Quality-By-Design-Based Development and Evaluation of Ivermectin-Loaded Invasomal Topical Gel

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Abstract

Background: Ivermectin is poorly water-soluble, making formulation strategies important for its topical delivery. Invasomes are phospholipid-based vesicles containing terpenes and ethanol that may facilitate skin delivery. Quality by Design (QbD) provides a systematic approach to evaluating formulation and process variables.

Objective: To develop ivermectin-loaded invasomes, screen formulation and process variables using a Plackett-Burman design, and incorporate the selected dispersion into an HPMC K15M-based topical gel.

Methods: Preformulation studies included organoleptic evaluation, melting point determination, solubility assessment, UV calibration, and FT-IR analysis. Invasomes were prepared by mechanical dispersion. Six formulation and process factors were screened using a 12-run Plackett-Burman design, with entrapment efficiency (%EE) and cumulative drug release (%CDR) as responses. The selected dispersion was incorporated into a topical gel and evaluated for appearance, pH, viscosity, spreadability, drug content, and in vitro drug release.

Results: Ivermectin was reported as a white crystalline powder with a melting point of 156-158 °C. The UV calibration equation was (y = 0.0373x + 0.0044) ((R^2 = 0.9996)). The %EE model was significant ((F = 32.30), (p = 0.0008)), with terpene concentration, stirring speed, and phospholipid type identified as significant factors. The %CDR model was also significant ((F = 6.39), (p = 0.0300)); phospholipid concentration and stirring speed were significant factors. The selected invasomal formulation exhibited an entrapment efficiency of 95.78% and drug content of 96.28 ± 0.75%. The gel had a pH of 6.77 ± 0.01, viscosity of 10,252 ± 779.31 cps, spreadability of 11.64 ± 0.60 g·cm/s, and drug content of 96.58 ± 0.51%. Cumulative drug release reached 92.44% at 480 min.

Conclusion: The findings demonstrate the preliminary feasibility of formulating ivermectin-loaded invasomes and incorporating them into a topical gel. Further characterization and verification of the formulation data and release kinetics are required before definitive conclusions regarding formulation performance can be drawn.

Keywords: Ivermectin; invasomes; topical gel; Plackett-Burman design; Quality by Design; entrapment efficiency; in vitro drug release.

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1. Introduction

The development of topical drug delivery systems requires consideration of drug solubility, vehicle composition, formulation properties, and the performance of the final dosage form. Ivermectin is a lipophilic drug with poor aqueous solubility [1-2]. In the present study, preformulation assessment indicated low solubility in water, phosphate buffer, and dilute hydrochloric acid, with higher solubility in methanol and ethanol [3]. These findings provided the rationale for investigating a vesicular delivery system for ivermectin. Invasomes are phospholipid-based vesicles containing ethanol and terpenes. Their composition may influence vesicle characteristics and skin permeation, making them a potential approach for topical and transdermal drug delivery. Previous studies have investigated invasomal systems containing candesartan, isoxsuprine, curcumin, luteolin, and antifungal agents [4-6]. However, findings obtained with other active ingredients cannot directly establish the performance of ivermectin-loaded invasomes. Quality by Design (QbD) provides a systematic framework for formulation development through the identification of the quality target product profile, critical quality attributes, and potentially

influential material and process variables. Design of experiments (DoE) enables the systematic assessment of these variables [7,8]. A Plackett-Burman design is particularly useful for screening multiple factors with a limited number of experiments, although it does not independently establish a complete response-surface optimum [8-9]. In this study, a 12-run Plackett-Burman design was used to screen six formulation and process factors against entrapment efficiency (%EE) and cumulative drug release (%CDR). Although one section refers to a Box-Behnken design, the available experimental results document the Plackett-Burman screening study; therefore, the statistical approach is described accordingly [10]. The study aimed to prepare ivermectin-loaded invasomes and incorporate the selected dispersion into an HPMC K15M-based topical gel. The specific objectives were to evaluate selected preformulation characteristics, screen formulation and process variables, characterize the selected invasomal formulation, evaluate the prepared gel, and compare its in vitro drug release profile with that of a marketed ivermectin gel.

2. Materials and Methods

2.1. Materials and Instruments

Ivermectin was used as the active pharmaceutical ingredient. Phospholipid, terpene(s), ethanol, and phosphate-buffered saline (PBS; pH 7.4) were used in invasome preparation. HPMC K15M, propylene glycol, methyl paraben, propyl paraben, triethanolamine, and distilled water were listed for topical gel preparation. The instruments included a digital weighing balance (US-300, Cyberlab, USA), an analytical balance (AUW220 D, Shimadzu, Japan), and a UV-visible spectrophotometer (UV-1700, Shimadzu Corporation, Japan).

2.2. Preformulation Assessment

The organoleptic characteristics, melting point, and solubility of ivermectin were evaluated. Solubility was assessed in water, phosphate buffer (pH 7.4), 0.1 N hydrochloric acid, methanol, ethanol, and acetone. A UV calibration curve was prepared over a concentration range of 0-25 µg/mL, and the calibration equation and coefficient of determination were recorded. FT-IR analysis was performed to examine characteristic absorption bands and support drug identification [11-12].

2.3. Preparation of Ivermectin-Loaded Invasomes

Ivermectin-loaded invasomes were prepared using a mechanical-dispersion method. Ivermectin and the selected terpene or terpene mixture were dissolved in an ethanolic phospholipid solution. The mixture was vortexed for 5 min and sonicated for 5 min to obtain a clear solution. PBS (pH 7.4) was then added using a syringe under continuous vortexing, followed by an additional 5 min of vortexing [13]. The resulting dispersion was extruded repeatedly through polycarbonate membranes of different pore sizes to obtain the invasomal preparation (Figure 1).

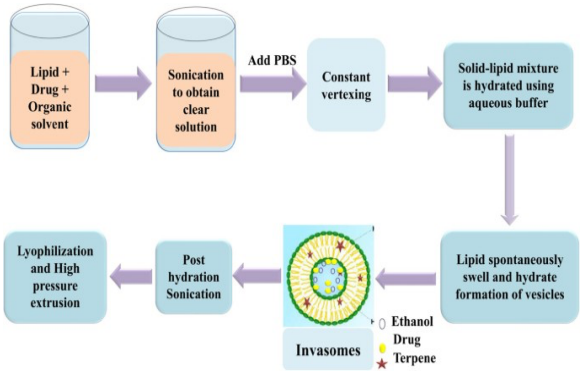


Figure 1. Mechanical Dispersion Technique

2.4 QbD factor screening

The study employed a 12-run Plackett-Burman design generated using Design-Expert software to screen six formulation and process variables: (A) terpene concentration, (B) type of terpene, (C) phospholipid concentration, (D) ethanol concentration, (E) stirring speed, and (F) type of phospholipid. The effects of these factors were evaluated using two responses: entrapment efficiency (%EE) and cumulative drug release (%CDR). The factor levels and experimental responses for each run are presented in Tables 1 and 2, respectively [14-16].

Table 1. Independent variables and levels reported for the Plackett-Burman screening design.

Factor	Variable	Low/high levels
A	Concentration of terpenes	0.5% / 1%
B	Type of terpenes	Fenchone / Limonene
C	Concentration of phospholipid	1% / 2%
D	Concentration of ethanol	2% / 3%
E	Stirring speed	400 / 600 rpm
F	Type of phospholipid	Egg lecithin / Phosphatidylcholine

2.5 Characterization of invasomes

Entrapment efficiency was determined by centrifuging 10 mL of invasomal suspension for 10 min. The clear fraction was used to determine free drug by UV/visible spectrophotometry at 245 nm [17]. The calculation provided in the study was:

Entrapment efficiency (%) = [(Ct - Cf) / Ct] × 100

where Ct is the concentration of total drug and Cf is the concentration of unentrapped (free) drug.

2.6 Preparation of HPMC K15M gel

Three preliminary gel formulations were prepared using HPMC K15M at concentrations of 1%, 1.5%, and 2% w/v. Each formulation contained 5 mL of propylene glycol, 0.1 mL of methyl paraben, 0.05 mL of propyl paraben, and 0.5 mL of triethanolamine, with distilled water added q.s. to the final volume. Formulation G1 was selected based on its reported viscosity and spreadability. The quantity of invasomal dispersion required to incorporate the intended drug dose into the gel was calculated to be approximately 637.93 mg and rounded to 650 mg for formulation purposes [18-19].

Table 2. Formulation design of topical gel trial batches

Batch	HPMC K15M (% w/v)	Propylene glycol (mL)	Methyl paraben (mL)	Propyl paraben (mL)	Triethanolamine (mL)	Water
G1	1	5	0.1	0.05	0.5	q.s.
G2	1.5	5	0.1	0.05	0.5	q.s.
G3	2	5	0.1	0.05	0.5	q.s.

2.7 Evaluation of Topical Gel

The prepared topical gel was evaluated for physical appearance, grittiness, pH, viscosity, spreadability, and drug content. The results for selected evaluation parameters were expressed as mean ± standard deviation (SD) for three replicates (n = 3). Instrument specifications, spindle and rotational speed settings, spreadability calculation details, and the drug-content extraction procedure should be reported according to the original experimental records [20-21].

2.8 In Vitro Drug Release and Kinetic Analysis

The in vitro drug release profiles of the marketed ivermectin gel and the optimized ivermectin-loaded invasomal gel were compared. Drug release was evaluated at 60-min intervals up to 300 min for the marketed gel and 480 min for the optimized invasomal gel. The release data were analyzed using zero-order, first-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas kinetic models. Based on the reported plots and coefficients of determination (R^2), the Higuchi model provided the best fit to the drug release data. The corresponding R^2 values are presented in the Results section [22].

2.9 Stability Assessment

The optimized ivermectin-loaded invasomal gel was subjected to a preliminary short-term stability assessment at room temperature over 30 days, with observations recorded on days 1, 15, and 30. The evaluated parameters included colour, clarity, pH, viscosity, spreadability, and cumulative drug release (%CDR). As detailed information regarding the packaging, storage conditions, monitoring protocol, and predefined acceptance criteria was unavailable, the findings were interpreted as preliminary stability observations [23].

2.10 Statistical Analysis

The experimental data were analyzed using analysis of variance (ANOVA), and the coded-factor equations were reported as obtained from the original study. Statistical significance was interpreted according to the p-values reported in the source. As the complete raw replicate data and software output were unavailable for independent recalculation, the statistical findings were reported as originally documented and were not independently validated [24].

3. Results

3.1 Preformulation characteristics

The preformulation characteristics of ivermectin were evaluated in terms of colour, odour, physical appearance, melting point, and solubility in different solvents. Ivermectin was observed to be white, with a characteristic odour and crystalline appearance. Its melting point was reported to be 156-158 °C. The solubility results indicated poor solubility in water, pH 7.4 phosphate buffer, 0.1 N HCl, and acetone, whereas higher solubility was observed in methanol and ethanol. The reported results are presented in Table 3.

Table 3. Preformulation characteristics and solubility of ivermectin.

Parameter	Reported result
Colour	White
Odour	Characteristic

Appearance	Crystalline
Melting point	156-158 °C
Water solubility	0.0086 ± 0.20 mg/mL
pH 7.4 phosphate buffer solubility	0.022 ± 0.09 mg/mL
0.1 N HCl solubility	0.0025 ± 0.58 mg/mL
Methanol solubility	13.28 ± 0.09 mg/mL
Ethanol solubility	15.34 ± 0.15 mg/mL
Acetone solubility	0.0016 ± 0.17 mg/mL

3.2 UV calibration and FT-IR identification

The UV calibration curve of ivermectin was established over a concentration range of 0-25 µg/mL. The reported linear regression equation was (y = 0.0373x + 0.0044), with a coefficient of determination ((R^2)) of 0.9996, indicating a strong linear relationship between concentration and absorbance over the investigated range. Absorbance is dimensionless; therefore, the unit reported in the original source should be verified against the instrument records. The wavelength of measurement should be expressed in nanometres (nm).

FT-IR analysis was performed to identify the characteristic functional groups of ivermectin. The spectral interpretation should be based on the characteristic absorption bands observed in the recorded spectrum and their corresponding functional-group assignments.

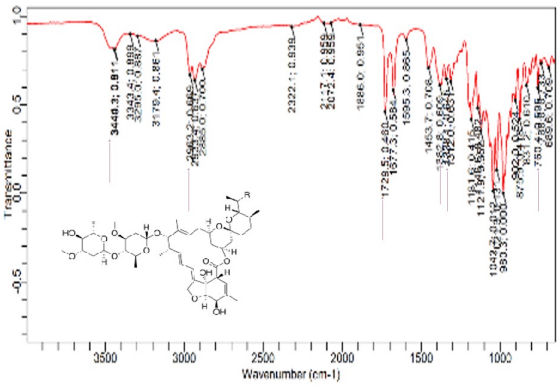


Figure 2. Calibration Curve

The FT-IR spectrum of ivermectin exhibited characteristic absorption bands at 3449.3, 2963.2, 1729.5, 1344.43, 1312.63, and 760.4 cm^{-1}. These bands were assigned to O-H stretching, C-H stretching, C=O stretching, C-N stretching, C-O stretching, and skeletal vibrations, respectively. The absorption bands supported the identification of characteristic functional groups in ivermectin.

Figure 3. Identification of Pure Drug Ivermectin by IR Spectrum

3.3 Screening design and observed responses

A 12-run Plackett-Burman screening design was employed to evaluate the effects of six formulation and process variables on entrapment efficiency (%EE) and cumulative drug release (%CDR). The investigated factors included terpene concentration, type of terpene, phospholipid concentration, ethanol concentration, stirring speed, and type of phospholipid. The experimental factor settings and corresponding observed responses for all 12 runs are presented in Table 4.

Table 4. Plackett-Burman screening design and observed responses

Run	A: Terpene Conc.	B: Terpene Type	C: phospholipid conc.	D: ethanol conc.	E: stirring (rpm)	F: phospholipid type	%EE	%CDR
1	1	Fenchone	2	3	400	Phosphatidylcholine	73.18	65.13
2	0.5	Fenchone	1	3	400	Phosphatidylcholine	60.21	42.34
3	1	Limonene	1	3	600	Phosphatidylcholine	63.27	41.33
4	0.5	Limonene	1	3	600	Egg lecithin	57.4	44.47
5	1	Limonene	1	2	400	Phosphatidylcholine	75.81	62.34
6	0.5	Fenchone	2	2	600	Phosphatidylcholine	50.48	35.19
7	1	Limo	2	2	400	Egg lecithin	76.	68.2

		nene					8	1
8	0.5	Limonene	2	2	600	Phosphatidylcholine	50.19	44.13
9	0.5	Fenchone	1	2	400	Egg lecithin	64.1	43.33
10	1	Fenchone	1	2	600	Egg lecithin	65.3	42.94
11	1	Fenchone	2	3	600	Egg lecithin	69.1	56.15
12	0.5	Limonene	2	3	400	Egg lecithin	71.1	85.8

3.4 ANOVA for Entrapment Efficiency

The ANOVA results indicated that the model for entrapment efficiency (%EE) was statistically significant (F = 32.30, p = 0.0008). Among the six investigated factors, terpene concentration (A), stirring speed (E), and phospholipid type (F) significantly influenced %EE ($p < 0.05$). Terpene concentration showed the highest F-value (90.89), followed by stirring speed (79.43) and phospholipid type (17.71). The remaining factors were not statistically significant at the 5% significance level. The ANOVA results are in Table 5.

Table 5. ANOVA for entrapment efficiency (%EE)

Factor	Sum of squares	F-value	p-value	Significance
Model	869.81	32.30	0.0008	Significant
A: Terpene concentration	407.98	90.89	0.0002	Significant
B: Terpene type	12.34	2.75	0.1582	Not significant
C: Phospholipid concentration	1.96	0.44	0.5380	Not significant
D: Ethanol concentration	11.47	2.55	0.1709	Not significant
E: Stirring speed	356.54	79.43	0.0003	Significant
F: Phospholipid type	79.52	17.71	0.0084	Significant
Residual	22.44	-	-	-

Significance was considered at $p < 0.05$.

The coded-factor equation reported in the study was: %EE = +64.76 + 5.83A + 1.01B + 0.40C + 0.98D - 5.45E - 2.57F.

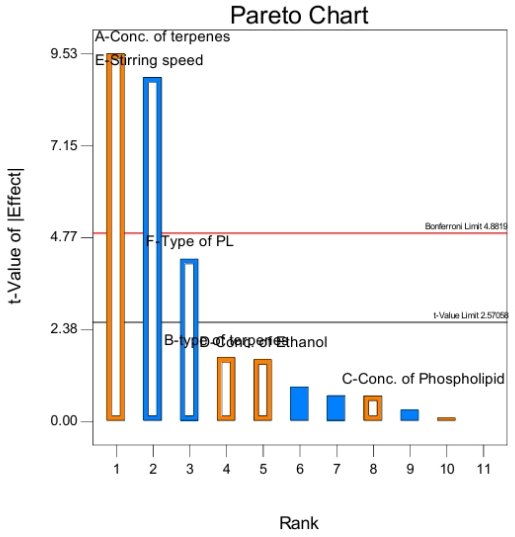


Figure 4. Pareto Chart for % E.E

3.5 Analysis of Variance for *In Vitro* Drug Release

The ANOVA results indicated that the model for in vitro drug release was statistically significant (F = 6.39, p = 0.0300). Among the six investigated factors, phospholipid concentration (C) and stirring speed (E) significantly influenced drug release ($p < 0.05$). Stirring speed showed the highest F-value (15.53), followed by phospholipid concentration (8.89). Terpene concentration, terpene type, ethanol concentration, and phospholipid type were not statistically significant at the 5% significance level. The ANOVA results are summarized in Table 6.

Table 6. ANOVA for *in vitro* Drug Release

Factor	Sum of squares	F-value	p-value	Significance
Model	2178.63	6.39	0.0300	Significant

A: Terpene concentration	138.99	2.45	0.1787	Not significant
B: Terpene type	312.12	5.49	0.0661	Not significant
C: Phospholipid concentration	505.18	8.89	0.0308	Significant
D: Ethanol concentration	127.27	2.24	0.1948	Not significant
E: Stirring speed	883.05	15.53	0.0109	Significant
F: Phospholipid type	212.02	3.73	0.1113	Not significant
Residual	284.22	-	-	-

Significance was considered at $p < 0.05$.

The coded-factor equation reported in the study was: In-vitro drug release = +52.61 + 3.40A + 5.10B + 6.49C + 3.26D - 8.58E - 4.20F.

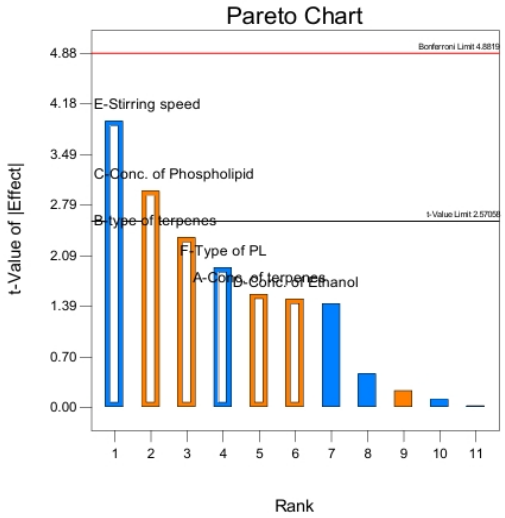


Figure 5. Pareto Chart for In Vitro Drug Release

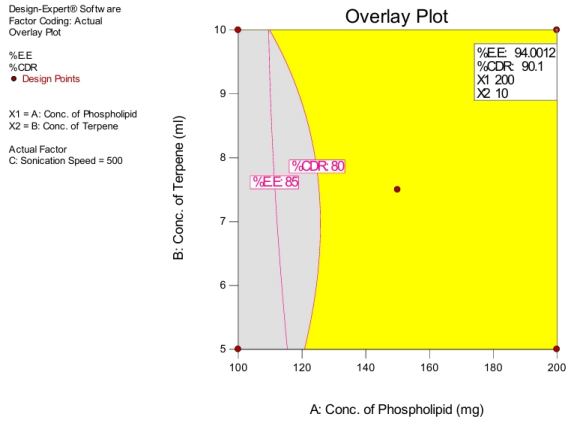
3.6 Risk assessment and response validation

Risk assessment identified terpene concentration and stirring speed as high-risk factors for entrapment efficiency (%EE), while phospholipid concentration and stirring speed were high-risk factors for cumulative drug release (%CDR). The risk assessment matrix is presented in Table 7.

Table 7. Risk assessment of variables affecting critical quality attributes

Critical quality attribute	A: terpene concentration	B: terpene type	C: phospholipid concentration	D: ethanol concentration	E: stirring speed	F: phospholipid type
%EE	High	Low	Low	Medium	High	Medium
%CDR	Low	Medium	High	Low	High	Low

Response validation showed good agreement between predicted and actual values. At phospholipid concentration 200 and terpene concentration 10, predicted versus actual %EE and %CDR were 94.00% versus 94.50% and 90.10% versus 91.21%, respectively. At terpene concentration 5, the corresponding values were 95.40% versus 95.74% for %EE and 91.82% versus 92.06% for %CDR. These results support the predictive performance of the model under the tested conditions.



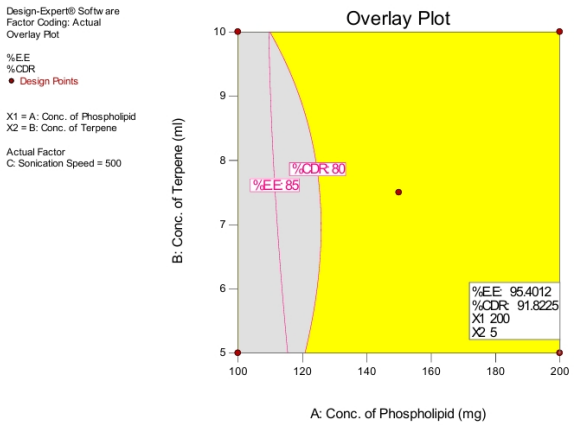


Figure 6. Overlay Plot

Table 8. Predicted and actual responses for the two validation batches

Validation point	Phospholipid concentration (X1)	Terpene concentration (X2)	Predicted %EE	Actual %EE	Predicted %CDR	Actual %CDR
Batch 1	200	10	94.00	94.50	90.10	91.21
Batch 2	200	5	95.40	95.74	91.82	92.06

The selected composition was listed as ivermectin invasomes 10 mg, phospholipid concentration 200 mg, terpene concentration 5 mg, ethanol 3% v/v and PBS q.s. The source labels this as an optimized formulation from a Box-Behnken design, although the presented factor-screening and validation information does not establish a full Box-Behnken design matrix. The design name and units should be verified before claiming formal response-surface optimization. The composition is in Table 9.

Table 9. Composition of the selected ivermectin-loaded invasomal formulation.

Ingredient / component	Composition
Ivermectin invasomes	10 mg
Phospholipid	200 mg
Terpene	5 mg
Ethanol	3% v/v
Phosphate-buffered saline (PBS)	q.s.

3.7 Characterization of Optimized Invasomes

The selected ivermectin-loaded invasomal formulation exhibited an entrapment efficiency (%EE) of 95.78% and a drug content of 96.28 ± 0.75%. Scanning electron microscopy (SEM) revealed predominantly spherical vesicles with some irregularities, while no visible aggregation was observed in the examined field. These findings provided preliminary evidence of successful formulation and the observed vesicular morphology.

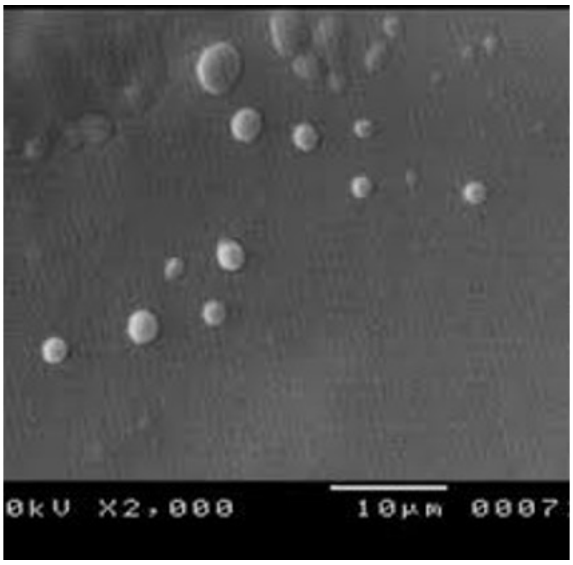


Figure 7. SEM image of optimized batch

3.8 Gel trial-batch results

Three topical gel formulations containing 1%, 1.5%, and 2% w/v HPMC K15M were evaluated. Viscosity increased with increasing polymer concentration, whereas spreadability decreased. The pH values remained similar across the three formulations. Based on the reported viscosity and spreadability, formulation G1 was selected for further development. The evaluation results are presented in Table 10.

Table 10. Evaluation of HPMC K15M topical gel trial batches.

Batch	Colour	Odour	pH (mean ± SD)	Viscosity (mean ± SD)	Spreadability (mean ± SD; g·cm/sec)
G1	White	Odorless	6.81 ± 0.08	10047 ± 447.49	11.84 ± 0.47
G2	White	Odorless	6.82 ± 0.05	13965 ± 800.96	10.95 ± 0.60
G3	White	Odorless	6.76 ± 0.06	16008 ± 474.97	9.04 ± 0.32

3.9 Optimized invasomal gel and comparison with marketed gel

The optimized ivermectin-loaded invasomal gel was described as homogeneous, smooth, opaque, and free from grittiness. The reported pH was 6.77 ± 0.01, spreadability was 11.64 ± 0.60 g·cm/s, and drug content was 96.58 ± 0.51%. The comparison data for the marketed and invasomal gels are presented in Table 11.

Table 11. Comparison of marketed ivermectin gel and ivermectin-loaded invasomal gel

Parameter	Marketed gel	Invasomal gel
Strength	1% w/w	30 mg/30 g
Appearance	Opaque	Opaque
Odour	Odourless	Odourless
pH (*mean ± SD; n = 3*)	6.10 ± 0.19	6.77 ± 0.01
Viscosity (*mean ± SD; n = 3*)	9987 ± 52.82	10047 ± 447.49
Spreadability (*g·cm/s; mean ± SD*)	12.92 ± 0.09	11.64 ± 0.60
Drug content *(%; mean ± SD*)	92.65 ± 0.36	96.58 ± 0.51

3.10 In-vitro Drug Release

The marketed gel released 94.87% by 300 min in the reported dataset. The invasomal gel showed 27.81% release at 60 min, 65.68% at 300 min and 92.44% at 480 min. The two formulations were not compared at a common final time point in the study table, so the values should be interpreted as the reported profiles rather than as a direct claim that one formulation is superior.

Table 12. Drug-release data of marketed gel and invasomal gel.

Time	Marketed ivermectin gel (%)	Optimized ivermectin invasomal gel (%)
0 min	0	0
60 min	37.64	27.81
120 min	51.25	39.05
180 min	64.58	50.59
240 min	82.19	59.46
300 min	94.87	65.68
360 min	-	76.03
420 min	-	84.31
480 min	-	92.44

3.11 Release kinetics

The study reports the following coefficients of determination (R^2) for marketed gel and optimized invasomal gel, respectively: zero-order 0.957 and 0.964; first-order 0.939 and 0.925; Higuchi 0.990 and 0.993; Hixson-Crowell 0.980 and 0.969; and Korsmeyer-Peppas 0.995 and 0.998. Although the study text identifies the Higuchi model as the best-fit model, the tabulated R^2 values are highest for Korsmeyer-Peppas for both formulations. This discrepancy must be resolved by checking the original calculations and model-fitting outputs before publication.

Table 13. Coefficients of determination (R^2) for release kinetic models.

Model	Marketed gel R^2	Invasomal gel R^2
Zero order	0.957	0.964
First order	0.939	0.925
Higuchi	0.990	0.993
Hixson-Crowell	0.980	0.969
Korsmeyer-Peppas	0.995	0.998

3.12 Short-term stability

At room temperature, the study reports measurements at days 1, 15 and 30. Colour remained yellow and clarity remained opaque. pH values were 6.77 ± 0.06, 6.75 ± 0.75 and 6.74 ± 0.05; viscosity values were 10,047 ± 447.49, 10,035 ± 432.26 and 10,030 ± 422.32; spreadability values were 11.64 ± 1.39, 11.63 ± 1.75 and 11.61 ± 0.7592; and %CDR values were 92.89 ± 0.95, 92.62 ± 0.75 and 91.96 ± 0.62, respectively.

Table 14. Stability analysis of ivermectin invasomal gel

Parameter	Day 1	Day 15	Day 30
Colour	Yellow	Yellow	Yellow
Clarity	Opaque	Opaque	Opaque
pH	6.77 ± 0.06	6.75 ± 0.75	6.74 ± 0.05
Viscosity	10047 ± 447.49	10035 ± 432.26	10030 ± 422.32
Spreadability	11.64 ± 1.39	11.63 ± 1.75	11.61 ± 0.7592
%CDR	92.89 ± 0.95	92.62 ± 0.75	91.96 ± 0.62

4. Discussion

This study describes the formulation and preliminary evaluation of an ivermectin-loaded invasomal gel using a quality-by-design-oriented approach. The preformulation findings indicated poor solubility in aqueous media and higher solubility in methanol and

ethanol, supporting the investigation of a vesicular delivery system for topical application.

The Plackett-Burman screening analysis identified response-specific effects of the formulation and process variables. Terpene concentration, stirring speed, and phospholipid type were significant factors for entrapment efficiency, whereas phospholipid concentration and stirring speed significantly influenced cumulative drug release. These findings highlight the importance of evaluating each critical quality attribute separately during formulation development.

The selected invasomal formulation exhibited an entrapment efficiency of 95.78% and drug content of 96.28 ± 0.75%. SEM observations indicated predominantly spherical vesicles, although some irregularities were present. Further characterization using vesicle-size distribution, polydispersity index, and zeta potential, where available, would provide additional information on the physicochemical properties of the formulation.

The gel evaluation showed that increasing HPMC K15M concentration increased viscosity and reduced spreadability. Formulation G1 was selected based on the reported evaluation results. The invasomal gel exhibited a pH of 6.77 ± 0.01 and drug content of 96.58 ± 0.51%. These findings describe the physicochemical characteristics of the prepared gel; however, skin tolerability and clinical suitability cannot be established from these measurements alone.

The in vitro release results showed lower cumulative release from the invasomal gel than from the marketed gel at matched early time points, followed by continued release up to 480 min. This profile is consistent with the possibility of prolonged drug release under the tested conditions. Nevertheless, differences in the total test duration and the absence of complete methodological details limit definitive comparative conclusions. Additional information on the release apparatus, membrane, receptor medium, temperature, agitation, sampling procedure, and sink conditions would strengthen the interpretation.

The kinetic analysis requires particular attention because the reported R^2 values were highest for the Korsmeyer-Peppas model for both formulations, whereas the original study identified the Higuchi model as providing the best fit. This discrepancy should be resolved using the original calculations and model-fitting outputs before a definitive release mechanism is proposed. Model selection should consider the assumptions and applicability of each model rather than relying solely on R^2.

The 30-day stability assessment showed relatively small changes in the reported physical and release parameters. However, the short observation period and the absence of a detailed stability protocol, packaging information, and predefined acceptance criteria limit the conclusions that can be drawn. Overall, the findings support further investigation of the ivermectin-loaded invasomal gel, including comprehensive physicochemical characterization, method validation, comparative permeation studies, and a more extensive stability assessment.

5. Conclusion

Ivermectin-loaded invasomes were incorporated into an HPMC K15M-based topical gel and evaluated for entrapment efficiency, drug content, physical characteristics, in vitro drug release, and short-term stability. The selected invasomal formulation exhibited an entrapment efficiency of 95.78% and drug content of 96.28 ± 0.75%. The prepared gel showed a pH of 6.77 ± 0.01 and drug content of 96.58 ± 0.51%, while cumulative drug release reached 92.44% at 480 min. The screening analysis identified different significant factors for entrapment efficiency and drug release. Although the preliminary findings support further development of the formulation, additional characterization, verification of the kinetic-model results, and comprehensive stability and skin-permeation studies are required before drawing conclusions regarding its delivery performance or therapeutic potential.

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