coefficient¹⁰.

Extrudability: The method is based on the quantity of gel that extrudes from the lacquered aluminium tube when weight is applied. The formulation in which maximum quantity extrudes out is said to have better extrudability. More the quantity extruded better was extrudability. The measurement of extrudability of each formulation was in triplicate, and the average values were

presented. The extrudability can be calculated by formula:

$$\text{Extrudability} = [I_w - F_w] \times 100$$

Whereas, I_w initial weight of product present in collapsible tube and F_w is the final weight of the product present in collapsible tube after extrusion

Viscosity: The viscosity of the formulated preparations was determined using brook field viscometer with spindle no 64 (Brookfield Engineering Laboratories).

The formulation whose viscosity was to be determined was added to a beaker covered with a thermostatic jacket. Spindle was allowed to pass into the emulgel, and the reading was noted at 30 rpm¹¹, the apparatus being maintained at 25 °C.

Drug Content: 1 g of prepared emulgel was mixed with methanol and was kept for shaking for 30 min. The solution was filtered and was diluted suitably using a phosphate buffer of 6.8 pH, and the absorbance was measured at 266 nm. From the absorbance reading, percentage drug content was calculated

In-vitro Release Studies: These studies were conducted in modified Franz diffusion (FD) cells. The prepared emulgel was applied on dialysis membrane, which was placed between donor and receptor compartment of the FD cell while maintaining the temperature of the cell at 37 °C.

1 ml samples were withdrawn at suitable time intervals and replaced with equal amounts of fresh dissolution media and were analyzed spectrophotometrically at 266 nm.

RESULTS AND DISCUSSION:

Evaluation Parameters:

Organoleptic Properties: Various formulations of the emulgel were checked visually for their homogeneity, colour, phase separation, and consistency and it was observed that all the formulation F1 to F13 appeared homogenous, pale yellow having a smooth consistency without having any phase separation.

Measurement of pH: The pH readings were taken as an average of three sample readings. The values exhibited by the emulgels are found to be in the

range of 6.21 to 6.96. Hence all the formulations were in the normal pH range of the skin.

Drug Content Estimation: The Quadratic Model developed by the software has an f value of 261.49, indicating the significance of the model. P-values of X_1 , X_2 , X_1^2 , X_2^2 and X_3^2 less than 0.0500 indicate model terms are significant, having an adequate signal with a good precision ratio of 47.524 **Fig. 1.** Experimentally percentage drug content estimation of all the runs was done was found to be in the range of 91 to 100.3%.

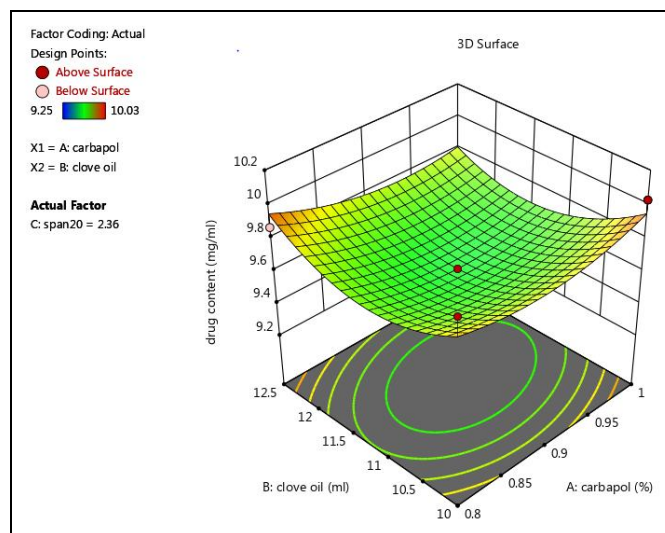


FIG. 1: RSM PLOTS FOR DRUG CONTENT

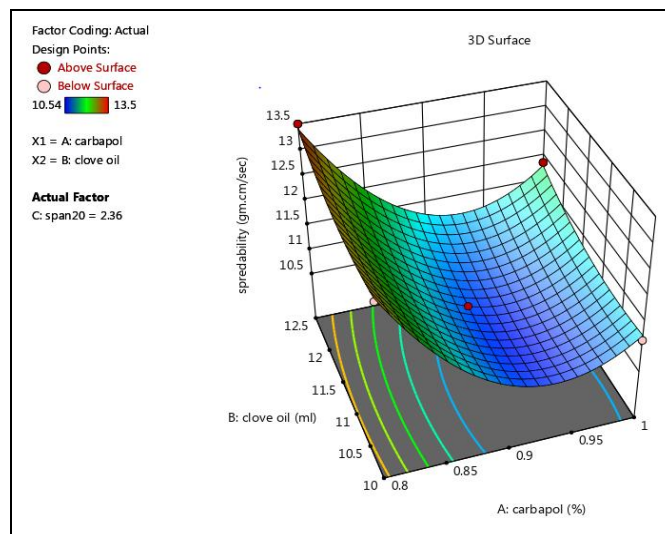


FIG. 2: RSM PLOTS FOR SPREADABILITY COEFFICIENT

Spreadability Studies: Spreadability is one of the essential criteria for an emulgel. Spreadability depends on the viscosity of the formulation. The linear Model generated from the central composite design has F value of 14.21 and P values less than 0.0500 implying the significance of the model.

Even the predicted R^2 of 0.7598 is in reasonable agreement with the adjusted R^2 of 0.7676, *i.e.* the difference is less than 0.2.

The signal is adequate, which is indicated by an adequate precision value of 8.8793. The experimental studies revealed that F11 formulation (F11 run) was having a good spreadability coefficient **Fig. 2**.

Extrudability Test: F value of 5.37 and P values of the developed model is less than 0.05 indicates significance of the model; the predicted R^2 of 0.3175 is not as close to the adjusted R^2 of 0.5221 having a difference of more than 0.2 having an adequate signal with the precision ratio of 6.566. Therefore the reason might be due to outlier values. Experimentally extrudability values ranging from 30.1 to 36.20 with f8 formulation having a maximum value which correlated with the viscosity values **Fig. 4** and **Table 2**.

TABLE 2: TABLE INDICATING EXTRUDABILITY VALUES

Formulation code	extrudability	Formulation code	extrudability
F1	34.36	F8	36.2
F2	35.8	F9	35.96
F3	34.02	F10	35.48
F4	33.26	F11	33.9
F5	32.39	F12	35.97
F6	34.28	F13	36
F7	30.1		

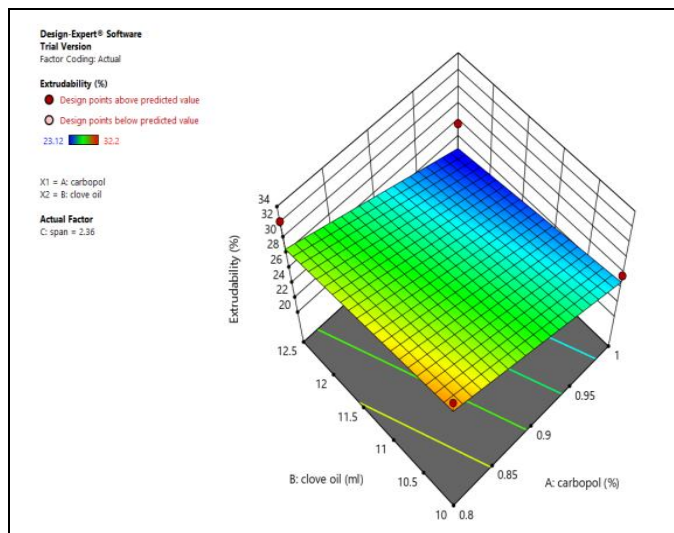


FIG. 4: RSM PLOT FOR EXTRUDABILITY

Determination of Viscosity of the Formulation: Formulated emulgels were evaluated for viscosity using Brooke field viscometer using spindle no 64 at 30 rpm . The f value of 1231.01 and p values less

than 0.0500 implies the model is significant. In this case Carbopol is having significance on the viscosity of the formulation. Higher the concentration of the polymer, the higher the viscosity.

The predicted R^2 of 0.9947 is in reasonable agreement with the adjusted R^2 of 0.9968; *i.e.*, the difference is less than 0.2 **Fig. 5**.

The experimental values correlated with predicted model with F8 and F2 formulation having low viscosity.

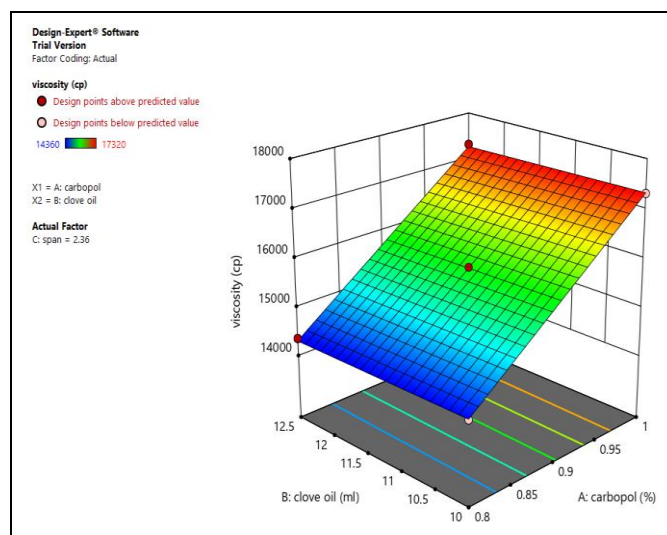


FIG. 5: RSM PLOT FOR VISCOSITY

In-vitro Drug Release Profile: The f value of 4.53 and p values less than 0.0500 indicates model terms are significant. In this case, Clove oil and the emulsifying agent is having a high significance on the drug release even though the adequate precision is 6.57 **Fig. 6** & **7**.

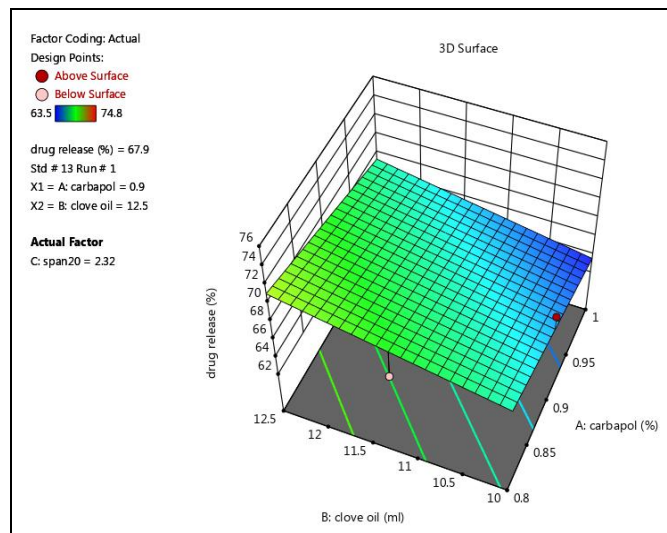


FIG. 6: RSM PLOT FOR % DRUG RELEASE

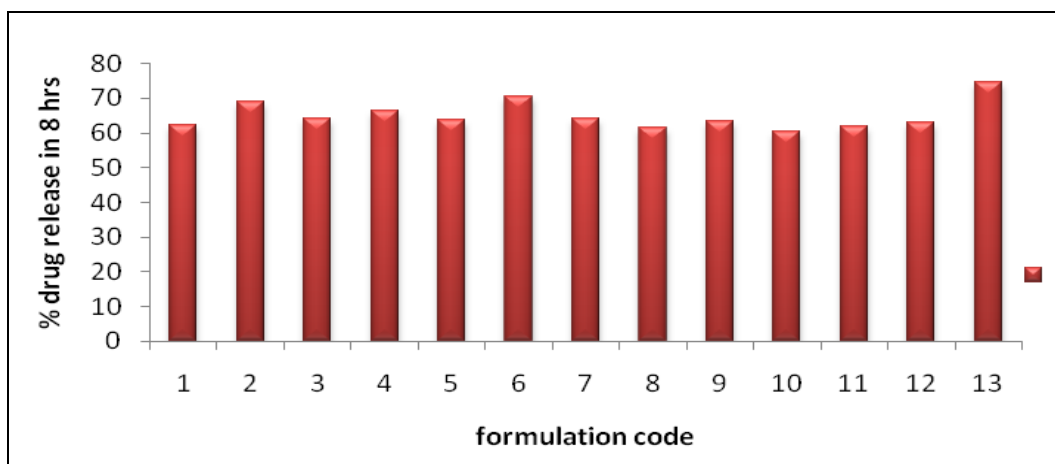


FIG. 7: GRAPH SHOWING % DRUG RELEASE OF RUTIN FROM CARBOPOL CONTAINING EMULGEL FORMULATIONS

Optimization of Factors by Post Analysis: All the factors are taken given equal importance giving desirability 1, and optimization is carried out by post analysis taking using carbopol 934(0.8%), clove oil (12.5 ml), and span (2.32%) **Fig. 8.** The observed values are given in **Table 3.**

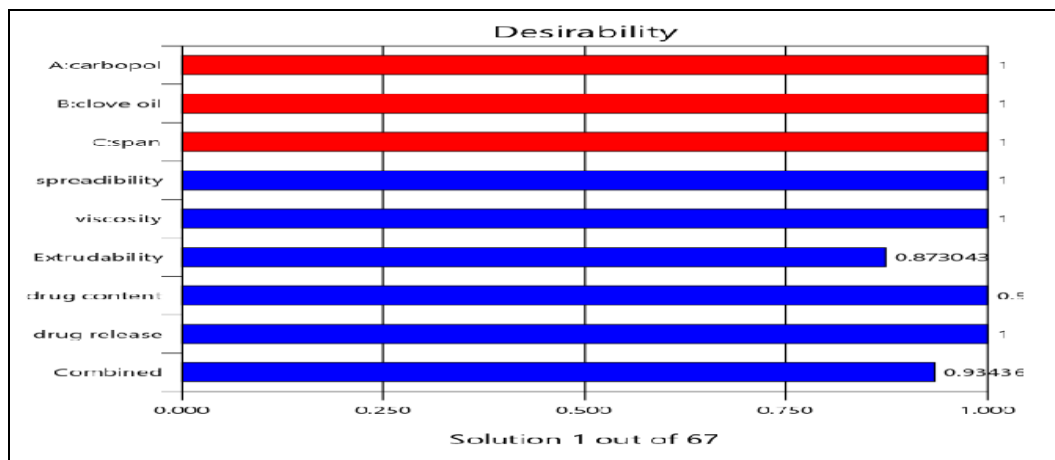


FIG. 8: GRAPH OF DESIRABILITY

TABLE 3: POINT PREDICTION

Solution 1 of 67 Response	Predicted Mean	Observed	Std ev	SE Mean	95% CI low for Mean	95% CI high for Mean	95% TI low for 99% Pop	95% TI high for 99% Pop
Spreadability	10.4409	13.02	0.413675	0.237603	9.90341	10.9784	8.2523	12.6295
viscosity	14377	14360	68.9147	39.5826	14287.4	14466.5	14012.4	14741.6
Extrudability	31.0472	36.2	2.29108	1.31593	28.0704	34.0241	18.9259	43.1685
drug content	9.28	9.72	0.158955	0.137659	8.84191	9.71809	7.76047	10.7995
drug release	66.85	74.03	3.99729	3.46175	55.8369	77.8706	28.6416	105.066

CONCLUSION: The present study demonstrates that the formulated Rutin trihydrate emulgel using 3 factors and 5 responses with the help of a central composite design. The quantitative responses: viscosity, spreadability and extrudability of gels, drug content and *in-vitro* release for different combinations of independent variables were obtained experimentally and the results were observed to fit in the designed model. The experimental responses of the optimized formulation were found to be close to the predicted

responses having a correlation coefficient value 1, which indicates that the Central composite design is a very useful tool in pharmaceutical pre-formulation studies.

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