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Original Article

# Development and Optimization of Febuxostat Emulgel for the Treatment of Gout

**Mahek Shah, Lajja Patel, Shailvi Shah, Khushali Parekh, Mohit Shah, Dhaivat Parikh, Tejal Mehta***

Department of Pharmaceutics, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, INDIA.

**ABSTRACT**

**Background:** Gout is a chronic disease caused by the accumulation of uric acid crystals in joints, resulting in sudden pain, stiffness, and swelling. Febuxostat (FBX), a xanthine oxidase inhibitor, is commonly used to treat gout but has poor solubility, which affects its bioavailability. **Materials and Methods:** To address this issue, a skin-permeating emulgel was developed using Cinnamon (CN) oil as an oil solvent, cremophor RH 40 (Cr. RH 40) as a co-surfactant/solubilizer, and Poloxamer 407 as an emulsifier. A solubility study was performed followed by optimization by $3^2$ factorial designs. The formulation was further evaluated for viscosity, globule size, drug release, and stability studies. **Results:** Solubility of FBX was found 1 in 10 parts in selected oil. The optimized emulgel containing 10% Cremophor RH 40 and 20% Poloxamer 407 shown improved drug release compared to the pure drug. All other parameters were found satisfactory. **Conclusion:** The formulated emulgel designed to penetrate the skin shown a good potential for topical formulations enhancing the effectiveness of drug. Moreover, creating a skin-permeating emulsion-based gel in a cost-effective and industrially viable manner could enhance drug penetration and absorption through the skin thereby faster cure of gout compared to the conventional product.

**Keywords:** Gout, Febuxostat, Emulgel, Gel, Skin penetration.

**Correspondence:**
**Dr. Tejal A. Mehta**
Professor and Head-Pharmaceutics, Department of Pharmaceutics, Institute of Pharmacy, Nirma University, S.G. Highway, Ahmedabad-382481, Gujarat, INDIA.
Email: tjshah3@gmail.com; tejal.shah@nirmauni.ac.in

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## INTRODUCTION

Febuxostat (FBX) is a xanthine oxidoreductase inhibitor recommended for the treatment of gout that lowers serum urate concentrations. Its approval by the FDA in 2009 was a significant advancement in the management of hyperuricemia.[1,2] FBX is administered orally once daily and is rapidly and well absorbed, with 99.2% plasma protein binding. Metabolism of the drug occurs via oxidation through the Cytochrome P450 (CYP) system and conjugation through the uridine diphosphate glucuronosyltransferase enzyme system. It is eliminated by the renal and hepatic systems. However, FBX is a BCS class II drug,[3] which is poorly soluble in water and has low solubility and wettability, leading to poor bioavailability.[4] To overcome this restriction, an emulsion-based topically applied formulation is developed, which incorporate hydrophobic therapeutic moieties and improve patient compliance. The half-life of FBX is 5 to 8 hr, and the topical route of administration avoids the first-pass metabolism, enhancing its bioavailability.[5] Topical medications like creams, lotions, and ointments have several drawbacks, including stickiness, instability, and low spreading coefficient, making the use of transparent gels popular in cosmetic and pharmaceutical preparations. Emulgels, which are a combination of gels and emulsions, have significant potential as drug delivery vehicles, improving permeation efficacy, reducing side effects, increasing drug absorption, and preventing enzymatic breakdown in the stomach. Therefore, the pharmaceutical industry is currently focusing on emulgel systems for drug delivery.[6,7] The present study focused on development of topical *in situ* gel of FBX in view to efficacious treatment of gout.

## MATERIALS AND METHODS

### Materials

FBX was obtained from Zydus Cadila as a gift sample. Cinnamon Oil, Castor Oil, PVA, Cremophor RH40 were purchased from Himedia. Poloxamer 407 was obtained from BSA as a gift sample. All other chemicals used were of analytical grade.

### Methods

#### *Solubility study*

The drug was dissolved in fatty oils and nonaqueous oils and it was mixed using a vortex mixer. The solubility study was performed in different oils.

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## Preliminary trials

Initially, emulsions were formed using FBX in DMSO or Transcutol or a combination of Transcutol and Cremophor RH 40 in the internal phase and 1% Tween 80 (1:2 ratio) solution in the external phase. Preliminary screening of formulation of emulsion was done using cinnamon oil, Cremophor RH and Span 80 in internal phase and Tween 80 and water as external phase. Trials were taken to check the effect of changes in the volume of the external phase using different ratios (1:1.5, 1:2, 1:2.5) of internal to external phase (1% Tween 80 solution) on drug precipitation and emulsion stability. Table 1 (Batch F1-F14) shows the preliminary screening of formulation parameters and the development of coarse emulsion.

Trials were taken to check the effect of benzyl alcohol and castor oil (in the internal phase) on drug precipitation and emulsion stability. Trials were taken using different concentrations of coconut oil as a carrier oil to reduce the volatility of cinnamon oil. Results for these trials are discussed in results and discussion section. Several batches of emulsions were prepared with different internal and external phase combinations and varying drug concentrations to find a suitable emulsifier that would ensure emulsion stabilization and prevent drug precipitation. The batches were labeled with internal and external phase compositions (% w/w) and drug concentration (% w/w) were recorded in Tables 2 and 3 with different ratios (Batch F15-F20).

The stability of an emulsion and the occurrence of drug precipitation are not significantly affected by altering the proportion of the internal and external phases. However, to achieve overall stability and avoid drug precipitation, it is necessary to use an optimal concentration of castor oil to reduce volatility and include cremophor RH 40 as a co-solubilizer in the internal phase. As a result, subsequent batches were designed using the optimal concentrations of castor oil and cremophor RH 40 in the internal phase, along with an aqueous PVA solution in the external phase which is shown in Table 4.

## Preparation of emulgel

FBX emulgel formulations and the preparation method involve cold mixing of the drug cinnamon oil, cremophor RH 40, and castor oil using a mortar and pestle. The water, Polyvinyl Alcohol (PVA), and poloxamer solution was kept to dissolve overnight in a freezer before adding the internal phase to the external phase in a controlled manner. The resulting mixture was thoroughly triturated and mixed at room temperature to obtain a milky white emulgel. Table 5 shows different batches with varying concentrations.

## Optimization by $3^2$-level factorial design

The experimental design i.e. a $3^2$-level factorial design to has been employed to investigate the impact of two independent variables, i.e. concentration of Cremophor RH40 (% w/w) and the concentration of Poloxamer 407 (% w/w), on two dependent variables, namely % cumulative drug release at 2 hr (Q2) and % cumulative drug release at 6 hr (Q6). The concentrations that were used in the design were 2.5% w/w for the drug, 12% w/w for cinnamon oil, 6% w/w for castor oil, 0.1% w/w for PVA, 5%-15% w/w for Cremophor RH40, and 15%-25% w/w for Poloxamer 407.

**Table 1: Preliminary screening of formulation parameters and development of coarse emulsion.**

| Batch No. | Internal Phase | | | | External Phase | |
|---|---|---|---|---|---|---|
| | FBX (w/w%) | CN Oil | Cr. RH 40 | Span 80 | Tween 80 | Water |
| F1 | 1.18 | 9.41 | - | 4.71 | 14.12 | 70.59 |
| F2 | 1.18 | 9.41 | 2.35 | 2.35 | 14.12 | 70.59 |
| F3 | 1.15 | 6.90 | 6.90 | 2.30 | 13.79 | 68.97 |
| F4 | 1.15 | 4.60 | 9.20 | 2.30 | 13.79 | 68.97 |
| F5 | 1.15 | 2.30 | 11.49 | 2.30 | 13.79 | 68.97 |
| F6 | 1.12 | 6.74 | 6.74 | 4.49 | 13.48 | 67.42 |
| F7 | 1.12 | 4.49 | 8.99 | 4.49 | 13.48 | 67.42 |
| F8 | 1.12 | 6.94 | 6.94 | - | 4.47 | 13.42 |
| F9 | 1.09 | 6.78 | 6.78 | 2.19 | 4.38 | 13.13 |
| F10 | 1.09 | 7.07 | 7.07 | 6.52 | 13.04 | 65.22 |
| F11 | 1.06 | 6.91 | 6.91 | 8.51 | 12.77 | 63.83 |
| F12 | 1.25 | 8.13 | 8.13 | 7.50 | - | 75.00 |
| F13 | 1.22 | 7.93 | 7.93 | 9.76 | - | 73.17 |
| F14 | 1.28 | 8.33 | 8.33 | 5.13 | - | 76.92 |

**Table 2: Ratio of internal phase to external phase (1:3) of emulsion.***

| Batch No. | Internal Phase | | | | External Phase | %Drug (% w/w) |
|---|---|---|---|---|---|---|
| | FBX | CN Oil | Castor Oil | Cr. RH 40 | 5% Cr. RH 40 and 0.1% PVA Solution | |
| F15 | 0.4 | 5 | 5 | 0 | 31.2 | 0.96 |
| F16 | 0.4 | 5 | 4 | 1 | 31.2 | 0.96 |
| F17 | 0.4 | 5 | 1 | 1 | 22.2 | 1.35 |

*All quantities are taken in grams.

**Table 3: Ratio of internal phase to external phase (1:1.5) of emulsion.***

| Batch No. | Internal Phase | | | | External Phase | %Drug (% w/w) |
|---|---|---|---|---|---|---|
| | FBX | CN Oil | Castor Oil | Cr. RH 40 | 5% Cr. RH 40 and 0.1% PVA Solution | |
| F18 | 0.4 | 5 | 5 | 0 | 15.6 | 1.54 |
| F19 | 0.4 | 5 | 4 | 1 | 15.6 | 1.54 |
| F20 | 0.4 | 5 | 1 | 1 | 11.1 | 2.16 |

*All quantities are taken in grams.

**Table 4: Optimized Ratio of internal phase to external phase of emulsion.***

| Batch No. | Internal Phase | | | | External Phase | %Drug (% w/w) |
|---|---|---|---|---|---|---|
| | FBX | CN Oil | Castor Oil | Cr. RH 40 | 0.1% PVA Solution | |
| Ratio of internal phase to external phase (1:3 and 1:1.5). | | | | | | |
| F21 | 0.4 | 5 | 2.5 | 2.5 | 31.2 | 0.96 |
| F22 | 0.4 | 5 | 2.5 | 2.5 | 15.6 | 1.54 |
| Ratio of internal phase to external phase (1:1.5). | | | | | | |
| F23 | 0.4 | 5 | 2.5 | 1 | 13.35 | 1.80 |
| F24 | 0.4 | 5 | 2.5 | 1.5 | 14.1 | 1.70 |
| F25 | 0.4 | 5 | 2.5 | 2 | 14.85 | 1.62 |
| F26 | 0.4 | 5 | 1.5 | 2.5 | 14.1 | 1.70 |
| F27 | 0.4 | 5 | 2 | 2.5 | 14.85 | 1.62 |
| F28 | 0.4 | 5 | 1 | 2.5 | 13.35 | 1.80 |
| Ratio of internal phase to external phase (1:3). | | | | | | |
| F29 | 0.4 | 5 | 2.5 | 1 | 8.9 | 2.25 |
| F30 | 0.4 | 5 | 2.5 | 1.5 | 9.4 | 2.13 |
| F31 | 0.4 | 5 | 2.5 | 2 | 9.9 | 2.02 |
| F32 | 0.4 | 5 | 1.5 | 2.5 | 9.4 | 2.13 |
| F33 | 0.4 | 5 | 2 | 2.5 | 9.9 | 2.02 |

*All quantities are taken in grams.

The concentration of formulation ingredients for optimization was fixed based on the preliminary trials and drug solubility study. Nine FBX emulgel formulations (D1 to D9) were prepared based on the independent and dependent variables listed in Table 7, using Cremophor RH40 and Poloxamer 407. The independent variables were set at three levels (-1, 0, and 1), while the dependent factors were % drug release in 2 hr (Q2) and % drug release in 6 hr (Q6). The levels of the independent variables were 5%, 10%, and 15% for the concentration of Cremophor RH40 and 15%, 20%, and 25% for the concentration of Poloxamer 407. The goal was to optimize the formulation for % drug release at both 2 and 6 hr. The dependent and independent variables are listed in Table 6. The *in vitro* drug release of D1-D9 is listed in Table 7.

**Table 5: Preliminary trials for the formulation of emulgel.***

| Batch No. | Internal Phase | | | | External Phase | | | | %Drug (% w/w) |
|---|---|---|---|---|---|---|---|---|---|
| | FBX | CN Oil | Castor Oil | Cr. RH 40 | A | B | C | D | |
| F33 | 0.4 | 5 | 2 | 2.5 | 9.9 | - | - | - | 2.02 |
| F34 | 0.4 | 5 | 2 | 2.5 | - | 9.9 | - | - | 2.02 |
| F35 | 0.4 | 5 | 2 | 2.5 | - | - | 9.9 | - | 2.02 |
| F36 | 0.4 | 5 | 2 | 2.5 | - | - | - | 9.9 | 2.02 |
| F37 | 0.4 | 5 | 2 | 1.5 | - | - | - | 8.9 | 2.25 |
| F38 | 0.4 | 5 | 2 | 2 | - | - | - | 9.4 | 2.13 |
| F39 | 0.4 | 5 | 1 | 1.5 | - | - | - | 7.9 | 2.53 |
| A-0.1% PVA+5% Poloxamer 407, B-0.1% PVA+10% Poloxamer 407, C-0.1%PVA+20% Poloxamer 407, D-0.1% PVA+ 15% Poloxamer 407. | | | | | | | | | |

*All quantities are taken in grams.

**Table 6: List of dependent and independent variables.**

| Independent Factors | | | | |
|---|---|---|---|---|
| Sl. No. | Level | -1 | 0 | 1 |
| 1. | Concentration of Cremophor RH40 (% w/w) | 5 | 10 | 15 |
| 2. | Concentration of Poloxamer 407 (% w/w) | 15 | 20 | 25 |
| **Dependent Factors** | | | | |
| 1 | Q2 | 20%-30% drug release in 2 hr. | | |
| 2 | Q6 | 70%-80% drug release in 6 hr. | | |

**Table 7: *In vitro* drug release of D1-D9 (Mean±sd, *n*=3).**

| Batch No. | Conc. Of Cremophor RH 40 (%w/w) | Conc. of Poloxamer 407 (%w/w) | Q2 | Q6 |
|---|---|---|---|---|
| D1 | 5 | 15 | 19.24±1.23 | 65.88±2.83 |
| D2 | 10 | 15 | 22.65±1.35 | 70.89±1.87 |
| D3 | 15 | 15 | 15.87±1.56 | 57.96±1.50 |
| D4 | 5 | 20 | 21.59±1.21 | 71.36±1.54 |
| D5 | 10 | 20 | 26.98±0.42 | 64.09±1.88 |
| D6 | 15 | 20 | 18.37±1.11 | 53.17±1.85 |
| D7 | 5 | 25 | 17.26±1.09 | 58.13±2.11 |
| D8 | 10 | 25 | 10.65±1.23 | 48.55±2.07 |
| D9 | 15 | 25 | 26.2±0.42 | 78.21±0.71 |

## Characterization of emulgel

### *Drug content*

FBX content in the emulsion is determined using High-Performance Liquid Chromatography (Agilent 1260 Infinity II Diode Array Detector) of ODS column using mobile phase 2.8 gm of sodium acetate buffer pH 3 in 500 mL milliQ water and methanol in the ratio of 30:60. Injection volume was 10µL. The drug content was determined at wavelength 254 nm. Experiments were carried out in triplicates.[6,8]

## Average globule size

Dynamic Light Scattering Particle Size Analyzer was used to measure globule size distribution. Operating range was 0.02 nm to 2.8 µm. Readings were collected after the emulsion was diluted from 1 mL to 250 mL with distilled water.[9]

### Viscosity

The viscosity of the prepared batches was measured by Anton Parr, MCR 102c rheometer. The liquid was added to the beaker and allowed to settle for 30 min at the room temperature (25±1°C) before the measurement. The parallel plate shear rate was 0.1 to 100 1/s and temperature 25°C and 35°C. The viscosity value was recorded. The viscosity of Emulgel was taken in triplicates.[10]

### *In vitro* drug release study

*In vitro* drug release study was performed using a modified Franz diffusion cell apparatus. The dialysis membrane with 2.4 nm pore size, and molecular cut of 12KD-14KD were used. 1 gm of emulgel was packed in a dialysis membrane which is equivalent to 25 mg of the drug. 1 mL of buffer was withdrawn at predetermined time points and an equivalent amount was replaced with fresh buffer to maintain sink conditions. The study was done in PBS pH 7.4 at 32±0.5°C temperature and 25 mL buffer volume.

### Stability study

Real-time and accelerated stability studies were performed at 5°C ± 3°C and 30°C ± 2°C/65% RH ± 5% RH for 6 months. After 6 months, batches were assessed for drug content, viscosity, and drug release.

**Table 8: Multiple regression analysis for Y1 and Y2 (Full model) (batch D1-D9).**

| | Q2 | Q6 |
|---|---|---|
| | p-value | p-value |
| X1 | 0.0005 | 0.0004 |
| X2 | <0.0001 | <0.0001 |

## RESULTS AND DISCUSSION

### Solubility study

FBX shows solubility in oils like Dimethyl sulfoxide (DMSO), Cinnamon Oil, Transcutol, Cremophor RH 40, Isopropyl alcohol, Abratil M 1944 CS, Corn Oil, Capryol 90, Lemon Oil, Cremophor EL. The results showed that the 10 mg of the drug was able to dissolve in 0.1 mL DMSO, 0.1 mL Transcutol, 0.1 mL Cinnamon Oil, and 0.2 mL Cremophor RH 40, while it showed little or no solubility in other oils. These findings suggest that the solubility of the drug can be enhanced by using specific oils as solvents. While Triacetin, Olive Oil, Camphor Oil, IPM, labrafac lipophile WL, 1349 Medium chain Triglyceride, Kollisolv P 124 (Poloxamer 124), IMWITOR 780K (Make: Cremer Oleo Division), Plurol Oleique CC 947 (Polyglyceryl-3 Dioleate), Lauroglycol 90 (Propylene Glycol Monolaurate), Maisine 35-1 (Glycerol Monolinoleate), caprylic acid, ethyl oleate, Castor Oil, Rose Oil, Dill Oil, Coconut Oil, Peppermint Oil FBX show very little or no solubility.

### Preliminary trials and preparation of emulgel

Drug precipitation was observed due to the miscibility of Transcutol and DMSO with the internal phase. Solubility trials revealed that the drug showed good solubility in Cinnamon oil and Cremophor RH 40. Cinnamon oil was incorporated into the oil phase for further optimization of the formulation due to its non-miscibility with the aqueous phase. However, the resultant emulsions were unstable and cracked immediately. Further trials were taken using different combinations of FBX, Cinnamon oil, Cremophor RH 40, and Span 80 in the internal phase and aqueous Tween 80 solution in the external phase. However, the resultant emulsion was initially yellowish opaque and became translucent after some time. Drug crystals were seen after 24 hr,

**Table 9: Analysis of variance table for Q2 Factor.**

| Analysis of variance table [Partial sum of squares-Type III] | | | | | | |
|---|---|---|---|---|---|---|
| Source | Sum of Squares | $D_f$ | Mean Square | F value | *p*-value Prob>F | |
| Model | 392.44 | 5 | 78.48 | 233.03 | <0.0001 | Significant |
| X1-Concentration of Cremophor RH 40 | 12.84 | 1 | 12.84 | 38.14 | 0.0005 | |
| X2-Concentration of Poloxamer 407 | 48.22 | 1 | 48.22 | 143.17 | <0.0001 | |
| X1X2 | 0.34 | 1 | 0.34 | 1.03 | 0.3432 | |
| X1^2 | 102.03 | 1 | 102.03 | 302.95 | <0.0001 | |
| X2^2 | 102.88 | 1 | 102.88 | 305.44 | <0.0001 | |
| Residual | 2.35 | 7 | 0.33 | | | |
| Lack of Fit | 1.66 | 3 | 0.55 | 3.20 | 0.1451 | Not significant |
| Pure Error | 0.69 | 4 | 0.17 | | | |
| Cor Total | 394.80 | 12 | | | | |

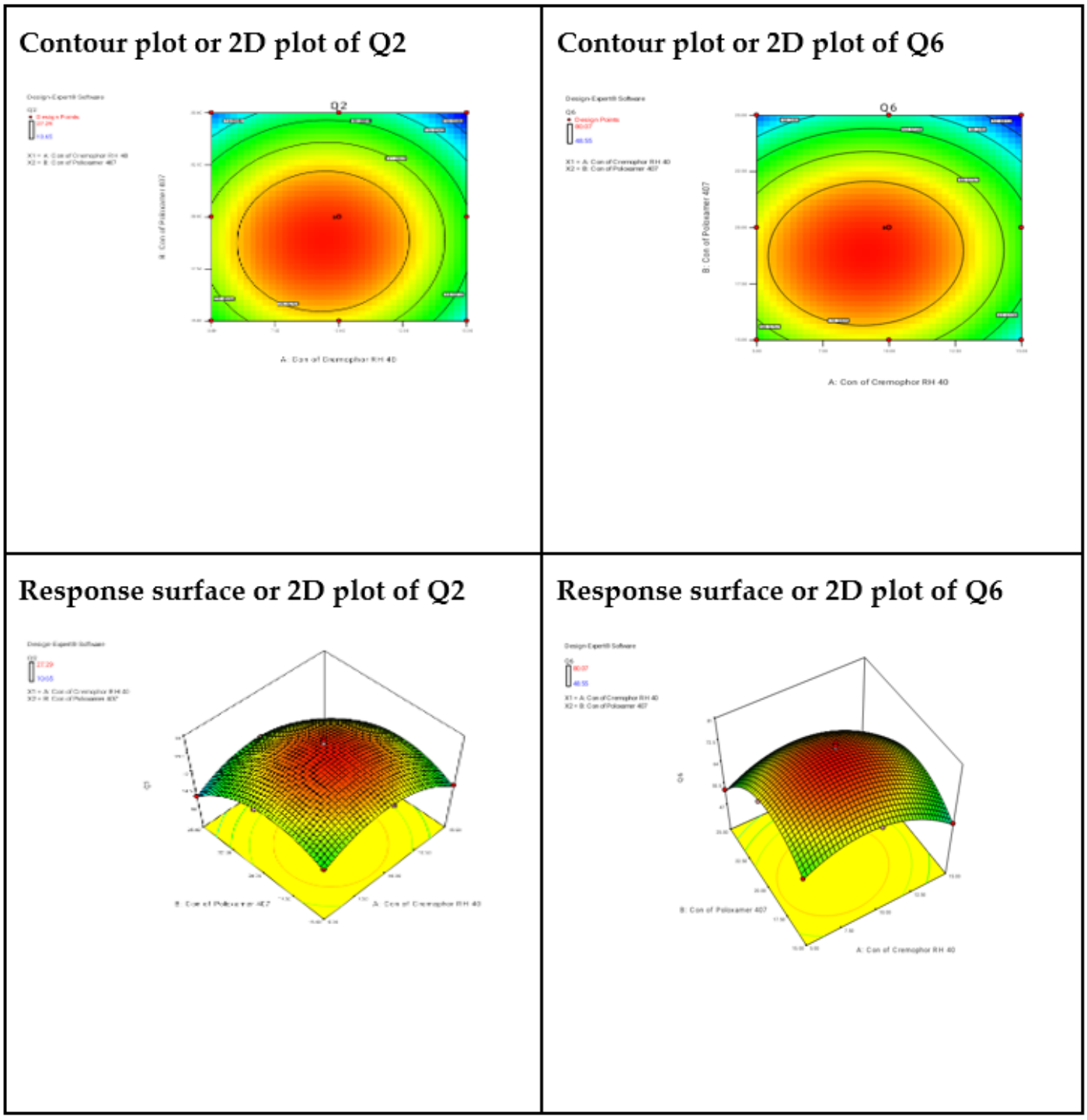


**Figure 1:** Contour plot and response surface plot of Q2 and Q6 factor.

indicating that the emulsion was unstable. Higher concentrations of Span 80 in combination with Tween 80 were also ineffective in addressing the issue of drug crystallization. Labrasol in place of Cremophor RH 40 was also ineffective. Trials taken with benzyl alcohol and castor oil (in the internal phase) on drug precipitation and emulsion stability resulted in cracked emulsion immediately. Trials were also taken using different concentrations of coconut oil as a carrier oil to reduce the volatility of cinnamon oil but the resultant emulsion was unstable, and drug crystallization was observed. As a result, subsequent batches were designed using the optimal concentrations of castor oil and cremophor RH 40 in the internal phase, along with an aqueous PVA solution in the external phase which is shown in Table 4. By incorporating castor oil and cremophor RH 40 in the internal phase, and using an aqueous PVA solution in the external phase, the stability of the emulsion is improved and the issue of drug precipitation is resolved. As the concentration of castor oil increases concerning cremophor RH 40, the viscosity of the emulsion also increases.

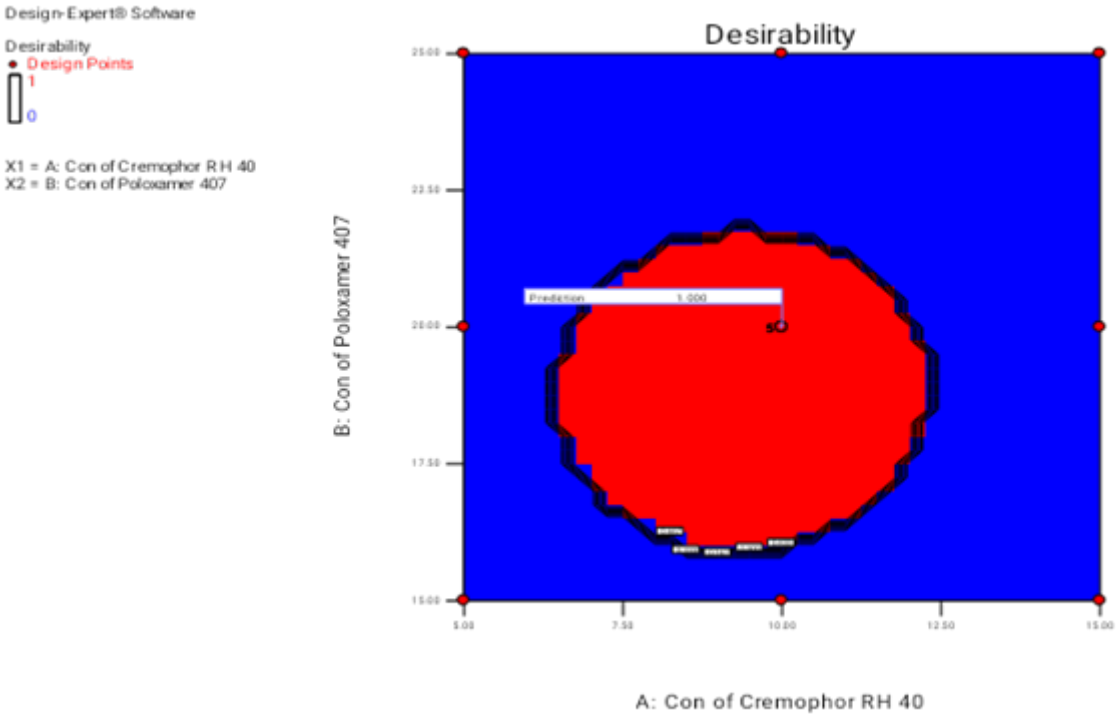


**Figure 2:** Desiribility Plot.

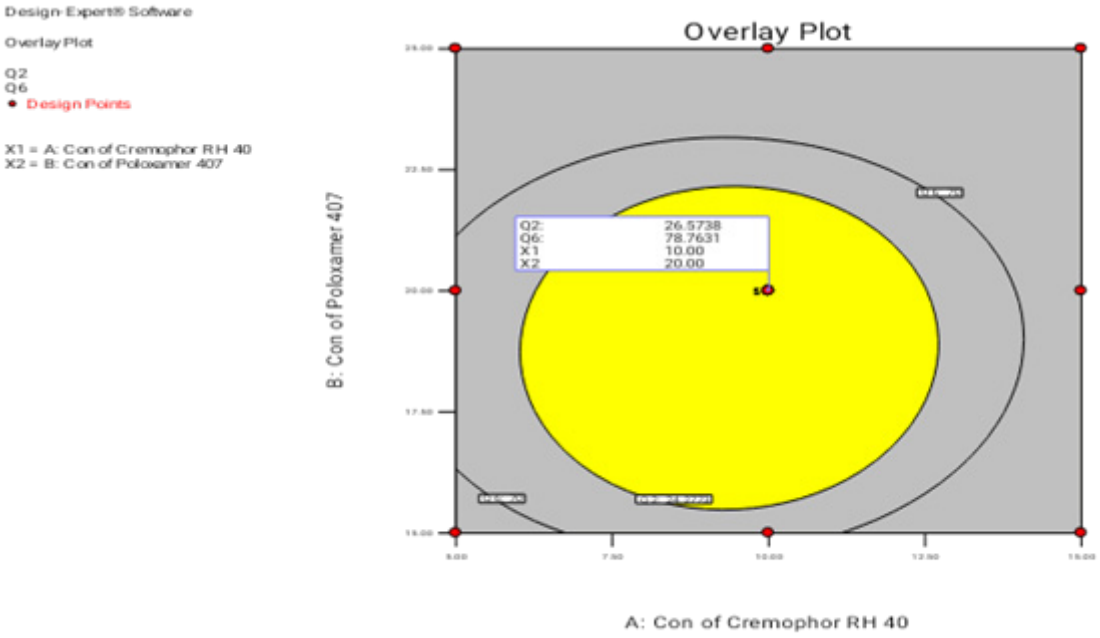


**Figure 3:** Overlay plot.

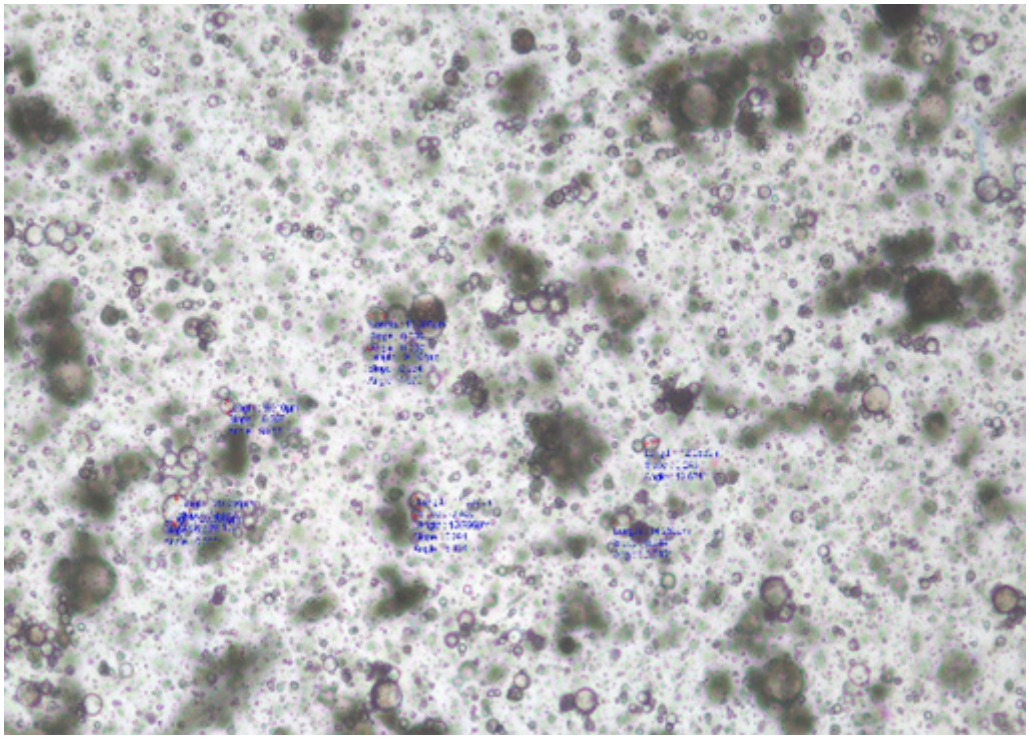

**Figure 4:** Globule size of optimized batch.

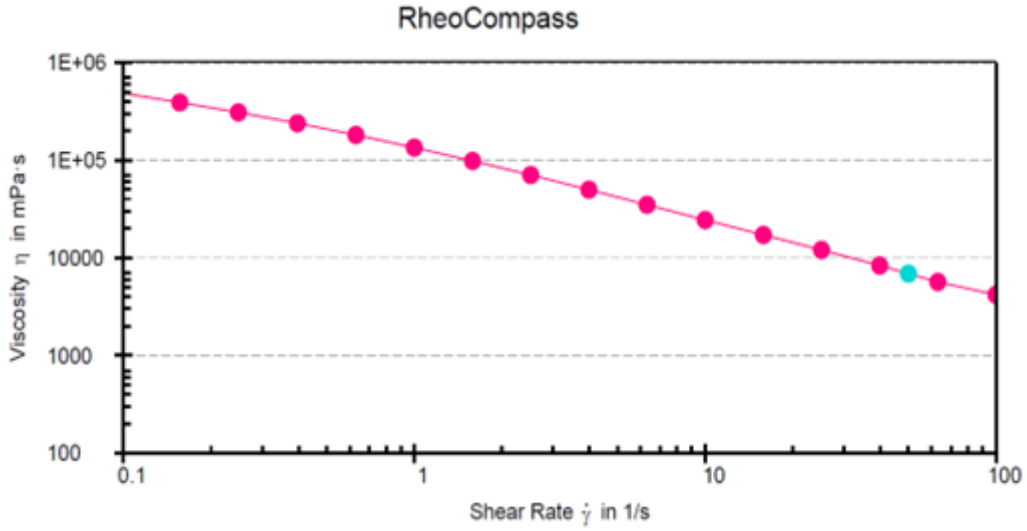


**Figure 5:** Rheocompass of optimized batch D5.

Using the above-mentioned ingredients, the next step involved incorporating gelling agents like Cremophor RH 40 and Poloxamer 407 to form an emulgel formulation.

## Data analysis and optimization

The study analyzed the results of a $3^2$ full factorial design, where multiple regression analysis was used to model the response (Y1 and Y2) obtained from different levels of two independent variables (X1 and X2). Table 8 presents the results of the multiple regression analysis for Y1 and Y2, while Tables 9 and 10 show the analysis of variance tables for Q2 and Q6 factors, respectively. The model *F*-value and Prob>F values indicate that the model terms were significant. The lack of fit *F*-value and Prob>F values suggest that the lack of fit was not significant, which is desirable.

Figure 1 presents the contour plot and response surface plot for Q2 and Q6 factors, which suggest that drug release is improved at optimal concentrations of Cremophor RH 40 and Poloxamer 407. Higher concentrations of these variables have a detrimental effect on drug release and increase viscosity. However, these parameters have a negligible effect on average globule size.

**Table 10: Analysis of variance table for Q6 Factor.**

| Analysis of variance table [Partial sum of squares-Type III] | | | | | | |
|---|---|---|---|---|---|---|
| Source | Sum of Squares | $D_f$ | Mean Square | *F* Value | *p*-value Prob>F | |
| Model | 1456.87 | 5 | 291.37 | 182.18 | <0.0001 | Significant |
| X1-Concentration of Cremophor RH 40 | 65.40 | 1 | 65.40 | 40.89 | 0.0004 | |
| X2-Concentration of Poloxamer 407 | 202.76 | 1 | 202.76 | 126.78 | <0.0001 | |
| X1X2 | 2.72 | 1 | 2.72 | 1.70 | 0.2332 | |
| X1^2 | 269.10 | 1 | 269.10 | 168.26 | <0.0001 | |
| X2^2 | 472.94 | 1 | 472.94 | 295.72 | <0.0001 | |
| Residual | 11.19 | 7 | 1.59 | | | |
| Lack of Fit | 9.19 | 3 | 3.06 | 6.14 | 0.0559 | Not significant |
| Pure Error | 1.99 | 4 | 0.49 | | | |
| Cor Total | 1468.06 | 12 | | | | |

**Table 11: Stability study data for drug content and Viscosity.**

| | 5°C ± 3°C | | 30°C ± 2°C/65% RH ± 5% RH | |
|---|---|---|---|---|
| | Drug content | Viscosity cps | Drug content | Viscosity cps |
| 0 Day | 99.45 ± 0.21 | 6890.2 ±19.23 | 99.59 ± 0.32 | 6890.2 ± 18.42 |
| 6 Months | 99.23 ± 0.26 | 6885 ± 23.96 | 99.53 ± 0.14 | 6813.2 ± 21.63 |

**Table 12: Stability study data for drug release.**

| | 5°C ± 3°C | | 30°C ± 2°C/65% RH ± 5% RH | |
|---|---|---|---|---|
| Time interval | 0 day | 6 Months | 0 day | 6 Months |
| 0 | 0 | 0 | 0 | 0 |
| 1 | 12.61 ± 0.43 | 13.02 ± 0.5 | 12.61 ± 0.43 | 14.26 ± 0.54 |
| 2 | 26.98 ± 0.42 | 25.75 ± 0.57 | 26.98 ± 0.42 | 27.66 ± 0.63 |
| 3 | 39.15 ± 0.53 | 40.25 ± 0.48 | 39.15 ± 0.53 | 40.98 ± 0.46 |
| 4 | 48.36 ± 0.25 | 49.69 ± 0.39 | 48.36 ± 0.25 | 48.97 ± 0.69 |
| 5 | 60.44 ± 0.56 | 62 ± 0.47 | 60.44 ± 0.56 | 61.69 ± 0.64 |
| 6 | 79.65 ± 0.71 | 79.19 ± 0.68 | 79.65 ± 0.71 | 80.01 ± 0.79 |
| 7 | 84.94 ± 1.99 | 85.55 ± 1.54 | 84.94 ± 1.99 | 85.64 ± 0.99 |
| 8 | 91.39 ± 1.02 | 90.36 ± 1.21 | 91.39 ± 1.02 | 90.36 ± 1.21 |

## Selection and Evaluation of Optimized Batch Using Desirability and Overlay Plot

To select the optimized batch, certain criteria were established, a Q2 of 20-30% release and a Q6 of 70-80% release. From a total of 30 suggested solutions, the solution with a desirability of 1% (D5) was chosen as the optimized batch. Figure 2 shows the desirability plot with points ranging from 0 to 1, and the variables X1 (concentration of Cremophor RH 40) and X2 (concentration of Poloxamer 407) were used. Figure 3 shows an overlay plot with the same variables X1 and X2.

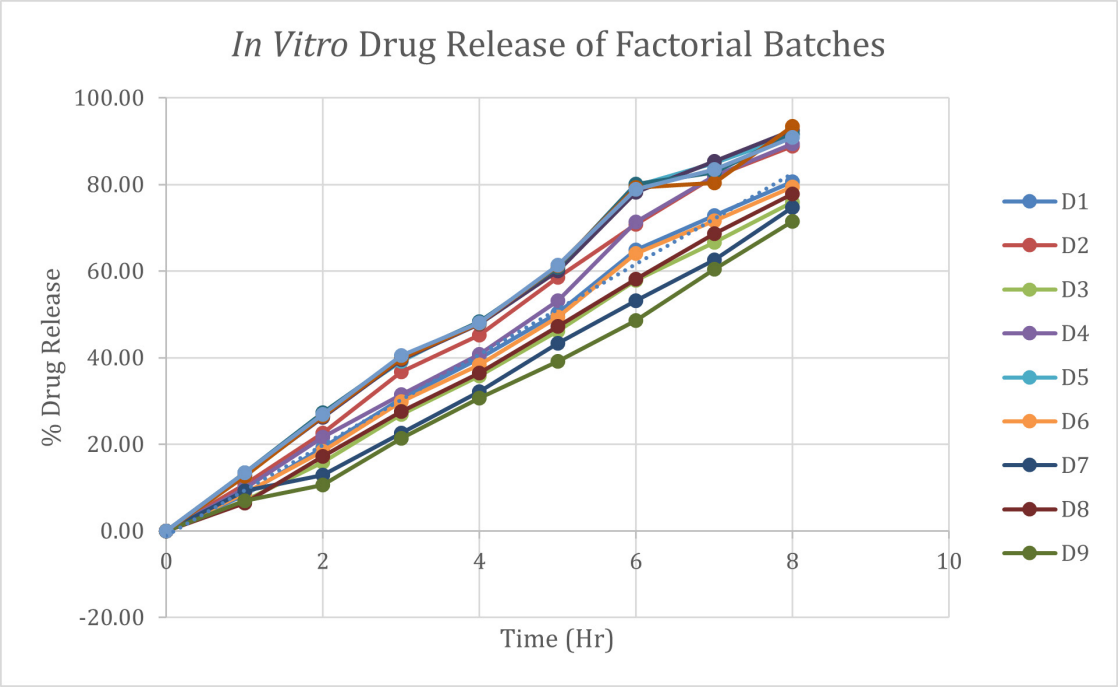


**Figure 6:** Comparative drug release study of batches D1-D9.

## Characterization of emulgel

### *Globule Size*

The results of the Globule size of the optimized batch D5 emulgel is shown in Figure 4. The average globule size of the formulation is 13.95 µ.

### Viscosity

The viscosity of the emulgel was measured at 12 rpm. The viscosity of the optimized batch D5 was found to be 6890.2 cps. Figure 5 shows the viscosity curve of optimized batch D5. The data indicates that the formulation is stable.

### *In vitro* drug release Study

Based on the design criteria of dependent factors Q2 and Q6, the optimum and linear release is obtained in batch number D5 (Figure 6) which is in accordance with the results of the response surface plot and contour plot.

### Stability study

Drug content, viscosity and drug release was checked after 6 months of stability study at 5°C ± 3°C and 30°C ± 2°C/65% RH ± 5% RH which is shown in Tables 11 and 12. The data indicates that the formulation is stable.

## CONCLUSION

The primary objective of the current research study was to formulate a skin-permeating emulgel for FBX, a xanthine oxidase inhibitor utilized in the treatment of gout. The poor solubility of FBX in water necessitated the strategic development of a formulation aimed at enhancing its bioavailability. Emulgels, distinguished by their amalgamation of gel and emulsion properties, have emerged as promising candidates for drug delivery due to their potential to enhance permeation efficacy, mitigate side effects, enhance drug absorption, and prevent enzymatic breakdown in the gastrointestinal tract. In the initial stages of the study, screening experiments were conducted to identify specific oils capable of increasing the solubility of FBX. Cinnamon oil emerged as the most efficacious oil solvent of all. Cremophor RH 40 and Poloxamer 407 were incorporated as co-surfactant/solubilizer and emulsifier, respectively, in the formulation. After preliminary screening, a systematic optimization approach utilizing a $3^2$-factorial design was used to optimize the emulgel formulation. Formulation optimization using a $3^2$-factorial design resulted in an optimized emulgel formulation containing 10% Cremophor RH 40 and 20% Poloxamer 407. The prepared emulgel is also effective in enhancing the solubility and bioavailability of FBX for the management of gout. Notably, this formulation exhibited desirable globule size, enhanced drug release, and maintained stability throughout 6 months of stability studies. The prepared emulgel not only effectively increased the solubility of FBX but also demonstrated enhanced bioavailability, thereby showcasing its potential as an efficacious carrier for topical formulations in the management of gout. Furthermore, the development of a cost-effective and industrially applicable skin-permeating emulsion-based gel presents an opportunity to further improve drug penetration and permeation through the skin. This study underscores the significant potential of

emulgel systems as versatile drug delivery vehicles, providing a robust platform for the topical administration of hydrophobic drugs. The findings herein contribute valuable insights into the optimization and efficacy of emulgel formulations, paving the way for advancements in therapeutic strategies for gout.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**FBX:** Febuxostat; **CN:** Cinnamon oil; **Cr.:** Cremophor; **PVA:** Polyvinyl alcohol; **DMSO:** Diemthyl sulfoxide.

## REFERENCES

1. Kamel B, Graham GG, Stocker SL, Liu Z, Williams KM, Carland JE, *et al*. A pharmacokinetic-pharmacodynamic study of a single dose of febuxostat in healthy subjects. Br J Clin Pharmacol. 2020;86(12):2486-96. 10.1111/bcp.14357.
2. Chewcharat A, Chen Y, Thongprayoon C, Harrison AM, Mao MA, Cheungpasitporn W. Febuxostat as a renoprotective agent for treatment of hyperuricaemia: a meta-analysis of randomised controlled trials. Intern Med J. 2021;51(5):752-62. 10.1111/imj.14814.
3. Sohn JS, Choi JS. Development and evaluation of febuxostat solid dispersion through screening method. Saudi Pharm J. 2023;31(9). 10.1016/j.jsps.2023.101724.
4. Grewal HK, Martinez JR, Espinoza LR. Febuxostat: Drug review and update. Expert Opin Drug Metab Toxicol. 2014;10(5):747-58. 10.1517/17425255.2014.904285.
5. Waller A, Jordan KM. Use of febuxostat in the management of gout in the United Kingdom. Ther Adv Musculoskelet Dis. 2017;9(2):55-64. 10.1177/1759720X16682010.
6. Khunt DM, Mishra AD, Shah DR. Formulation design & development of piroxicam emulgel. Int J PharmTech Res. 2012;4(3):1332-44.
7. Hasan S, Bhandari S, Sharma A, Garg P. Emulgel: A Review. Asian J Pharm Res. 2021;11(4):263-8. 10.52711/2231-5691.2021.00047.
8. Ahmad J, Gautam A, Komath S, Bano M, Garg A, Jain K. Topical Nano-emulgel for Skin Disorders: Formulation Approach and Characterization. Recent Pat Antiinfect Drug Discov. 2018;14(1):36-48. 10.2174/1574891x14666181129115213.
9. Ambhore NP, Dandagi PM, Gadad AP, Mandora P. Formulation and characterization of tapentadol loaded emulgel for topical application. Indian J Pharm Educ Res. 2017;51(4):525-35. 10.5530/ijper.51.4.81.
10. Baibhav J, Gurpreet S, Rana AC, Seema S. Development and characterization of clarithromycin emulgel for topical delivery. Int J Drug Dev Res. 2012;4(3):310-23.

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