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QUALITY BY DESIGN APPROACH FOR THE DEVELOPMENT AND OPTIMIZATION OF CETIRIZINE HYDROCHLORIDE EMULGEL: FORMULATION, CHARACTERIZATION, AND IN VITRO EVALUATION

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ABSTRACT

Emulgels combine the formulation attributes of emulsions and gels and are increasingly investigated as topical drug-delivery systems because their rheological and release properties can be tuned through excipient selection. Cetirizine hydrochloride is a second-generation H1-antihistamine that is often used orally. Using Carbopol 940, HPMC K100M, and xanthan gum as gelling agents, the current work created and assessed cetirizine hydrochloride emulgels. A Design of Experiments (DoE) method was then used to optimize the xanthan gum-based system. Preformulation comprised DSC, FTIR, and solubility. The initial emulgels were evaluated for viscosity, drug content, spreadability, extrudability, pH, appearance, and in vitro release. The evaluation of Tween 80, liquid paraffin, and xanthan gum as formulation factors was done using a 2^3 factorial design with a single central point, with responses being cumulative drug release and viscosity. Cetirizine hydrochloride and xanthan gum were found to be compatible by FTIR and DSC analysis. The xanthan gum formulation (F3) had the highest drug concentration (91.3 ± 0.50%) and the largest cumulative release over a 6-hour period (94.48 ± 0.45%) among the initial formulations. Xanthan gum concentration was found to be the primary factor influencing both responses by DoE analysis. pH 6.8 ± 0.1, viscosity 9327 ± 12 mPa•s, spreadability 6.4 ± 0.2 g•cm/s, extrudability 172 ± 3 g/cm², drug content 98.2 ± 0.4%, and cumulative drug release 85.3 ± 0.5% were all observed in the stated optimal formulation (F9). During the reported 60-day accelerated stability assessment, the formulation maintained its physical stability. Overall, the results indicate that Cetirizine hydrochloride emulgel based on xanthan gum is a suitable formulation platform.

KEYWORDS: Cetirizine hydrochloride; emulgel; xanthan gum; topical drug delivery; Design of Experiments; formulation optimization; semisolid dosage form

1. INTRODUCTION

In addition to potentially lowering gastrointestinal exposure and first-pass effects related to oral administration, topical medication delivery can offer direct access to the skin and specific tissues. Because they may be applied directly to the target site and are designed to offer adequate residence, spreadability, and drug release, semisolid dosage forms are very appealing. Emulgels combine the rheological and application benefits of a gel with the solubilization ability of an emulsion by integrating an emulsion phase with a gel matrix [1, 2].

Emulgel performance depends strongly on the oil phase, emulsifier system, gelling polymer, drug–excipient interactions, and composition of the formulation. Recent literature emphasizes that polymer type and concentration can markedly affect viscosity, microstructure, release, and physical stability [3, 4]. Natural gums such as xanthan gum are of interest because they can provide thickening and stabilization while offering an alternative to synthetic polymer systems [5].

A second-generation H1-antihistamine, cetirizine hydrochloride is used to treat urticaria, allergic rhinitis, and associated allergic symptoms. Cetirizine's topical delivery has been investigated experimentally, including vesicular techniques, despite its established oral administration [6, 7]. This suggests that scientists are interested in localized skin delivery. In order to create a physically acceptable semisolid dosage form and find an appropriate gelling agent, the current study examined cetirizine hydrochloride in an emulgel platform [8, 9].

DoE and Quality-by-Design (QbD) offer a methodical way to connect formulation factors to important quality characteristics (CQAs). Instead of depending just on one-factor-at-a-time testing, DoE can be used to identify important

formulation factors and develop a logical optimization strategy for topical semisolids [10, 11]. DoE is still a key instrument in topical semisolid development and control-strategy design, according to recent data [12].
The objective of the present study was to formulate cetirizine hydrochloride emulgel using Carbopol 940, HPMC K100M, and xanthan gum; characterize the formulations by physicochemical, compatibility, drug-release, and stability studies; and optimizes the xanthan gum-based formulation using a factorial DoE approach.

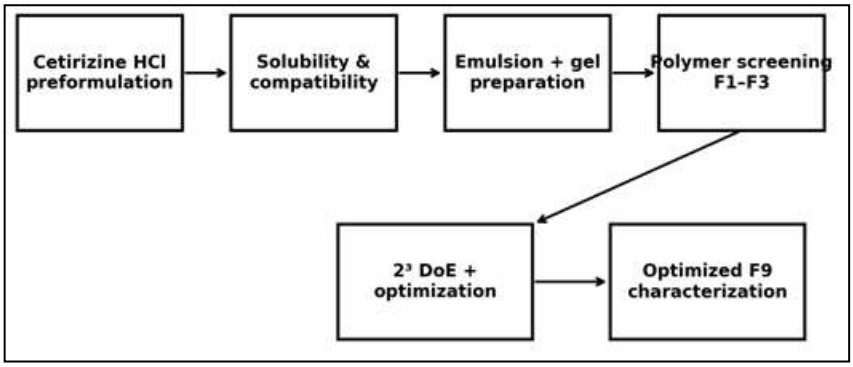

Figure 1. Schematic workflow of Cetirizine hydrochloride emulgel development and optimization

2. MATERIALS AND METHODS

2.1 Materials

A gift sample of cetirizine hydrochloride BP was acquired from Karunesh Remedies in Gujarat, India. We purchased Carbopol 940, HPMC K100M, xanthan gum, Span 80, Tween 80, liquid paraffin, propylene glycol, methyl and propyl paraben, EDTA, and triethanolamine from Modern Industries, Sinnar, and Research-Lab Fine Chem Industries, Mumbai, India. Other solvents and compounds were of analytical quality.

2.2 Preformulation studies

2.2.1 Organoleptic evaluation

Color, odor, and physical appearance of cetirizine hydrochloride were examined before formulation.

2.2.2 FTIR compatibility study

FTIR spectra of pure cetirizine hydrochloride and its physical mixture with xanthan gum were recorded using a JASCO FT/IR-4100 spectrometer (Japan) over 4000–400 cm^{-1} using the KBr pellet technique.

2.2.3 Differential scanning calorimetry

Approximately 5–10 mg of sample was analyzed using a DSC 60 PLUS (Shimadzu, Japan). Samples were heated from 25 to 300 °C at 10 °C/min under nitrogen at 50 mL/min.

2.2.4 Solubility study

Cetirizine hydrochloride excess was equilibrated for 24 hours at 25 ± 0.5 °C with constant shaking in 10 mL of distilled water, phosphate buffer pH 6.8, methanol, ethanol, propylene glycol, PEG 400, or liquid paraffin. Samples were diluted, filtered via a 0.45-µm membrane, and then measured at 231 nm using UV Spectrophotometry [13, 14].

2.3 Formulation of emulgel

The emulsion was prepared, the gel basis was prepared, and the emulsion was incorporated into the gel base as part of the formulation process. Cetirizine hydrochloride was dissolved in the aqueous phase after Tween 80, ethanol, and PEG 400 were combined with methyl paraben and EDTA in water. At 70 °C, the aqueous phase was heated. Span 80 was heated at 70 °C and dissolved in liquid paraffin for the oil phase. To create a homogenous emulsion, the oil phase was progressively added to the aqueous phase while being continuously stirred. The mixture was then cooled while being continuously stirred. To create the corresponding gel bases, carbopol 940, HPMC K100M, or xanthan gum were individually hydrated and dispersed. The emulsion was then added while being constantly stirred [15-17].

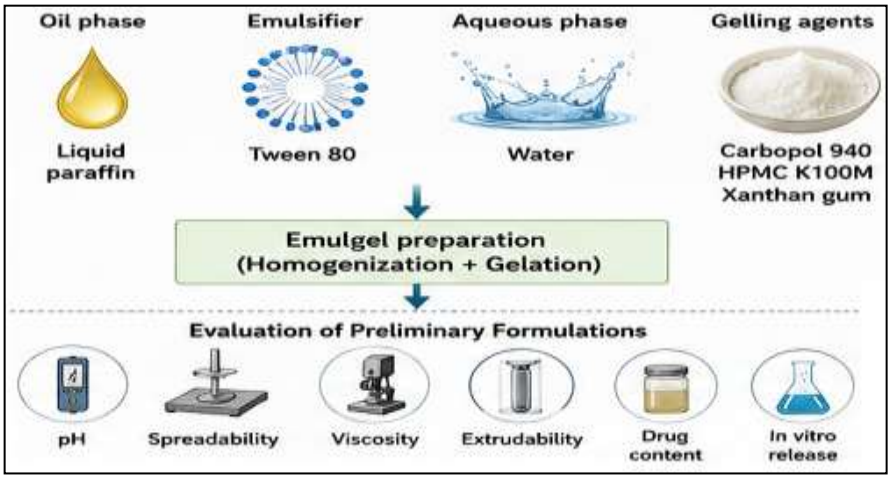

Figure 2. Formulation development

Table 1. Composition of preliminary cetirizine hydrochloride emulgels (F1–F3)

Ingredient	F1	F2	F3	Function
Cetirizine hydrochloride BP (g)	1	1	1	Active pharmaceutical ingredient
Ethanol (mL)	5	5	5	Cosolvent
Propylene glycol (mL)	5	5	5	Penetration enhancer
Methyl paraben (g)	0.03	0.03	0.03	Preservative
Span 80 (mL)	0.5	0.5	0.5	Emulsifier
Tween 80 (mL)	1	1	1	Emulsifier
EDTA (g)	0.02	0.02	0.02	Chelating agent
Liquid paraffin (mL)	7.5	7.5	7.5	Oil phase
Propyl paraben (g)	0.02	0.02	0.02	Preservative
Carbopol 940 (g)	1	–	–	Gelling agent
HPMC K100M (g)	–	1	–	Gelling agent
Xanthan gum (g)	–	–	1	Gelling agent
Triethanolamine	q.s.	q.s.	q.s.	pH adjustment
Purified water	up to 100	up to 100	up to 100	Vehicle

2.4 Evaluation of emulgel

The color, consistency, homogeneity, and phase separation of the formulations were visually inspected. A digital pH meter was used to measure the pH. Spreadability was measured in g•cm/s using a modified double-glass-slide method with 1 g of formulation and a 10-cm transit distance. An applied load was used to assess the extrudability of a lacquered collapsible aluminum tube. A Thermo Scientific HAAKE Viscotester 3 with rotor R1 was used to determine rheological viscosity at 25 ± 1 °C.

A Franz diffusion cell with a 20-mL receptor compartment and a 3.14 cm² diffusion area was used to assess in vitro drug release. The donor and receptor compartments were divided by a dialysis membrane that had been pre-soaked in phosphate buffer pH 7.4 for a whole day. The receptor phase was agitated at 100 rpm and kept at 37 ± 0.2 °C. At prearranged intervals, one-milliliter aliquots were removed and replaced with new buffer. At 231 nm, the drug concentration was measured [18, 19].

A weighed amount of formulation was extracted using phosphate buffer pH 6.8: methanol (80:20, v/v), sonication, filtering, dilution, and UV analysis at 231 nm to determine the drug content.

2.5 Stability studies

After centrifugation at 5000 rpm for 30 minutes at 25 °C, physical stability was assessed visually for phase separation or cracking. Accelerated stability testing was conducted at 40 ± 2 °C/75 ± 5% RH for 60 days. Phase separation, appearance, pH, viscosity, and in vitro release were observed at 0, 30, and 60 days [20, 21].

2.6 Design of Experiments and optimization

Xanthan gum was chosen for optimization based on first screening. Nine experimental formulations are reported in the source study using a 2^3 full-factorial design with a single center point. Cumulative drug release and viscosity were the responses, while the independent variables were the concentrations of xanthan gum (A), liquid paraffin (B), and Tween 80 (C). Model fitting, ANOVA, and desirability-based batch selection were all done using Design-Expert software [22].

Table 2. Independent variables used in the reported factorial optimization

Factor	Symbol	Low level (−1)	High level (+1)
Xanthan gum concentration (g)	A	0.5	1.5
Liquid paraffin concentration (mL)	B	5	10
Tween 80 concentration (mL)	C	0.5	0.7

3. RESULTS AND DISCUSSION

3.1 Organoleptic and preformulation findings

Cetirizine hydrochloride was described as a crystalline powder that was nearly white and odorless. High solubility in polar and aqueous mediums and extremely poor solubility in liquid paraffin were found in the studied solubility profile. This validated the use of a gel containing a biphasic emulsion to hold the medication in a topical semisolid matrix.

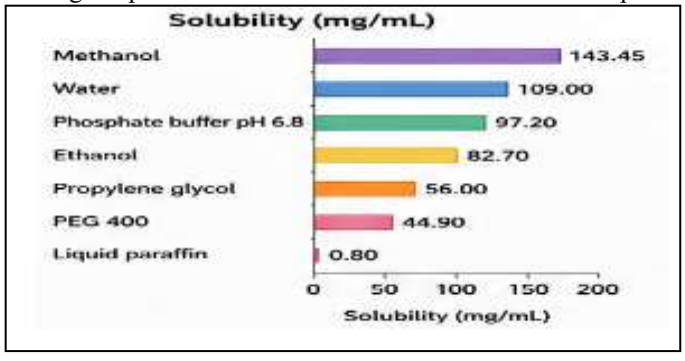

Figure 3. Observed solubility profile

Table 3. Solubility of cetirizine hydrochloride reported in the source study

Solvent/medium	Solubility (mg/mL)	Interpretation
Methanol	143.45	Freely soluble/highest among tested media
Distilled water	109.0	High solubility
Phosphate buffer pH 6.8	97.2	High solubility
Ethanol	82.7	High solubility
Propylene glycol	56.0	Moderate-to-high solubility
PEG 400	44.9	Lower solubility
Liquid paraffin	0.8	Practically insoluble

3.2 Drug–excipient compatibility

The main distinctive drug bands were preserved in the FTIR spectra of both pure Cetirizine hydrochloride and the Cetirizine hydrochloride–xanthan gum physical combination. The source research supported the lack of obvious chemical incompatibility by seeing only slight fluctuations in intensity/position and no notable peak disappearance or emergence. Pure Cetirizine hydrochloride's DSC thermogram revealed an endothermic peak at 205.52 °C (onset 172.74 °C; endset 211.74 °C). The drug-related thermal event was still visible, but the physical mixture including xanthan gum showed a widened peak at 199.37 °C with decreased intensity. Rather than the development of a novel chemical interaction, these results were viewed as consistent with physical dispersion and decreased crystallinity.

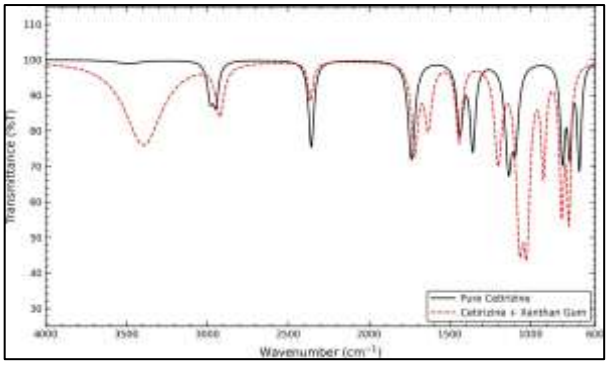

Figure 4. FTIR spectra of pure cetirizine hydrochloride and the cetirizine hydrochloride–xanthan gum physical mixture

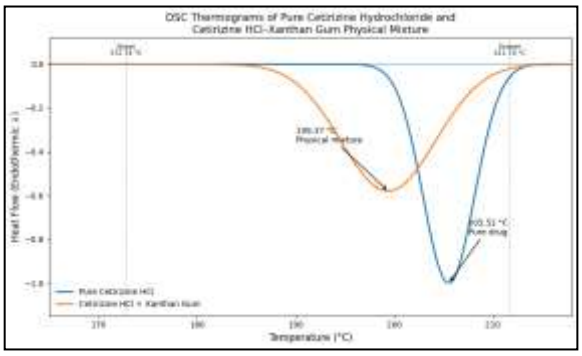

Figure 5. DSC thermogram of pure Cetirizine hydrochloride and the Cetirizine hydrochloride–xanthan gum physical mixture

Table 4. Compatibility findings from FTIR and DSC analysis

Parameter	Pure cetirizine HCl	Cetirizine HCl - xanthan gum	Interpretation
Principal DSC endotherm (°C)	205.52	199.37	Peak retained with broadening/reduced intensity
Onset/endset (°C)	172.74 / 211.74	Not reported	Drug thermal event remained evident
FTIR major drug bands	Retained	Retained	No major new band reported

3.3 Physical evaluation of preliminary emulgels

According to reports, every first formulation was white, homogeneous, and devoid of any discernible phase separation. The pH values for F1, F2, and F3 were 5.9 ± 0.2, 6.0 ± 0.3, and 6.5 ± 0.5, respectively. Carbopol 940 generated the maximum viscosity (12662 mPa•s), whereas Xanthan gum (F3) demonstrated the highest spreadability (5.0 ± 0.5 g•cm/s) and intermediate viscosity (9427 mPa•s). Out of the three initial systems, HPMC K100M produced the lowest spreadability (4.5 ± 0.5 g•cm/s) and the lowest viscosity (8373 mPa•s).

Table 5. Preliminary physicochemical evaluation of Cetirizine hydrochloride emulgels

Formulations	Polymer	pH	Spreadability (g·cm/s)	Extrudability (g/cm²)	Viscosity (mPa·s)
F1	Carbopol 940	5.9 ± 0.2	4.8 ± 0.5	28.7	12662
F2	HPMC K100M	6.0 ± 0.3	4.5 ± 0.5	22.3	8373
F3	Xanthan gum	6.5 ± 0.5	5.0 ± 0.5	18.5	9427

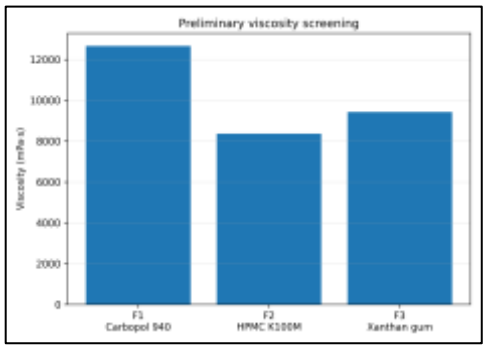

Figure 6. Comparative viscosity of preliminary emulgels F1–F3

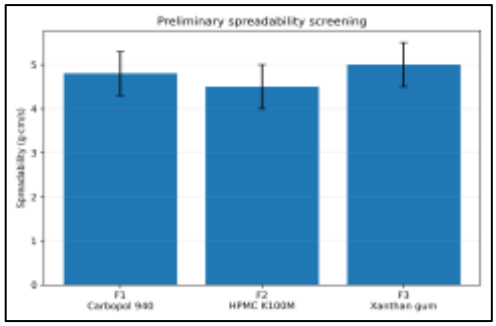

Figure 7. Comparative spreadability of preliminary emulgels F1–F3

3.4 In vitro drug release

Over the course of the six-hour research, the xanthan gum formulation F3 showed the largest cumulative release, reaching 94.48 ± 0.45% at 6 hours, compared to 82.64 ± 0.35% for F2 and 74.32 ± 0.36% for F1. F3 was chosen for further DoE modification because of its quicker release and acceptable spreadability and viscosity. The observed polymer-dependent variations align with the way viscosity and gel microstructure regulate drug diffusion from semisolid systems.

Table 6. In vitro cumulative drug release of preliminary Cetrizine hydrochloride emulgels

Time (h)	F1 Carbopol 940	F2 HPMC K100M	F3 Xanthan gum
1	18.42 ± 0.42	22.15 ± 0.36	25.34 ± 0.41
2	31.68 ± 0.38	38.72 ± 0.45	44.28 ± 0.52
3	45.24 ± 0.44	53.16 ± 0.41	60.35 ± 0.47
4	56.83 ± 0.39	65.42 ± 0.36	74.26 ± 0.43
5	66.57 ± 0.41	75.38 ± 0.40	85.17 ± 0.39
6	74.32 ± 0.36	82.64 ± 0.35	94.48 ± 0.45

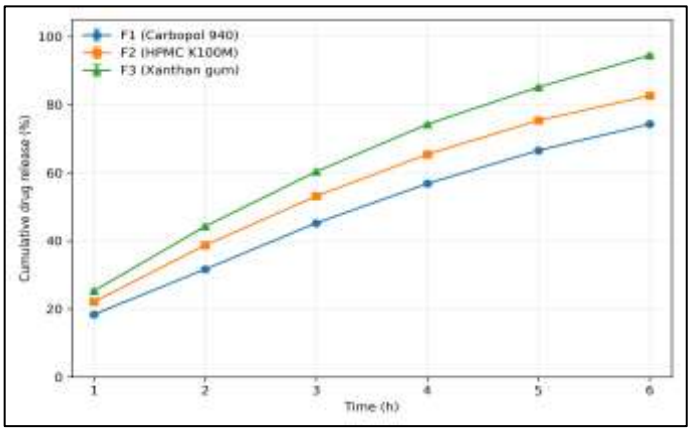

Figure 8. In vitro cumulative drug-release profiles of preliminary Cetirizine hydrochloride emulgels

3.5 Drug content

The results of the drug-content analysis were 86.6 ± 0.20% for F1, 64.7 ± 0.76% for F2, and 91.3 ± 0.50% for F3. Thus, among the initial formulations, the xanthan gum formulation had the highest drug concentration. Since the source material claims that all formulations were acceptable while simultaneously reporting a significantly lower numerical value for F2, the relatively low value provided for F2 should be independently verified against the original analytical data prior to journal submission.

Table 7. Drug content of preliminary formulations

Formulation	Drug content (%)
F1 (Carbopol 940)	86.6 ± 0.20
F2 (HPMC K100M)	64.7 ± 0.76
F3 (Xanthan gum)	91.3 ± 0.50

3.6 Stability assessment

According to the obtained results, there was no discernible phase separation and all formulations stayed stable throughout the centrifugation investigation. No significant alterations in appearance, pH, viscosity, or in vitro release were noted during 60 days of accelerated storage at 40 ± 2 °C/75 ± 5% RH. There were very slight variations in viscosity and a slight shift in pH. Longer-term stability and packaging compatibility should be determined in a thorough stability program; however these observations support short-term physical stability under the studied accelerated settings.

3.7 DoE-based optimization

A significant decreased quadratic model was revealed by the reported ANOVA for cumulative drug release ($F = 5.58$; $p = 0.0437$). In the reported model, the linear terms for Tween 80, liquid paraffin, and xanthan gum were not significant separately, but the quadratic term for xanthan gum concentration (A^2) was significant ($p = 0.0056$). Liquid paraffin and Tween 80 were found to be non-significant, while the linear model for viscosity was very significant ($F = 85.73$; $p = 0.0001$), with xanthan gum content being the major factor ($F = 257.20$; $p < 0.0001$).

Table 8. ANOVA for the reported reduced quadratic model for cumulative drug release

Source	SS	df	MS	F-value	p-value
Model	45375.50	4	11343.88	5.58	0.0437
A – xanthan gum	8.82	1	8.82	0.0043	0.9501
B – liquid paraffin	722.00	1	722.00	0.3549	0.5773
C – Tween 80	718.20	1	718.20	0.3530	0.5783
A^2	43926.48	1	43926.48	21.59	0.0056
Residual	10172.41	5	2034.48	–	–

Table 9. ANOVA for the reported linear model for viscosity

Source	SS	df	MS	F-value	p-value
Model	2.629 × 10	3	8.765 × 10	85.73	0.0001
A – xanthan gum	2.629 × 10	1	2.629 × 10	257.20	<0.0001
B – liquid paraffin	0.0000	1	0.0000	0.0000	1.0000
C – Tween 80	0.0000	1	0.0000	0.0000	1.0000
Residual	5.111 × 10	5	1.022 × 10	–	–

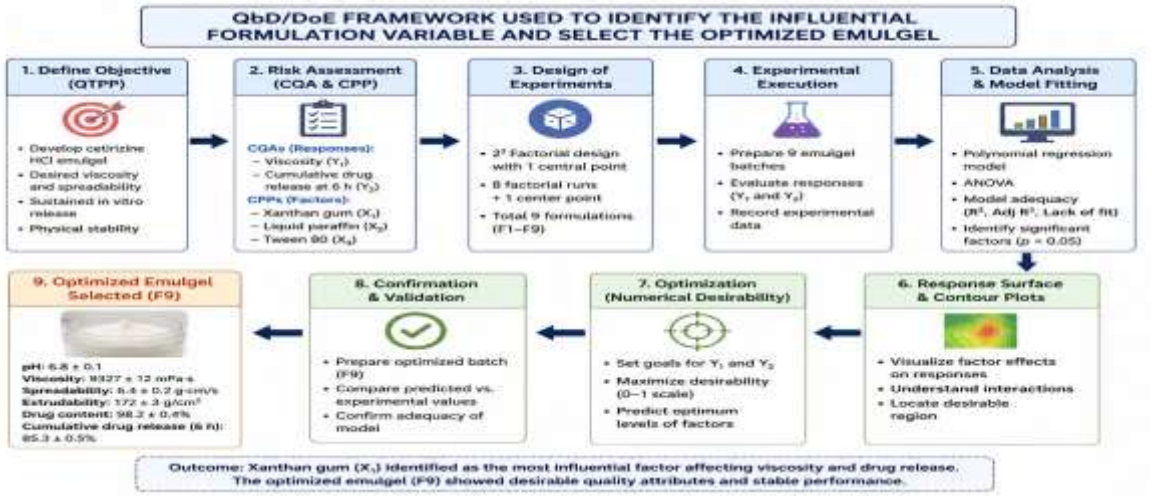

Figure 9. QbD/DoE framework used to identify the influential formulation variable and select the optimized emulgel

DISCUSSION OF OPTIMIZATION

The optimization study revealed that xanthan gum is the significant variable that controls the two responses. As the concentration of the polymer decreases, the formulations become less viscous and have high drug release; conversely, when the polymer concentration is high, viscosity rises significantly, and drug release becomes minimal since diffusion into the polymer matrix becomes limited. On the other hand, liquid paraffin and Tween 80 play relatively minor roles in controlling the responses of interest.

Formulation F9 was chosen to be the optimal one because of its balance between viscosity and the drug release rate. Low-viscosity formulations such as F5 and F7 exhibited a high degree of release, but their body and retention were low and they would not be effective as topical gels. On the other hand, highly viscous gels such as F2, F4, F6, and F8 did not have a high level of drug release rates. Thus, F9 could be considered to be the optimal emulgel.

3.8 Characterization of the reported optimized batch F9

Based on a desirability-based trade-off between viscosity and cumulative drug release, the source study determined that F9 was the best formulation. F9 has the following characteristics: pH 6.8 ± 0.1, viscosity 9327 ± 12 mPa•s, spreadability 6.4 ± 0.2 g•cm/s, extrudability 172 ± 3 g/cm², drug content 98.2 ± 0.4%, and cumulative drug release 85.3 ± 0.5%. In comparison to the initial systems, these values show a balanced semisolid profile.

Table 10. Reported quality attributes of optimized Cetirizine hydrochloride emulgel F9

Parameter	Reported F9 value
Appearance	Smooth, homogeneous, white
pH	6.8 ± 0.1
Viscosity	9327 ± 12 mPa·s
Spreadability	6.4 ± 0.2 g·cm/s
Extrudability	172 ± 3 g/cm²
Drug content	98.2 ± 0.4%
Cumulative drug release	85.3 ± 0.5%

3.8 Comparison with marketed formulation

In the present study, the improved formulation's appearance, pH, viscosity, spreadability, extrudability, drug content, and in vitro release were compared to those of Voveran® Emulgel. The improved formulation's qualitative physicochemical properties were described as being largely comparable. According to reports, the marketed formulation had a larger cumulative release (92.0 ± 0.4%) than F9 (85.3 ± 0.5%).

Table 11. Qualitative comparison of optimized F9 with the marketed comparator as reported in the source study

Parameter	Optimized F9	Marketed Voveran® Emulgel	Interpretation reported
Appearance/color	Comparable	Comparable	Similar qualitative appearance
pH	Comparable	Comparable	Similar qualitative pH
Spreadability	Comparable	Comparable	Similar qualitative performance
Extrudability	Comparable	Comparable	Similar qualitative performance
Drug content	Acceptable	Acceptable	Both reported within acceptable range
Cumulative drug release	85.3 ± 0.5%	92.0 ± 0.4%	Marketed product higher

4. CONCLUSION

Based on the described physicochemical and release characteristics, xanthan gum was found to be the most advantageous preliminary polymer in the successful development of Cetirizine hydrochloride emulgel employing three distinct gelling systems. The maximum initial drug content and cumulative release were found in the xanthan gum formulation. The reported optimized batch F9 demonstrated acceptable pH, rheology, spreadability, extrudability, drug content, cumulative release, and short-term accelerated stability. DoE-based optimization revealed that xanthan gum concentration was the primary variable influencing viscosity and release. The work offers a potential basis for Cetirizine hydrochloride emulgel formulation and development.

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Conflict of interest

There is no any conflict-of-interest.

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