

Quality by Design-Based Formulation and Optimization of Ivermectin-Loaded Invasomal Topical Gel for Scalp Psoriasis Management

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ABSTRACT

Background: Scalp psoriasis, a chronic inflammatory skin disorder, identify by accelerated keratinocyte proliferation, skin patches and persistent inflammation, leading to debilitating symptoms. Conventional therapies often face limitations in efficacy, penetration, and side-effect profiles. This study investigates the optimized formulation of Ivermectin-loaded invasomal gel, using the drug's anti-inflammatory and anti-parasitic properties paired with the enhanced transdermal delivery of invasomes to target psoriatic lesions effectively.

Method: Ivermectin loaded invasomes were prepared using mechanical dispersion method.

Results: The optimized invasomal gel (IVIG2) exhibited excellent spreadability (facilitating ease of application) and ideal viscosity. In-vitro release studies demonstrated sustained and controlled drug delivery having $6.49 \pm 1.23\%$ cumulative drug release (CDR) over 12 hours, significantly surpassing conventional formulations. Progressive release kinetics showing 4.41% (1 hour) to 82.34% (11 hours), ensuring prolonged therapeutic action.

Conclusion: The QbD-driven Ivermectin invasomal gel offers a promising strategy for targeted scalp psoriasis management, combining enhanced permeation, sustained release, and minimized side effects.

1. Introduction

Scalp psoriasis, a chronic inflammatory skin condition, significantly impacts patients' quality of life due to persistent itching, scaling, and visible plaques.^[1] Traditional treatments, like topical corticosteroids, often provide only temporary relief and are associated with adverse effects such as skin atrophy and systemic absorption. This necessitates the

development of novel therapeutic strategies that offer enhanced efficacy, reduced side effects, and improved patient adherence.^[2]

Transdermal drug delivery offers several advantages over conventional oral administration, including avoidance of first-pass metabolism, sustained drug release, and improved patient compliance. However, the stratum corneum, the outermost

layer of the skin, presents a significant barrier to drug permeation. [3] To overcome this challenge, various nanocarriers have been explored, including invasomes, which enhance transdermal drug administration. [4-5] Topical gels are homogeneous semi-solid preparations used for the treatment and prevention of skin diseases.

Invasomes are composed of phosphatidylcholine, lysophosphatidylcholine, ethanol, and terpenes, which synergistically enhance drug penetration. [6-7] Phosphatidylcholine forms the invasomal bilayer, while lysophosphatidylcholine acts as an edge activator, increasing flexibility. [8] Ethanol and terpenes further boost drug penetration by disrupting the lipid structure of the stratum corneum. [9-10] This study investigates the potential of an Ivermectin-loaded gel for the treatment of scalp psoriasis, utilizing a Quality by Design (QbD) approach to screen and optimize formulation parameters and enhance therapeutic outcomes.

1. Material and Methods

1.1. Materials

Ivermectin was obtained as a gift sample from Kivi Lab, Por, India. Phospholipids (Soya-phosphatidylcholine and Dimyristoylphosphatidylcholine) and terpenes (D-limonene and fenchone) were purchased from Kivi Lab, Por, India. All other chemicals and solvents used were of analytical grade.

1.2. Screening and optimization of Invasomes

A Plackett-Burman design (Design Expert® Software version 13.0.1, Stat-Ease, Minneapolis, MN, USA) was employed to screen significant factors affecting the formulation. Factors studied included phospholipid concentration, terpene concentration, type of terpene, ethanol concentration, and sonication time. The responses evaluated were entrapment efficiency (% EE) and cumulative drug release (% CDR). Further, optimization was carried out by applying the 3-factor and 2-level Full Factorial Design (Design Expert® Software version 13.0.1). The phospholipid concentration and terpene concentration were independent variables whereas, % EE and % CDR are the dependent variables.

1.3. Preparation of Ivermectin-loaded Invasomes

Ivermectin (10 mg) was loaded in to invasomes by mechanical dispersion technique. Soyaphosphatidylcholine was added to ethanol and vortexed for 5 minutes. The drug and selected terpenes were dissolved in a phospholipid-ethanol solution, followed by vortexing, sonication, and gradual addition of phosphate buffer saline (PBS, pH 7.4) with syringe under constant vortexing. It was vortexed for additional 5 minutes to obtain final invasomal preparation.

1.4. Evaluation of Ivermectin-loaded Invasomes

1.4.1. Entrapment efficiency

Entrapment efficiency of ivermectin loaded invasomes formulation was determined using centrifugation method. [11-13] The entrapment efficiency of ivermectin in invasomes vesicle was determined by ultracentrifugation, 10mL of invasomes formulation were collect in test tube. The amount of drug not entrapped in the invasomes was determined by centrifuging at 3,000 rpm and collect the supernatant, the supernatant layer was separated, diluted with water suitably and drug concentration was determined at 245 nm using UV spectrophotometer. The entrapment efficiency was calculated using the following formula:

$$\%EE = \frac{(Ct - Cf)}{Ct} \times 100$$

Where, % EE = Entrapment Efficiency

Ct = Concentration of total drug

Cf = Concentration of free (unentrapped) drug

1.4.2. Scanning Electron Microscopy (SEM)

A scanning electron microscope was used to study the morphology of the optimum invasomes.

1.4.3. In vitro drug release study

Samples of loaded invasomes were kept into dialysis bags, sealed, and submerged in a dissolution medium. The USP Dissolve Test Apparatus, Type II, was used to drug release study at 37±0.5° and 100 rpm. 5 mL of sample were taken at each interval and replaced with brand-new buffers. Following suitable dilutions, spectrophotometric evaluation was performed on the samples.

1.5. Preparation of ivermectin loaded invasomal gel (IVIG) [14-16]

The optimized invasomal formulation was converted into a gel form to improve the transdermal delivery by incorporating it into carbopol 934 gel. Three preliminary batches (IVIG1, IVIG2, IVIG3) with varying Carbopol concentrations (0.5-1.5%). The gel base was prepared by suspending different concentrations of Carbopol 934 (1–2.5% w/v) in distilled water (Table 2). Propylene glycol, methyl paraben and propyl paraben are added for hydration. Then the mixture was incubated overnight for complete swelling of Carbopol. The ivermectin loaded invasomes were added to the gel base and neutralized with triethanolamine and transparent and clear gel was formed.

1.6. Evaluation parameter of ivermectin loaded invasomal gel (IVIG)

1.6.1. pH

The digital pH meter was used to determine the gel's pH. After agitating 1 g of invasomal gel in distilled water until a homogenous suspension was achieved, the pH of the mixture was determined.

1.6.2. Spreadability

To compress the sample to a consistent thickness, an excess of gel (2 g) was sandwiched between petri dishes, and 50 g of weight was placed on slides for 5 sec. The tin (sec) required to separate the two slides, was taken as a measure of spreadability.

It was calculated using the formula,

$$S = \frac{M \times L}{T}$$

Where, S = Spreadability

M = Weight tied to upper slide

L = Length of glass slide

T = Time taken in min

1.6.3. Viscosity

The gel's viscosity was measured with a Brookfield viscometer (LV) of the Di type. As spindle number four is

non-Newtonian in nature, it is utilized. Viscosity was measured at 0.3 rpm for a predetermined duration of 2 min.

1.6.4. Visual Observation

Color matters when it comes to patient compliance. We visually examined the prepared gels to ensure they were stable, uniform, and had a pleasing texture.

1.6.5. Stability study

The stability of invasomal gel was determined by identifying the change in drug entrapment efficiency. The vesicles were stored in room temperature. Then, the drug content of the vesicles was estimated every 15 days for 45 days.

2. Result and Discussion

2.1. Screening of ivermectin loaded invasomes

Table: 1 Parameters feed in Design Expert® to run Plackett Burman Design

Variable Code	Variables	Units	Levels	
			Low (-1)	High (+1)
Independent Variables: X -Inputs				
X1	Phospholipid Concentration	mg	100	200
X2	Terpene Concentration	mL	5	10
X3	Type of Terpenes	Categoric	Fenchone	Limonene
X4	Concentration of Ethanol	% v/v	3	4
X5	Sonication Time	Min	3	5
Dependent Variables: Y -Inputs				
Y1	Entrapment Efficiency (EE)	%		
Y2	Cumulative Drug Release (CDR)	nm		

Table: 2 Screening of significant risk factors using Placket Burman Design

Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Response 1	Response 2
A: PL Conc.	B: Terpene Conc.	C: Type of Terpene	D: Ethanol Conc.	E: Sonication Time	%EE	CDR
mg	ml	NA	%v/v	Min	%	nm
100	10	Fenchone	4	5	82.9	80
200	10	Limonene	3	3	96.7	89
200	5	Limonene	4	5	91.3	91
100	5	Fenchone	4	3	77.82	72
100	10	Limonene	4	3	84.5	75
200	10	Fenchone	4	5	92.1	95
100	5	Limonene	3	5	78.34	86
200	5	Limonene	4	3	87.77	90
200	5	Fenchone	3	5	84.2	96
200	10	Fenchone	3	3	88.15	85
100	10	Limonene	3	5	83.6	72
100	5	Fenchone	3	3	76.74	68

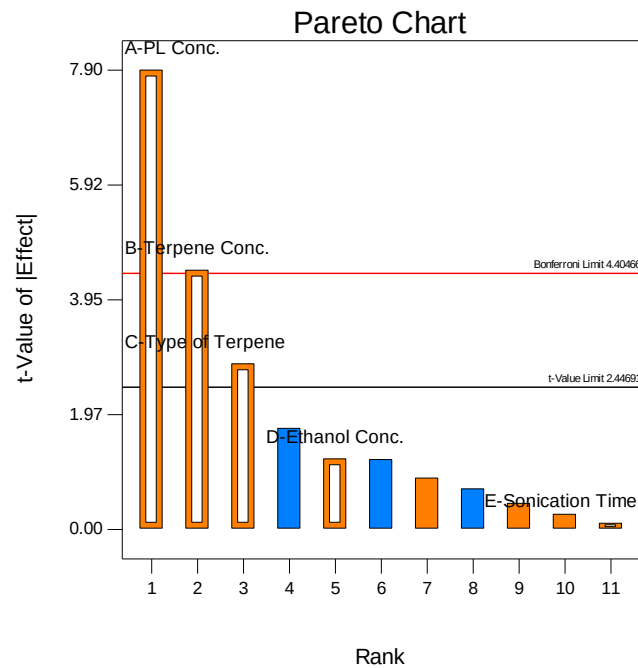


Figure: 1 Pareto chart of Y1 Response - EE (%)

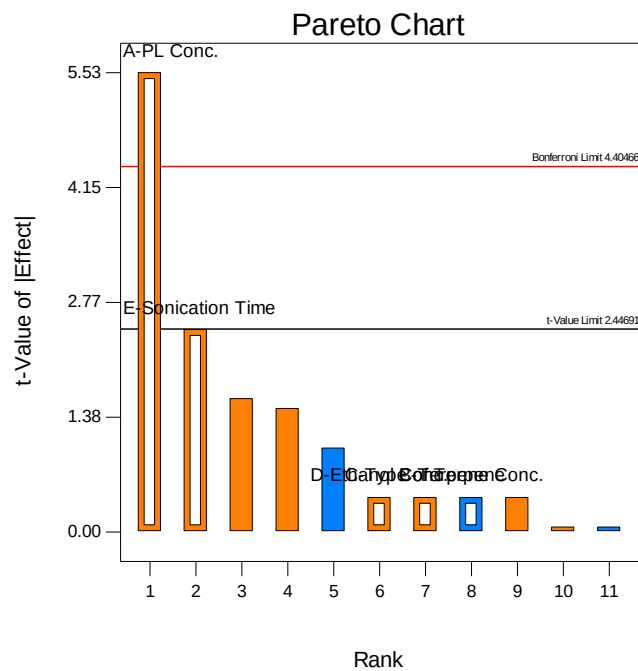


Figure: 2 Pareto chart of Y2 Response - CDR (nm)

2.2. Risk Assessment of Critical Quality Attributes (CQAs)

The Critical Quality Attributes (CQAs) are categorized in high, medium and low risk parameters based on knowledge space to check influence of formulation and process

parameters. Usually, high risk parameters are considered important for Design of Experiments (DoE) as they are having more effect than others and need to be in accepted multivariate ranges.

Table: 3 Risk Assessment to identify variables affecting drug product quality*[Red = High risk, Yellow = Medium risk, Green = No risk]*

Drug Product CQAs	PL Conc.	Terpene Conc.	Type of Terpene	Ethanol Conc.	Sonication Time
%EE	High	Low	Low	High	Medium
CDR	Medium	Low	Low	High	Medium

2.3. Optimization of ivermectin loaded invasomes

Table: 4 3² Full Factorial Design (FFD)-inputs

Variable Code	Variables	Units	Levels		
			Low (-1)	Medium (0)	High (+1)
	Independent Variables: X -Inputs				
X1	Phospholipid Concentration	mg	100	150	200
X2	Terpene Concentration	mL	5	7.5	10
	Dependent Variables: Y -Inputs				
Y1	Entrapment Efficiency (EE)	%			
Y2	Cumulative Drug Release (CDR)	nm			

Table: 5 3² Full Factorial Design (FFD)- output matrix with results

Factor 1	Factor 2	Response 1	Response 2
A: PL Conc.	B: Terpene Conc.	E.E	CDR
		5	%
200	5	96.27	93.78
100	5	83.29	78.13
150	5	90.56	89.24
150	10	90.27	88.53
100	10	82.88	80.92
100	7.5	83.88	82.78
200	7.5	96.2	92.51
200	10	93.42	90.47
150	7.5	89.78	86.31

2.4. Statistical analysis

2.4.1. Effect of independent variables on Entrapment Efficiency (%EE) -Y1 Response

The Analysis of Variance (ANOVA) disclose a statistical difference between the batches. From the result, it is evident

that phospholipid concentration (0.0004) and terpene concentration (0.1742) significantly affect the entrapment efficiency %EE which have been confirmed earlier by Pareto chart. When the higher EE is desired within selected factor range, factor X1 and X2 have positive coefficients which

indicate that increasing factor value increases the response concentration increases the %EE of invasomes.
which means that increasing phospholipid and terpene

Table: 6 ANOVA table for response surface Y1

Response 1: Entrapment Efficiency						
ANOVA for Response Surface Quadratic model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob > F	
Model	219.73	5	43.95	65.83	0.0029	significant
A-PL Conc.	214.08	1	214.08	320.70	0.0004	
B-Terpene Conc.	2.10	1	2.10	3.15	0.1742	
AB	1.49	1	1.49	2.23	0.2322	
A ²	1.55	1	1.55	2.32	0.2251	
B ²	0.51	1	0.51	0.76	0.4464	
Residual	2.00	3	0.67			
Cor Total	221.73	8				

The final equation in terms of coded factors; Entrapment Efficiency (EE)=+90.54+5.97* A-0.59* B-0.61* AB-0.88* A²-0.51* B²

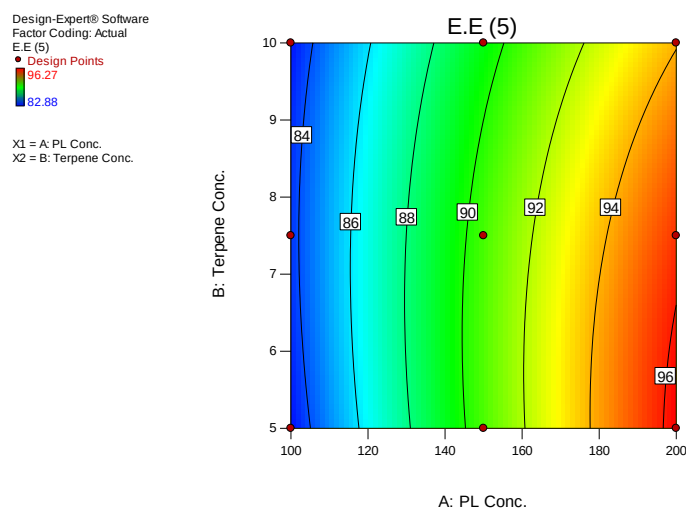


Figure: 3 Response surface plot of A: phospholipid concentration and B: terpene concentration on EE

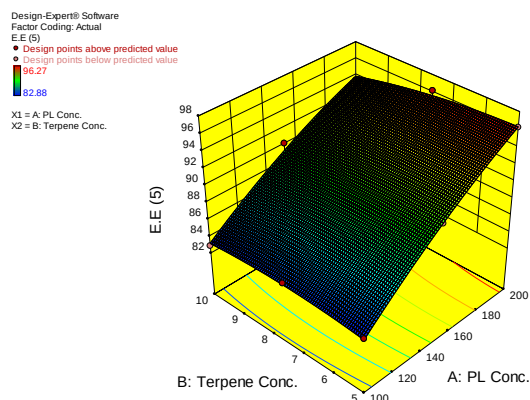


Figure: 4 3D surface plot of A phospholipid concentration and B terpene concentration on EE

2.4.2. Effect of independent variables on CDR -Y2

Response

Similar to R1 for R2, from the result, it is evident that phospholipid concentration (0.0053) and terpene

concentration (0.8134) significantly affects the CDR which also have been confirmed earlier by Pareto chart. When the concentration of phospholipid and terpenes increases, then desired CDR within selected range can be obtained.

Table: 7 ANOVA table for response surface Y2

Response 2: CDR						
ANOVA for Response Surface Quadratic model						
Analysis of variance table [Partial sum of squares - Type III]						
Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	218.25	5	43.65	11.49	0.0359	significant
A-PL Conc.	203.35	1	203.35	53.52	0.0053	
B-Terpene Conc.	0.25	1	0.25	0.066	0.8134	
AB	9.30	1	9.30	2.45	0.2156	
A ²	5.09	1	5.09	1.34	0.3309	
B ²	0.25	1	0.25	0.066	0.8134	
Residual	11.40	3	3.80			
Cor Total	229.64	8				

The final equation in terms of coded factors;
 $CDR = +88.26 + 5.82 \cdot A - 0.20 \cdot B - 1.53 \cdot AB - 1.60 \cdot A^2 - 0.36 \cdot B^2$

Design-Expert® Software
 Factor Coding: Actual
 CDR (%)
 • Design Points
 93.78
 78.13
 X1 = A: PL Conc.
 X2 = B: Terpene Conc.

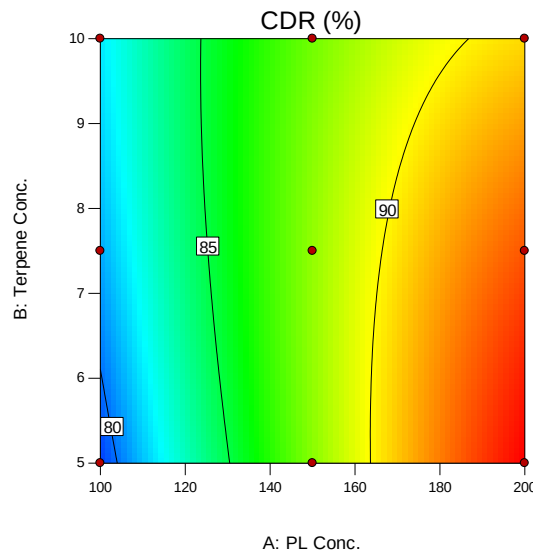


Figure: 5 Response surface plot of A: phospholipid concentration and B: terpene concentration on CDR

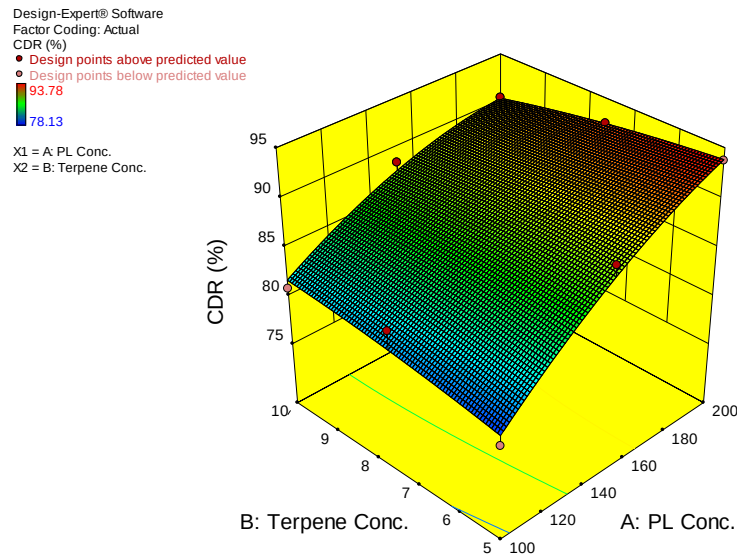


Figure: 6 3D surface plot of A phospholipid concentration and B terpene concentration on CDR

2.4.3. Validation

From polynomial equation generated for response, intensive grid and integrated examine was performed over experiment field using (Design Expert® Software version 13.0.1, Stat-Ease, Minneapolis, MN, USA). During independent variable

characterization study, impact of parameter phospholipid concentration (mg) and Terpene concentration (ml) were assessed. Design space shown in figure also called as overlay plot which is shaded region (greyish color) with yellow color indicates that region of successful operating ranges.

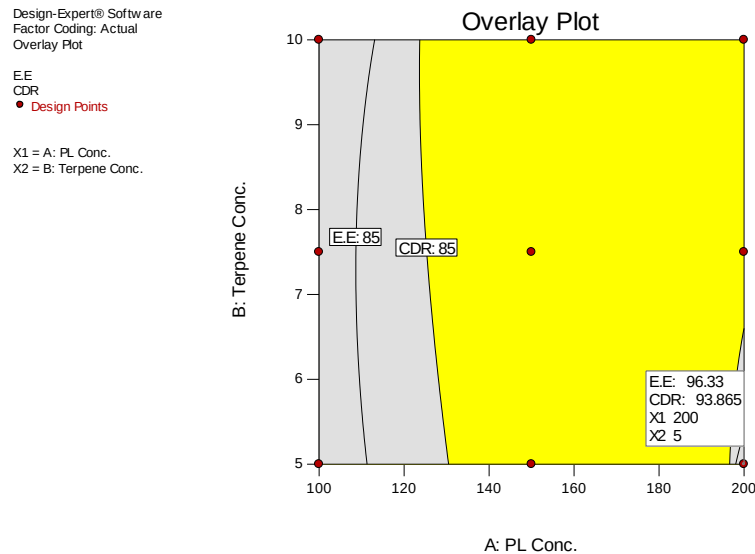


Figure: 7 Overlay plot-batch 1

Design-Expert® Software
Factor Coding: Actual
Overlay Plot

E.E
CDR
● Design Points

X1 = A: PL Conc.
X2 = B: Terpene Conc.

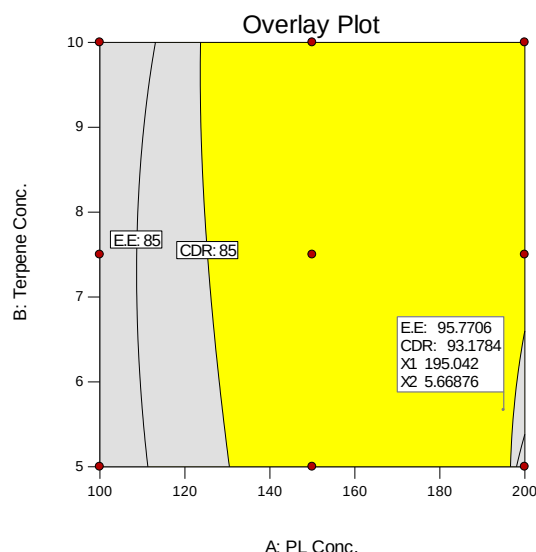


Figure: 8 Overlay plot-batch 2

2.4.4. Check point analysis of validation batches

Table: 8 Validation batch: Prediction response

Batch no.	PL C onc. (X1)	Terpene Conc. (X2)	Entrapment efficiency (Y1)	%CDR (Y2)
Batch1	200	5	96.33	93.83
Batch2	195.04	5.66	95.77	93.17

Table: 9 Validation batch: Actual response

Batch no.	PL Conc. (X1)	Terpene Conc. (X2)	Entrapment efficiency (Y1)	%CDR (Y2)
Batch1	200	5	94.55	91.61
Batch2	195.04	5.66	93.99	88.28

2.5. Selection of Optimized Formulation

Batch 1 was selected as validated optimized batch and further considered for formulating into Gel which was having % EE 94.55 %, % CDR 91.61.

2.5.1. Dose Calculation of Ivermectin Invasomes for Topical Gel

30 gm of marketed Ivermectin Gel ^[17-21] contains 0.1% Ivermectin as drug

So, for loading Ivermectin as drug

30 gm of gel = 30 gm Ivermectin i.e. 100% Ivermectin as Drug.

So, (?) gm gel 0.1 % Ivermectin

$30 \times 0.1 / 100 = 0.03 \text{ gm} = 0.3 \times 1000 = 30 \text{ mg}$ Ivermectin required.

So, marketed Ivermectin Lovastatin gel contains 30 mg Ivermectin as Drug.

Now, 100 mg Ivermectin Invasomes contains 4.3 mg of drug, so, for meeting the requirement of 30 mg i.e. 0.1% Invasomes gel we require 420 mg of Invasomes

4.3 mg drug is present in 100 mg Invasomes
 30 mg of drug requires (?) mg of Invasomes
 $30 \times 100 / 4.3 = 697.67$ mg Invasomes

≈ 700 mg of Invasomes

2.6. Preliminary trial batches of ivermectin loaded invasomal gels

Table: 10 The composition of different ivermectin loaded invasomal gels

Ingredient	IVIG1	IVIG2	IVIG3
Carbopol 934 (%w/v)	0.5	1.0	1.5
Propylene glycol(mL)	5	5	5
Methyl paraben	0.1	0.1	0.1
Propyl paraben	0.05	0.05	0.05
Triethanolamine(mL)	0.25	0.25	0.25
Water(mL)	100	100	100

Table: 11 Result table of evaluation of carbopol gel

Ingredient	Colour	Odour	pH (Mean $\pm$ S.D.) (n = 3)	Viscosity Spindleno:61 (Mean $\pm$ S.D.) (n = 3)	Spreadability (gm.cm/sec) (Mean $\pm$ S.D.) (n = 3)
IVIG1	Colourless	Odourless	6.2 $\pm$ 0.1	9578 $\pm$ 87	11.36 $\pm$ 0.67
IVIG2	Colourless	Odourless	6.5 $\pm$ 0.3	9067 $\pm$ 79	14.62 $\pm$ 1.15
IVIG3	Colourless	Odourless	6.1 $\pm$ 0.2	15678 $\pm$ 34	12.67 $\pm$ 1.97

The IVIG2 shows good spreadability and viscosity. Therefore, it was taken as optimized formula for further formulation of promising alternative invasomal loaded gel.

2.7. Characterization of optimized ivermectin loaded invasomal gel batch

2.7.1. Physical appearance and odour

All three formulated invasomal gel was homogenous, smooth in texture, transparent and odourless.

2.7.2. Measurement of pH

pH of all the invasomal gel formulations was found to be that 6.5 $\pm$ 0.3 that suits pH of skin indicating skin compatibility especially for scalp.

2.7.3. Viscosity determination

The viscosity of invasomal gel formulation was found 10252 $\pm$ 779.31cps.

2.7.4. Spreadability

The value of spreadability of ivermectin loaded invasomal gel was found to be 14.62 $\pm$ 1.15 gm cm/sec which indicates good spreadability of formulation.

2.7.5. Estimation of Drug content

% Drug content of ivermectin loaded invasomal gel was found to be 95.45 $\pm$ 0.46 which indicate good amount of drug in the formulation.

Table 12: Result of ivermectin loaded-invasomal gel

Parameter	Results
Clarity	Transparent
Odour	Odourless
pH (Mean $\pm$ S.D.) (n = 3)	6.5 $\pm$ 0.3
Spreadability (Mean $\pm$ S.D.) (n = 3)	14.62 $\pm$ 1.15
Viscosity (Mean $\pm$ S.D.) (n = 3)	9067 $\pm$ 79
% Drug content	95.45 $\pm$ 0.46

(Mean $\pm$ S.D.) (n = 3)	
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2.8. In-vitro release study

Table 13: In-vitro drug release data-at per hour interval

Time (hrs)	% Drug Release
0	0
1	4.41 $\pm$ 1.15
2	8.72 $\pm$ 1.34
3	14.34 $\pm$ 1.26
4	26.63 $\pm$ 1.58
5	36.35 $\pm$ 1.45
6	45.68 $\pm$ 1.64
7	51.23 $\pm$ 1.26
8	57.44 $\pm$ 1.67
9	65.22 $\pm$ 1.78
10	73.68 $\pm$ 1.45
11	82.34 $\pm$ 1.64
12	96.49 $\pm$ 1.23

The in-vitro release study of the optimized invasomal gel formulation showed a sustained release profile over 12 hours, with 96.49 $\pm$ 1.23% cumulative drug release at the end of the study period. The release kinetics demonstrated a progressive increase from 4.41% at 1 hour to 82.34% at 11 hours,

indicating a controlled and prolonged drug release suitable for topical application.

2.9. Stability Study

Table 14: Stability study of ivermectin-loaded invasomal gel at room temperature for 1 month

Parameter	Room Temperature		
	Time (Days)		
	0 day	15 days	30 days
Spreadability	6.5	6.5	6.5
Viscosity	9067	9054	9047
% Drug content	95.45	95.35	95.24

The stability study conducted at room temperature over 30 days showed no significant changes in the formulation's spreadability, viscosity, and drug content, indicating good stability of the invasomal gel formulation.

3. Conclusion

The developed Ivermectin-loaded invasomal gel formulation shows promising potential for the treatment of scalp psoriasis. The optimized formulation, created using a Quality by Design (QbD) approach, demonstrated high entrapment efficiency, sustained drug release, and good stability. The optimized invasomal gel (IVIG2) demonstrates excellent spreadability and ideal viscosity, facilitating ease of application. In-vitro release studies show sustained and controlled drug delivery, with 6.49 $\pm$ 1.23% cumulative drug release over 12 hours, significantly outperforming conventional formulations. The

progressive release kinetics range from 4.41% at 1 hour to 82.34% at 11 hours, ensuring prolonged therapeutic action. IVIG2 exhibits superior characteristics compared to traditional formulations, including excellent spreadability for uniform distribution, ideal viscosity for improved retention, and a controlled release profile maintaining therapeutic levels over an extended period. The gradual release pattern suggests extended therapeutic efficacy, potentially reducing dosing frequency and improving patient compliance. The consistent release profile indicates good formulation stability, crucial for maintaining drug potency during storage and application. The combination of Ivermectin's anti-inflammatory and anti-parasitic properties with the enhanced transdermal delivery capabilities of invasomes addresses limitations of traditional therapies while potentially reducing side effects associated with systemic administration. While these results are

promising, further in-vivo studies are necessary to fully evaluate the therapeutic potential and clinical efficacy of this

novel formulation in treating scalp psoriasis.

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