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Research

Formulation and invitro characterization of tofacitinib citrate emulsion based gel for topical delivery

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Abstract

The transdermal route of drug administration is an effective approach for managing various indications. This study aimed to develop a Tofacitinib citrate emulgel to achieve systemic effects, minimize side effects, and reduce the frequency of administration. Tofacitinib citrate, a Janus kinase (JAK) inhibitor, is commonly used to treat atopic dermatitis, psoriasis, and rheumatoid arthritis. The emulgel formulation incorporated liquid paraffin, Tween 80, Span 80, propylene glycol, Carbopol 940, and suitable preservatives. The concentrations of liquid paraffin (1 ml) and Carbopol 940 (150 mg) were optimized using response surface methodology with Design Expert 13 software. The prepared emulgel was evaluated for physicochemical properties, including pH, viscosity, spreadability, drug content, and drug release. All formulations demonstrated acceptable characteristics, such as homogeneity, color, consistency, pH stability, and effective drug release. F3 exhibited superior drug release among the formulations, as determined by response surface optimization. The findings also indicated that lower concentrations of liquid paraffin and the gelling agent significantly enhanced drug release from the emulgel.

Keywords: Tofacitinib citrate, Carbopol, liquid paraffin, Response surface optimization.

INTRODUCTION

Topical medication is a straightforward and effective method for treating localized and systemic conditions. The skin's accessibility as both a diagnostic and therapeutic organ presents unique opportunities in dermatological pharmacology. Topical drug delivery systems offer several advantages, including targeted application, reduced gastrointestinal incompatibility, and avoidance of metabolic degradation commonly associated with oral administration. By bypassing first-pass metabolism and providing sustained drug release, topical formulations often enhance bioavailability. However, challenges remain, such as ensuring effective drug

dissolution and diffusion for hydrophobic drugs, as well as permeation through the stratum corneum for hydrophilic drugs. Emulgel formulations address these limitations by utilizing oil-in-water and water-in-oil emulsions as carriers, making them effective for delivering both hydrophilic and hydrophobic drugs. These formulations enhance drug solubility and facilitate skin penetration, improving therapeutic outcomes.

Emulgel represents an emerging and promising field in topical medication delivery, though only a few products have been commercialized to date, making its exploration both exciting and challenging. To understand the advantages of Emulgel, it is essential to first examine the benefits of emulsions and gels in topical drug delivery. Emulsions are controlled-release systems consisting of two immiscible phases: the internal (dispersed) phase and the external (continuous) phase, stabilized by an emulsifying agent. Drug particles encapsulated in the internal phase gradually diffuse through the external phase, allowing for controlled absorption into the skin. On the other hand, gels function by trapping small drug particles in a cross-linked network of colloidal solid particles, which contain a high concentration of aqueous or hydroalcoholic liquid. These liquid forms a three-dimensional polymeric matrix, cross-linked physically or chemically, resulting in a solid, homogeneous, and often transparent structure. The gel matrix ensures regulated drug release. Gels can be broadly classified into two types: hydrophobic (organo gels) and hydrophilic (hydrogels). Hydrophobic gels are based on organic solvents, such as liquid paraffin with polyethylene or fatty oils, thickened using colloidal silica or metallic soaps (e.g., aluminium or zinc soaps). Hydrophilic gels, on the other hand, are water-based and use glycerol or propylene glycol as the liquid medium. Despite their many advantages, gels face limitations in delivering hydrophobic drugs effectively.[1] To overcome this limitation, the concept of emulgel was developed. In an emulgel, hydrophobic drugs are first incorporated into an emulsion and then gelled, combining the controlled-release benefits of both emulsions and gels. This innovative approach enhances the solubility and penetration of hydrophobic drugs, making emulgels a versatile and effective option for topical drug delivery. Janus kinase inhibitor's role in the management of atopic dermatitis [2] Baricitinib and Tofacitinib citrate is a Janus kinase (JAK) 1/2 inhibitor. It has already been approved for the treatment of other inflammatory diseases, such as rheumatoid arthritis.

MATERIALS AND METHODS

Tofacitinib citrate was obtained as a gift sample., span and tween 80 used as emulsifier, propylene glycol used as penetration enchancer was purchased from mohini organics, mumbai, Carbopol 940 used as gelling agent and received from saimirra pharmaceuticals, chennai, methyl and propyl paraben used as preservatives.

Optimization of Tofacitinib citrate Emulgel using central composite design [3-7]

Response Surface Methodology (RSM) is a widely used tool for designing experiments, particularly in the development and optimization of drug delivery systems. Central Composite Design (CCD) facilitates the simultaneous investigation of multiple independent variables with a minimal number of experiments. In this study, CCD-RSM was employed to systematically evaluate the effects of independent and dependent variables and optimize the formulation. The experimental design was constructed using Design-Expert 13 software, applying a 2-factor, 2-level CCD to explore quadratic response surfaces and develop second-order polynomial models. The design matrix included 9 runs, comprising midpoints on the edges and replicated center points of a multidimensional cube. Independent and dependent variables are detailed in Table 1. The polynomial equation generated from this design provided a comprehensive understanding of the main, interaction, and quadratic effects on the formulation.

$$Y = \beta 0 + \beta 1X1 + \beta 2X2 + \beta 12X1X2 + \beta 11X12 + \beta 22X22.$$

Here, YY represents the dependent variable, β0β0 is the intercept, β1β1 to β3β3 are the regression coefficients, and X1X1, X2X2, and X3X3 are the independent variables identified through preliminary experiments. The experimental design is outlined in Table 1

Optimization validation and data analysis

The Tofacitinib citrate emulgel formulation was optimized using a central composite design (CCD) with Design Expert software (version 13). Two factors at two levels were selected as independent variables: liquid paraffin (A: -1 = 1 mL, +1 = 2 mL) and Carbopol 940 concentration (B: -1 = 150 mg, +1 = 250 mg). The dependent variables included drug release (R1), viscosity (R2), and drug content (R3). Statistical validation of the polynomial equation and ANOVA was performed using the software. The experimental response values were compared with predicted values to assess prediction error.

Table 1: Summary of experimental design

Independent variables	**Units**	**Levels**	
		-1	+1
Liquid paraffin (A)	ml	1	2
Carbopol 940 (B)	mg	150	250
Dependent variables	**Units**	**Constraints**	
drug release (r1)	%	Maximize	
Viscosity (r2)	cps	In range	
drug content(r3)	%	Minimize	

Formulation of Tofacitinib citrate loaded emulgel [8-10]

The following steps are involved in the formulation of emulgel.

Step 1: Formulation of Tofacitinib citrate emulsion

The oil phase of the emulsion was prepared by dissolving Span 80 in Liquid paraffin, whilethe aqueous phase was prepared by dissolving tween 80 in purified water. To the oil phase, propylene glycol and drug dissolved in ethanol were added. Both the oily and aqueous phaseswere separately heated to 70° to 80°C then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature.

Step 2: Formulation of gel base.

The gel was prepared by dispersing the gelling agent in water under a magnetic stirrer, and the dispersion was cooled and left overnight.

Step 3: Incorporation of the emulsion into the gel base.

The obtained emulsion was incorporated into the gel in a 1:1 ratio with gentle stirring to obtain the emulgel.

Table 2: Formulation of Tofacitinib citrate loaded emulgel (central composite design)

S.NO	**INGREDIENTS**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1.	Tofacitinib citrate (mg)	100	100	100	100	100	100	100	100	100
2.	Span 80(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
3.	Propylene glycol(ml)	5	5	5	5	5	5	5	5	5
4.	Liquid paraffin(ml)	1.5	2.2071	1	1.5	0.7928	1	1.5	2	2
5.	Ethanol (ml)	2	2	2	2	2	2	2	2	2
6.	Tween 80(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
7.	Carbopol940(mg)	270.71	200	250	200	200	150	129.28	150	250
8.	Triethanolamine (ml)	1	1	1	1	1	1	1	1	1
9.	Methyl paraben	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
10.	Propyl paraben	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
11.	Dis.water (ml)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation parameters

Physical appearance

The prepared emulgel formulations were inspected visually for their color,homogeneity, consistency, and P^H.

pH measurement [11]

The pH values of 1% aqueous solutions of the prepared gellified emulsion were measuredby a p^H meter (Digital p^H meter).

Spreadability[12]

The efficacy of emulgel depends on its spreading. The spreading helps in the applicationof gel to the skin, therefore the prepared emulgel should have good spreadability. The parallel-plate method was used to measure the spreadability, A required amount of gel was placed withina circle of 1cm diameter which is pre-marked on a glass plate, above which another glass platewas placed, to estimate the spreadability. A weight of 500 gm was permitted to rest on the upperglass plate for 5 min. The increase within the diameter spreading was noted.

Rheological Study[13]

The viscosity of the emulgels was determined using a Brookfield Viscometer with spindle 64. The viscosity of the formulations to be determined was added to the beaker and allowed to settle down for 30 minutes at the assay temperature (25° ± 1°C) before the measurement was taken. The spindle was lowered

perpendicularly to the center of the gel; taking care that the spindle did not touch the bottom of the beaker and rotated at a speed of 30 rpmfor 10 min. The viscosity reading was noted down. The average of three readings taken in 10 minutes was noted as gel viscosity.

Drug Content Determination

Weigh a specific quantity of gel containing 10 mg of the drug add a sufficient quantity of of methanol diluted with phosphate buffer pH 7.4 and stir the solution for 2 hours on a magnetic stirrer. The resulting solution was filtered using Whatman filter paper, and after appropriate dilution, the samples were analyzed spectrophotometrically at 287nm against blankusing UV- Visible spectrophotometer.

In-Vitro Release Study [14]

In vitro drug release studies were carried out using Franz diffusion cells. 0.5 g of gel wasapplied to the egg membrane as the donor compartment. Phosphate buffer pH 7.4 was placed in the receptor compartment as the dissolution medium. The whole assembly was placed on a magneticstirrer with a thermostat maintained at 37ºC. Samples were collected at a regular time interval and sink conditions were maintained by replacing them with a new buffer solution. Collected samples areanalyzed at 287 nm using a UV spectrophotometer

RESULTS AND DISCUSSION

Determination of calibration curve of tofacitinib citrate

Solutions of Tofacitinib citrate in methanol were suitably diluted with phosphate buffer pH7.4 to give varying concentrations of 5-25µg/ml. The absorbance was measured at 287nm and the values are given in Table 3 and fig 1.

Table 3: Absorbance of Tofacitinib Citrate

S.NO	Concentration (µg/mL)	Absorbance (nm)
1	5	0.184
2	10	0.345
3	15	0.534
4	20	0.685
5	25	0.841

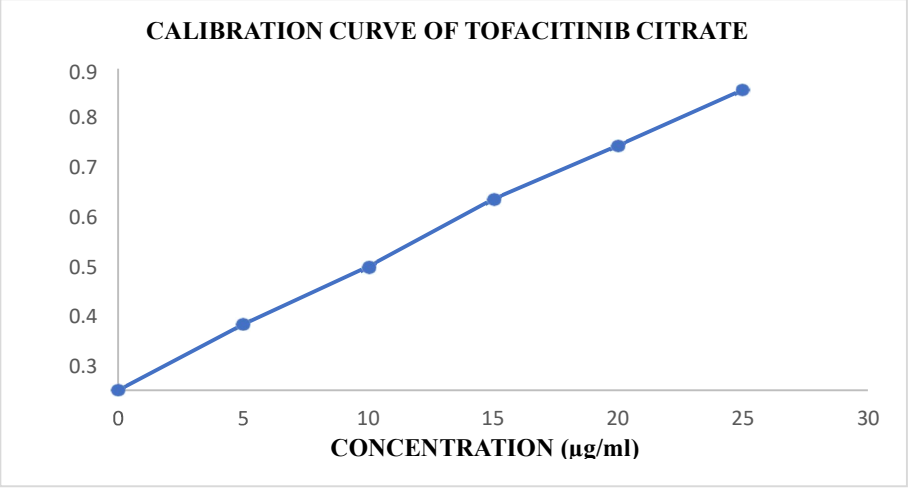

Fig: 1 Calibration curve of Tofacitinib citrate

Central composite design (CCD)

In this study, a CCD was used to optimize the formulation variables of Tofacitinibcitrate loaded emulgel containing 2 factors and evaluated at 2 levels. Amount of Liquid paraffin (A), amount of Carbopol 940 (B) and drug release (R1), viscosity (R2) and drug content (R3) were selected as dependent responses. The independent factors and their rangelevels used in the study are presented in Table 4. The experiments were designed by using Design Expert software (Version13, Stat-Ease Inc.,) and the layout of the design is shown in Table 5. A total of 9 formulations were designed by the software with 2 center points.

Table 4: Variables used in CCD

S.NO	VARIABLES	UNITS	LEVELS	
			LOW	HIGH
1.	LIQUID PARAFFIN	ml	1	2
2.	CARBOPOL 940	mg	150	250

***CCD-**Central composite design*

Table 5: Actual design of central composite design fortofacitinib citrate emulgel

Run	Factor 1	Factor 2	Response 1	Response 2	Response 3
	A: Liquidparaffin	B: Carbopol 940	Drug release	Viscosity	Drug content
1	1.5	270.711	43.25	4259	93.46
2	2.20711	200	58.22	5921	96.48
3	1	250	70.68	4627	97.86
4	1.5	200	50.65	4975	96.45
5	0.792893	200	71.36	5739	98.07
6	1	150	68.23	5435	97.12
7	1.5	129.289	61.78	4982	96.07
8	2	150	62.33	4832	98.32
9	2	250	49.56	5199	93.04

Table 6: Polynomial analysis

Response	Name	Min	Max	Mean	Std. Dev.	Model
R1	Drug release	43.25	71.36	59.56	4.94	Quadratic
R2	Viscosity	4259	5921	5107.67	211.56	Quadratic
R3	Drug content	93.04	98.32	96.32	0.5668	Quadratic

Numerical optimization

Table 7: Constraints

Name	Goal	Lower Limit	Upper Limit	Lower Weight	Upper Weight	Importance
A: Liquidparaffin	is inrange	1	2	1	1	3
ırbapol940	is inrange	150	250	1	1	3
Drug release	Maximize	43.25	71.36	1	1	3
Viscosity	is inrange	4259	5921	1	1	3
Drug content	Maximize	93.04	98.32	1	1	3

Table 8: Confirmation

Solution 1of 11 PredictedMean Response		PredictedMedian	Std Dev	n	SE Pred	95% PI low	95% PI high
Drug release	60.2103	60.2103	4.93984	1	6.21502	40.4313	79.9893
Viscosity	5166.92	5166.92	211.556	1	266.168	4319.86	6013.99
Drug content	97.3903	97.3903	0.566752	1	0.713054	95.1211	99.6596

Final Equation in Terms of Actual Factors

Drug release = 144.20060-77.94319 Liquid paraffin-0.174113 Carbopol 940-0.152200 Liquid paraffin*Carbopol 940+ 32.32750 Liquid paraffin^2+0.000778 Carbopol 940

Viscosity = 8895.84313-6817.40328 Liquid paraffin + 15.15631 Carbopol 940 + 11.75000 Liquid paraffin*Carbopol 940+1508.0000 Liquid paraffin^2-0.091100 Carbopol 940^2

Drug content = 78.47002+3.92785 Liquid paraffin+0.181922 Carbopol 940- 0.060200 Liquid paraffin*Carbopol 940+2.21500 Liquid paraffin^2-0.000280Carbopol 940^2

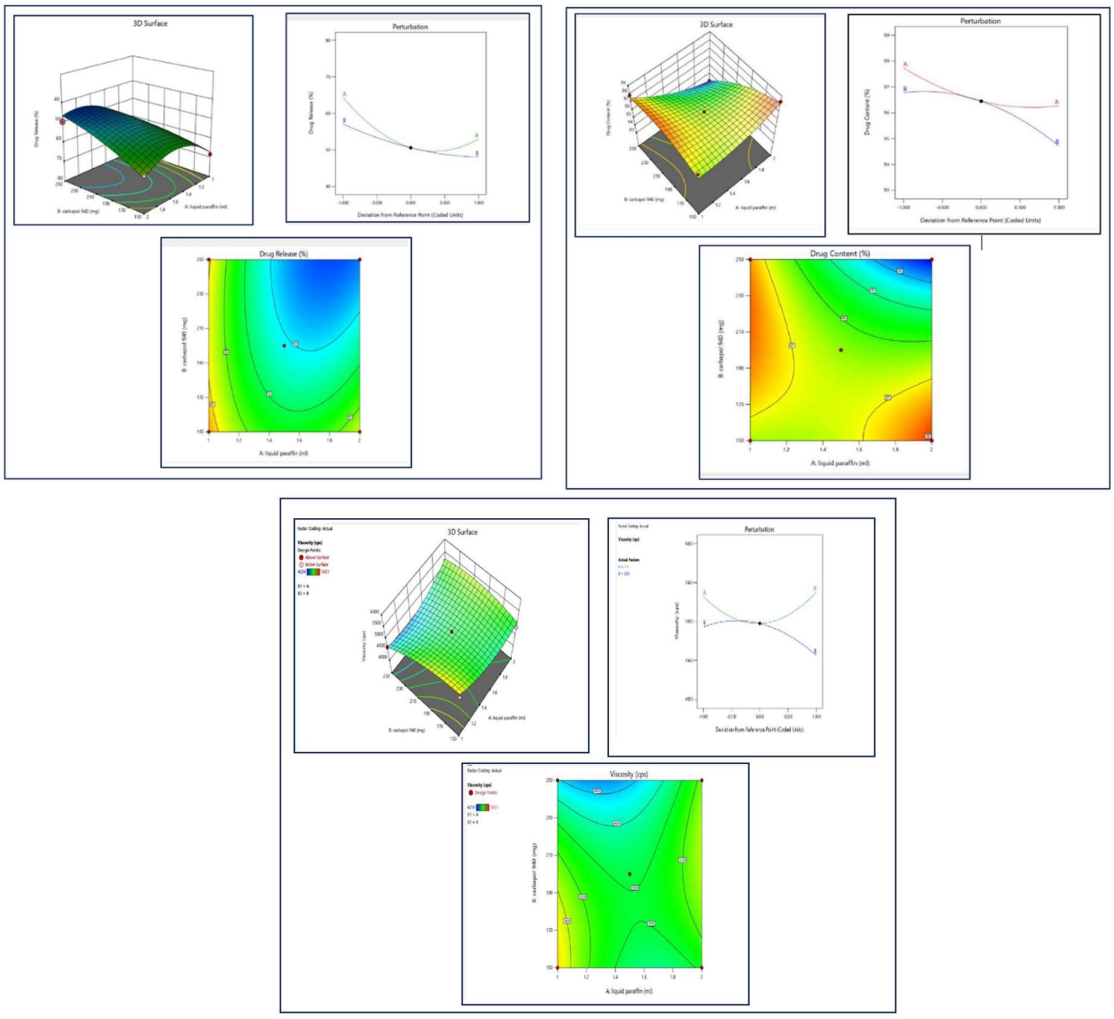

Fig 2: 3D, contour and 3D surface design of Drug release, viscosity, drug content

Characterization of tofacitinib citrate emulgel

Characterization of Tofacitinib citrate emulgel involved evaluating its physical appearance, p^H, and spreadability to ensure stability and user acceptability were presented in Tables 9 and 10.

Table 9: Physical Characters of optimized formulation

S.NO	Physical characters	Tofacitinib emulgel
1.	Colour	White
2.	Homogeneity	Excellent
3.	Consistency	Excellent
4.	Phase separation	None

Table 10: $p^{H,}$ Spreadability of optimized Formulation

Formulation	p^H	Spreadability
Optimized emulgel (F3)	5.5±0.05	5.69±0.30

Invitro drug release study

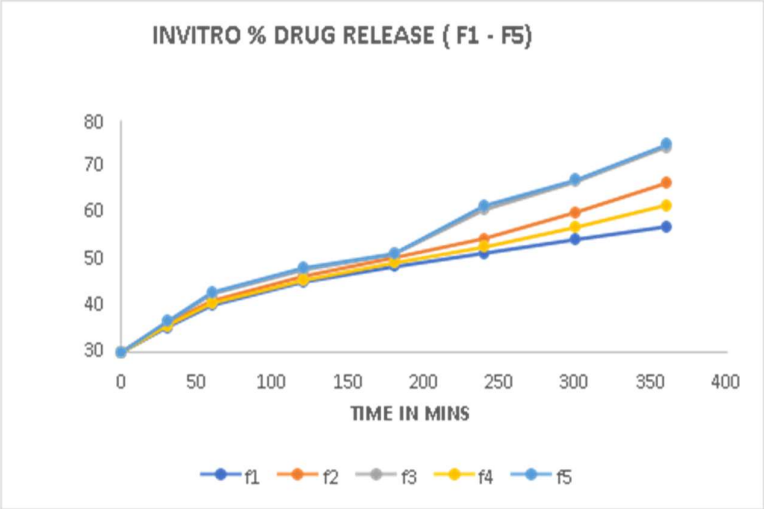

Fig 3: *Invitro* drug release (F1-F5)

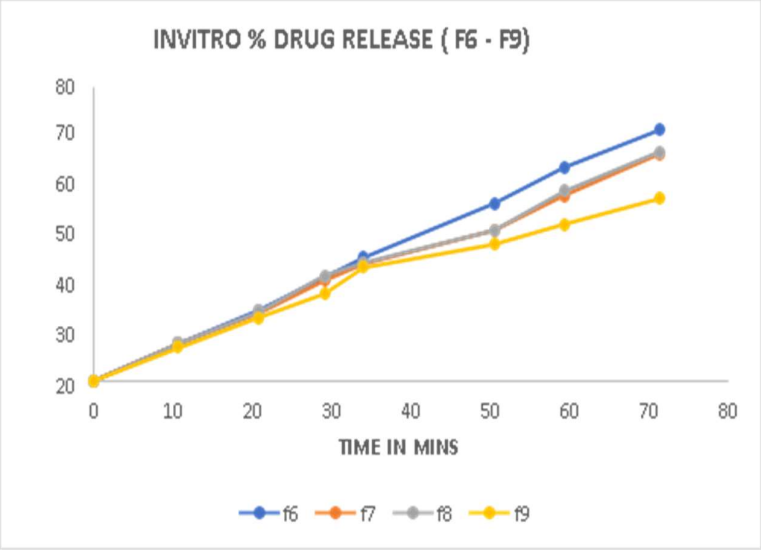

Fig 4: *Invitro* drug release (F6-F9)

Invitro Drug Release of Various Formulations were shown in Fig 3 and 4. Among these nine formulations, F3 formulation showed better drug release due to low concentration of liquid paraffin and Carbopol 940 using design expert 13 software.

Drug release kinetics study

Based on the findings, it was indicated that the Korsmeyer-Peppas model yielded the highest correlation coefficient, (R2 = 0.9958) making it the best fit for the optimized Tofacitinib citrate emulgel. Additionally, the calculated value of "n" was 0.7121 (within the range of 0.45 to 0.89), suggesting that the drug release from the polymeric matrix follows non-anomalous transport. The release mechanism involves a combination of diffusion and other processes, such as matrix swelling, erosion, and relaxation were presented in Table 11.

Table 11: Drug Release Kinetics Study of Optimized Formulation

S. No	Data Fitted in	X-axis	Y-axis	Slope	Intercept	R^2	Linear equation
1	Zero-order release kinetics	Time	Cumulative % drugrelease	0.184	4.1708	0.9857	Y=0.184x+ 4.1708
2	First order kinetics	Time	Log cumulative % drug remaining	0.0014	2.0145	0.9576	Y =- 0.0014x + 2.0145
3	Higuchi release kinetics	Cumulative % drug release	Square roottime	0.258	2.4424	0.9452	Y=0.258x+ 2.4424
4	Korsmeyer Peppas kinetics	Log time	Log cumulative% drugrelease	0.712	0.0109	0.9958	Y=0.712x- 0.0109
5	Hixson Crowell kinetics	Time	Cube root of cumulative % drug remaining	-0.004	4.6265	0.9733	Y=-0.004x+ 4.6265

CONCLUSION

This study focused on developing a safe, effective and affordable topical emulgel formulation to enhance drug permeation. Among the tested formulations, the F3 formulation exhibited superior drug release, as determined through the response surface optimization technique. This method highlighted the significant role of formulation components, particularly the low concentrations of liquid paraffin and the gelling agent, in influencing the drug release profile. The unique combination of an oil phase and a water-soluble gel base within the emulgel enhances the penetration of Tofacitinib citrate through the skin, enabling it to reach targeted tissues more efficiently. Compared to traditional topical preparations such as ointments and creams, the emulgel offers several advantages. Its innovative structure ensures improved drug permeation and bioavailability while maintaining affordability and safety. This study demonstrates the potential of emulgel-based formulations as a promising alternative for topical drug delivery, particularly for medications like Tofacitinib citrate, by combining efficacy with ease of application and enhanced therapeutic performance.

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Conflicts of interest

There are no conflicts of interest regarding the publication of this article to disclose.

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