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Formulation, Optimization and Characterization of Ornidazole Nanostructured Lipid Carrier Gel for Topical Delivery

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ABSTRACT

The study aimed to formulate, optimize and characterize ornidazole NLCs using glyceryl monostearate (GMS), oleic acid and Tween 80 and to incorporate the optimized dispersion into a topical gel. NLCs were prepared by hot homogenization followed by ultrasonication. A three-factor, three-level Box–Behnken design comprising 17 runs was used to investigate GMS concentration, Tween 80 concentration and homogenization time. Particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, drug content and in vitro drug release were evaluated. FTIR and SEM were used for physicochemical and morphological characterization. The NLC dispersion was incorporated into a Carbopol 934-based gel and evaluated for pH, spreadability, viscosity and stability. The optimized formulation (F13) had a particle size of 222.8 nm, PDI 0.289, zeta potential −26.7 mV, entrapment efficiency 83.6% and drug content 91.0%. The optimized formulation showed sustained drug release, with 82.3% cumulative drug release reported at 12 h in the response-optimization section. The optimized gel showed pH 5.73 ± 0.03, spreadability 6.28 ± 0.21 g·cm/s and viscosity 5080 ± 78 cP. FTIR analysis showed retention of characteristic ornidazole peaks without major drug–excipient interaction. The optimized formulation remained physically stable during the reported 60-day study. The study demonstrates the feasibility of developing an ornidazole-loaded NLC topical gel using a Box–Behnken design. The optimized formulation exhibited nanoscale particle size, acceptable PDI, measurable negative zeta potential, good entrapment and sustained drug release, supporting further investigation as a topical delivery system.

Keywords: Ornidazole; nanostructured lipid carriers; topical gel; glyceryl monostearate; oleic acid; Tween 80; Box–Behnken design; sustained release.

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INTRODUCTION

Topical drug delivery offers the possibility of delivering an active pharmaceutical ingredient directly to the site of application while potentially reducing unwanted systemic exposure. However, conventional topical dosage forms may show limited drug residence, variable release and inadequate penetration into the desired skin layers. Lipid-based nanocarriers have therefore been investigated as systems capable of modifying drug release and improving contact between the formulation and the skin.

Nanostructured lipid carriers (NLCs) are lipid nanoparticles composed of a solid lipid combined with a liquid lipid. The incorporation of the liquid lipid produces a less ordered lipid matrix than a conventional solid lipid nanoparticle and can provide additional space for drug incorporation. NLCs have been investigated for topical, transdermal and other routes because of their small particle size, lipidic composition, potential for controlled release and ability to incorporate different classes of drugs. The thesis describes NLCs as a second-generation lipid nanocarrier developed to address limitations associated with solid lipid nanoparticles.[1-5]

Ornidazole is a 5-nitroimidazole antimicrobial with antiprotozoal and antibacterial activity. According to the thesis, the nitro group is reduced within susceptible anaerobic microorganisms and protozoa to reactive intermediates that damage microbial DNA and interfere with nucleic-acid synthesis. The drug is used against infections associated with susceptible anaerobic bacteria and protozoa. The development of a topical lipid-based system was therefore investigated as a means of providing localized and sustained drug delivery.

Quality by Design and Design of Experiments (DoE) approaches can be used to evaluate the effect of formulation and process variables systematically. In the present work, Box–Behnken design (BBD) was selected as a three-factor, three-level response-surface design. GMS, Tween 80 and homogenization time were selected as independent variables, while particle size, entrapment efficiency and cumulative drug release were used as responses.

The objective of the present study was to formulate ornidazole-loaded NLCs, optimize the formulation using BBD, characterize the optimized NLC and incorporate it into a topical gel for physicochemical evaluation and stability assessment.

MATERIALS AND METHOD

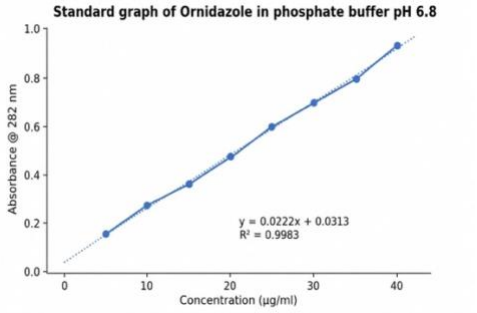
Materials

Ornidazole was used as the active pharmaceutical ingredient. Glyceryl monostearate (GMS) was used as the solid lipid, oleic acid as the liquid lipid and Tween 80 as surfactant. Carbopol 934 and glycerol were used for preparation of the topical gel. Purified/double-distilled water and phosphate

buffer pH 6.8 were used as aqueous media according to the experimental procedures described in the thesis.

Preliminary compatibility and analytical studies

For quantitative analysis, ornidazole was analyzed by UV spectrophotometry in phosphate buffer pH 6.8. The wavelength maximum was reported as 282 nm. The calibration curve was reported as $y = 0.0222x + 0.0313$ with $R^2 = 0.9983$.



Preparation of ornidazole NLC

Ornidazole-loaded NLCs were prepared by hot homogenization followed by ultrasonication. GMS and oleic acid were used as the solid and liquid lipid components, respectively, and Tween 80 was used as the surfactant. The thesis reports optimization of homogenization and ultrasonication times at 10 min and 20 min, respectively. The resulting NLC dispersion was characterized for particle size, PDI, zeta potential, drug content, entrapment efficiency and in vitro drug release.

Preparation of NLC-loaded topical gel

Carbopol 934 was dispersed at 2% w/v in double-distilled water containing glycerol (10%). NLC dispersion equivalent to 20% was incorporated into the hydrogel and mixed using a high-speed stirrer at approximately 100 rpm for 5 min. The prepared NLC-loaded gels were stored at room temperature for the reported stability period.

Box–Behnken experimental design

A three-factor, three-level BBD was generated using Design-Expert software. Seventeen experimental runs were performed, including replicated centre points. The independent variables were GMS (A), Tween 80 (B) and homogenization time (C). Particle size (R1), entrapment efficiency (R2) and cumulative drug release (R3) were selected as dependent responses. The factor ranges reported in the thesis are presented in Table 1.

Table 1. Independent variables used in the Box–Behnken design.

Factor	Code	Lower level	Upper level
Glyceryl monostearate	A	600 mg	800 mg
Tween 80	B	300 mg	400 mg
Homogenization time	C	15 min	20 min

Characterization of NLC

Particle size and PDI were determined by dynamic light scattering. Zeta potential was measured using a Malvern zeta sizer. Entrapment efficiency was determined by separating the aqueous phase from the NLC dispersion and quantifying the unentrapped drug. Drug content was determined by the analytical UV method. Morphology was examined by scanning electron microscopy (SEM).

In vitro drug release was studied using a Franz diffusion method as described in the thesis. Release data were fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models. The thesis reports R^2 values of 0.9464, 0.9974, 0.9803 and 0.9879, respectively, for the optimized formulation. The reported Korsmeyer–Peppas exponent was 0.7356.

Evaluation of NLC topical gel

The gel formulations were evaluated for appearance/homogeneity, pH, spreadability and viscosity. pH was measured after dispersion of the gel in distilled water. Spreadability was measured by the glass-slide method using $S = M \times L/T$. Viscosity was determined using a Brookfield viscometer at 25 ± 1°C with spindle 63 at 50 rpm after equilibration.

Stability study

The optimized formulation was stored in tightly closed glass containers and evaluated at 0, 30 and 60 days. The reported parameters included physical appearance, phase separation, drug content and cumulative drug release.

Evaluation and Characterization

The prepared formulation were evaluated for pre-formulation, post-formulation and in-vitro characteristics.

Pre-formulation Studies

Ornidazole was evaluated for melting point, drug-excipient compatibility was assessed by FT-IR spectroscopy.

Post-formulation Studies

Drug was evaluated for Particle size analysis shall be carried out using Malvern zeta sizer, Determination of zeta potential by Malvern zeta sizer, Loading efficiency, Drug entrapment efficiency, Characterization by SEM, Determination of pH, spreadability and viscosity of gels.

RESULTS AND DISCUSSION

Pre-formulation Studies

The melting point of Ornidazole was determined by the Thiele's tube method. The observed melting point was 85°C, with an experimental range of 80-85°C

Drug–excipient compatibility

An FT-IR spectroscopy study has been carried out separately to check the compatibility between the drug (Ornidazole) and the lipids (Glyceryl monostearate and Oleic acid) and surfactant (Tween 80) used for the preparation of Nanostructured lipid carriers. The FT-IR was performed for the drug, the lipids, the surfactant, and a physical mixture of the drug and excipients. The spectra obtained from the FT-IR spectroscopy study at wave numbers from 4000 to 400 cm^{-1} are shown below.

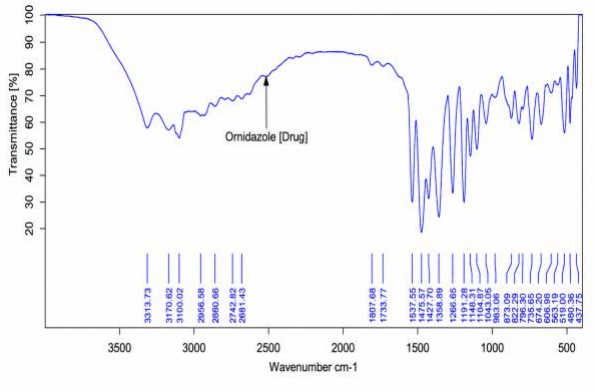


Figure 1: FTIR Spectrum of ornidazole API

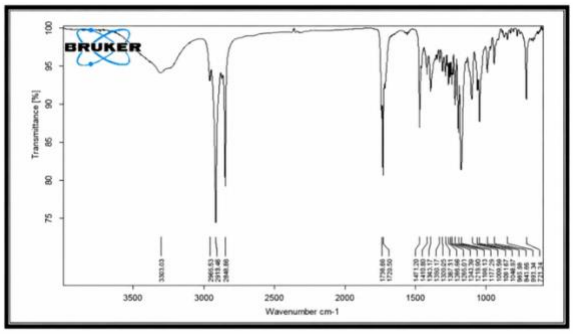


Figure 2: FTIR Spectrum of Glyceryl monostearate (GMS)

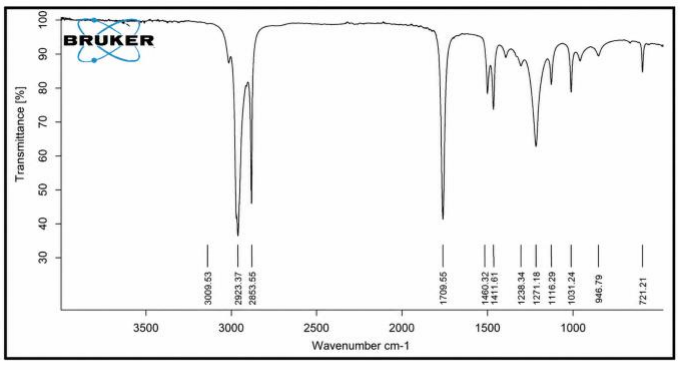


Figure: FT-IR spectrum of Oleic acid

Figure 3: FTIR Spectrum of Oleic acid

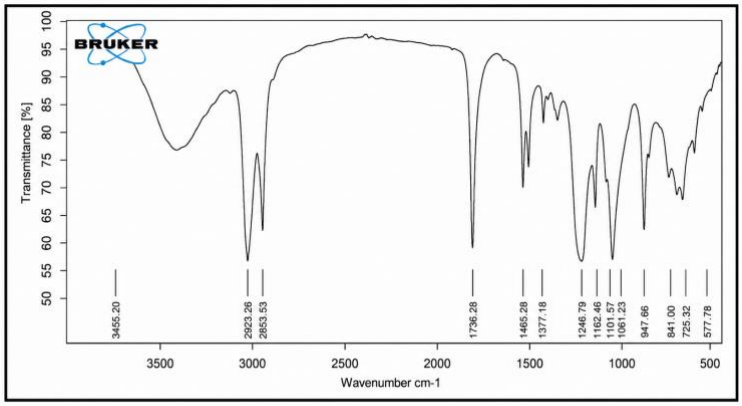


Figure: FTIR spectrum of Tween 80

Figure 4: FTIR Spectrum of Tween 80

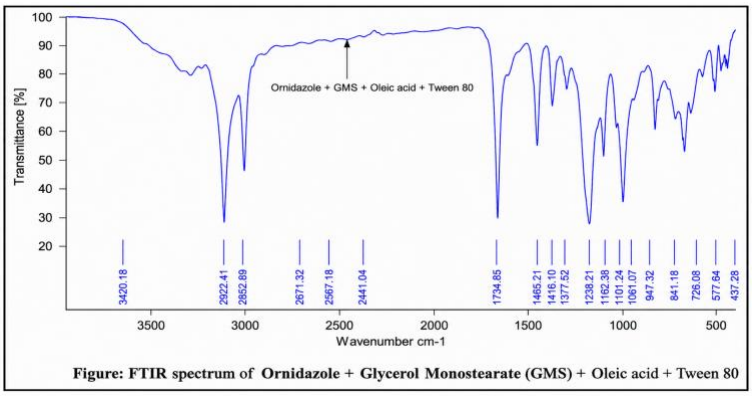


Figure: FTIR spectrum of Ornidazole + Glycerol Monostearate (GMS) + Oleic acid + Tween 80

Figure 5: FTIR Spectrum of Ornidazole-NLC (Ornidazole + GMS + Oleic acid + Tween 80)

Table 2: Interpretation of FTIR spectrum of above figures

SL. No.	Name of Compound	Functional Group	Observed Peaks(cm^{-1})
1	Ornidazole API	C–H	2957
		NO_2 asymmetric	1538
		Imidazole C=N	1476
		NO_2 symmetric	1359
		C–Cl	735
2	Glyceryl Monostearate	O–H	3303
		C–H	2966, 2913
		C=O	1758, 1721
3	Oleic Acid	C=O	1710
		C–H	2923, 2854
4	Tween 80	C=O	1736
		O–H	3455
		C–O–C	1101, 1061
5	Ornidazole–NLC (Physical Mixture)	C–H	2922
		C=O	1735
		O–H	3420
		Imidazole C=N (retained)	1465

Formulation optimization

The BBD allowed simultaneous evaluation of the effects of GMS concentration, Tween 80 concentration and homogenization time. The thesis identifies F13 as the optimized formulation. The optimized composition was 100 mg ornidazole, 800 mg GMS, 350 mg Tween 80 and 15 min homogenization time.

Table 3: Composition of the optimized F13 formulation.

Formulation	Ornidazole	GMS	Tween 80	Homogenization
F13 (optimized)	100 mg	800 mg	350 mg	15 min

Optimized NLC characteristics

Table 4: Key characteristics of optimized ornidazole NLC (F13).

Parameter	Observed value
Particle size	222.8 nm
PDI	0.289
Zeta potential	−26.7 mV
Entrapment efficiency	83.6%
Drug content	91.0%
12-h cumulative drug release	82.3% (response-optimization section)

Statistical model performance

For entrapment efficiency, the thesis reports a significant 2FI model with $F = 84.69$ and $p < 0.0001$, $R^2 = 0.9807$, adjusted $R^2 = 0.9691$ and predicted $R^2 = 0.9755$. GMS, Tween 80 and homogenization time were reported as significant main effects, and the AB, AC and BC interaction terms were also significant.

For cumulative drug release, the thesis reports a significant quadratic model with $F = 61.93$ and $p < 0.0001$, $R^2 = 0.9876$, adjusted $R^2 = 0.9716$ and predicted $R^2 = 0.9776$. GMS showed a negative effect on release, whereas Tween 80 and homogenization time showed positive effects. The AB interaction was significant, while AC and BC were reported as borderline non-significant. Significant quadratic terms indicated non-linear effects of the three factors.

The thesis also describes the particle-size response as being influenced by the formulation variables, with response-surface, contour and one-factor plots used to visualize the design space.

Effect of independent variables on Particle size

The 2FI model for **particle size** was statistically significant ($F = 1183.70$, $p = <0.0001$), indicating that the selected variables meaningfully influenced the outcome.

Fit Summary

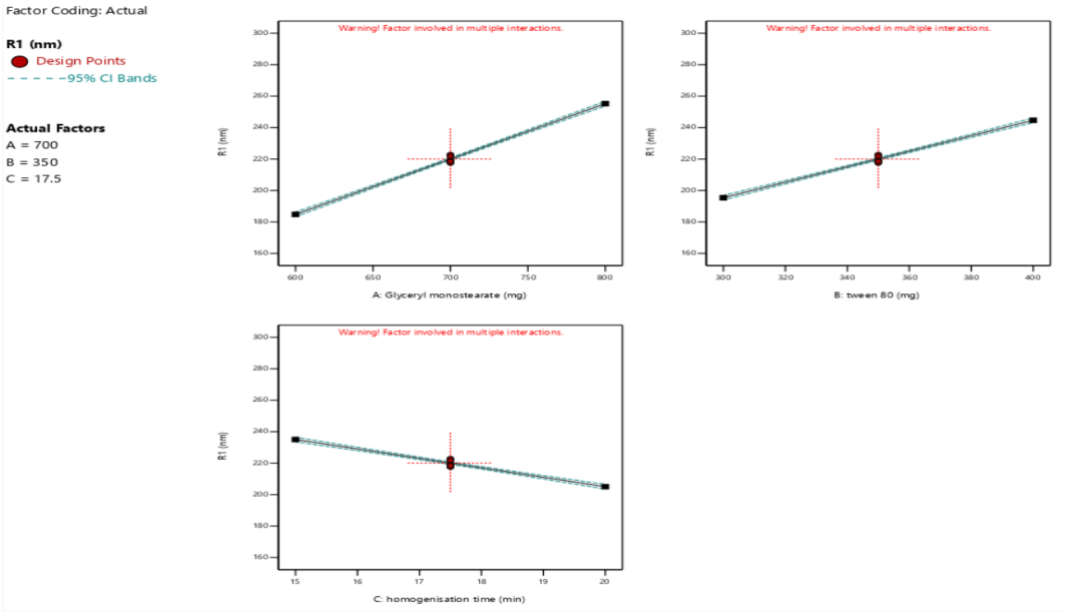
Response 1: R1

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
Linear	< 0.0001	0.0184	0.9647	0.9410	
2FI	**< 0.0001**	**0.9818**	**0.9978**	**0.9975**	**Suggested**
Quadratic	0.9758	0.8678	0.9969	0.9949	
Cubic	0.8678		0.9954		**Aliased**

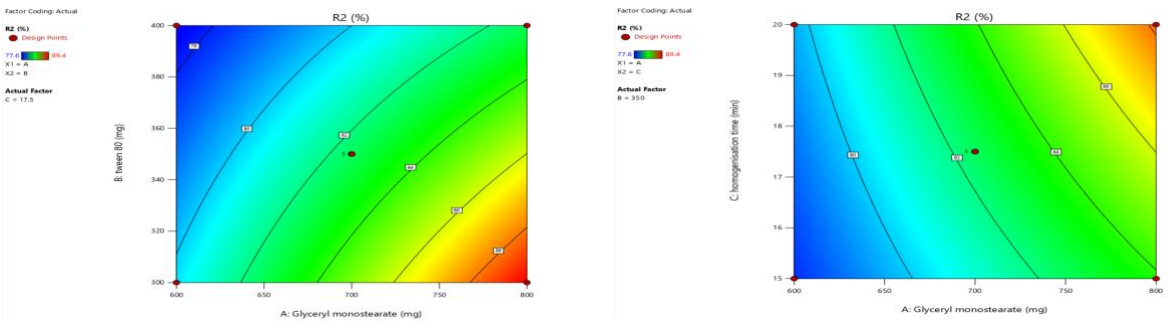
The resulting polynomial Equation can be used to illustrate the total impact of independent variables on particle size:

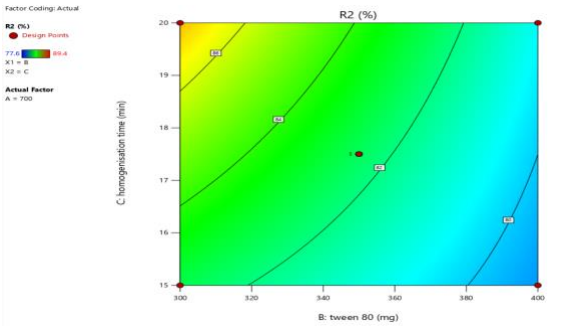
Particle size (R1) = **341.30 + 0.177A − 1.419B − 10.48C + 0.00146AB − 0.0191AC + 0.051BC**

Model Graphs obtained from Box-Behnken Design

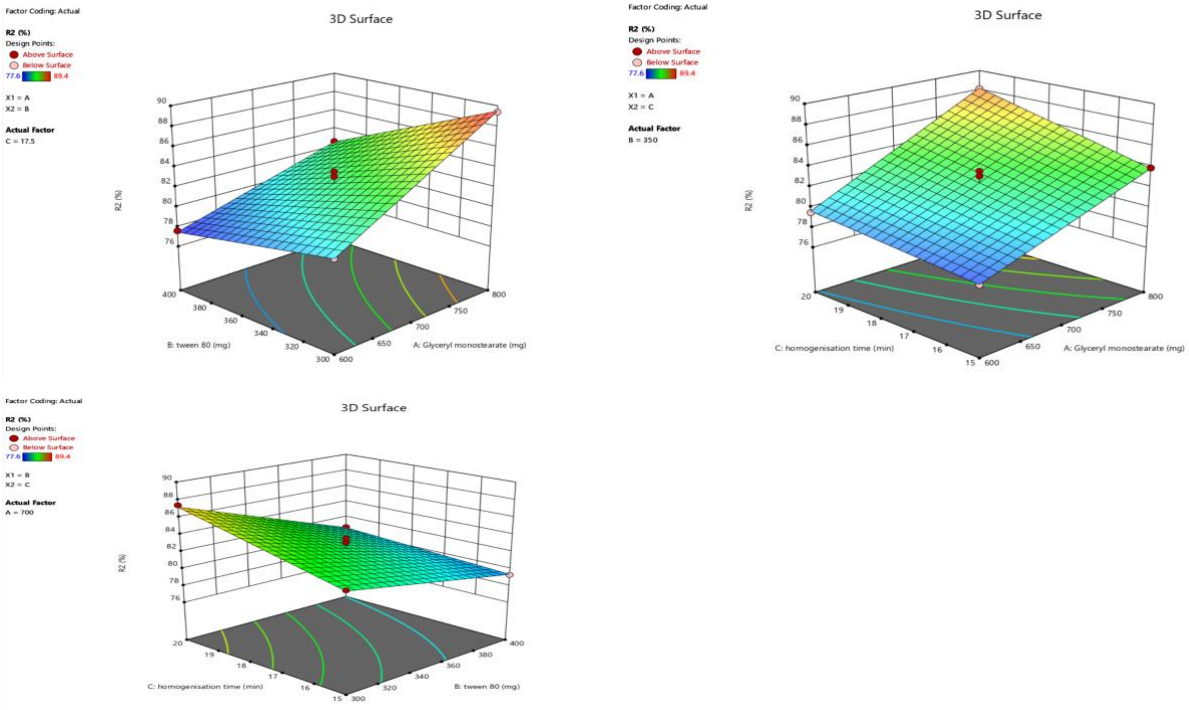


One factor plot: Effect of [a] GMS, [b] Tween 80 and [c] Homogenization time on particle size.





Contour surface plots on entrapment efficiency of THC-NLCs [a] GMS & Tween 80, [b] GMS & Homogenization time and [c] Tween 80 & Homogenization time.



3D-Response surface plots on entrapment efficiency of THC-NLCs [a] GMS & Tween 80, [b] GMS & Homogenization time, and [c] Tween 80 & Homogenization time

<u>Effect of independent variables on Percentage CDR</u>

The Quadratic model for percentage CDR was statistically significant (F =235.00, p = <0.0001), indicating that the selected variables meaningfully influenced the outcome.

Fit Summary

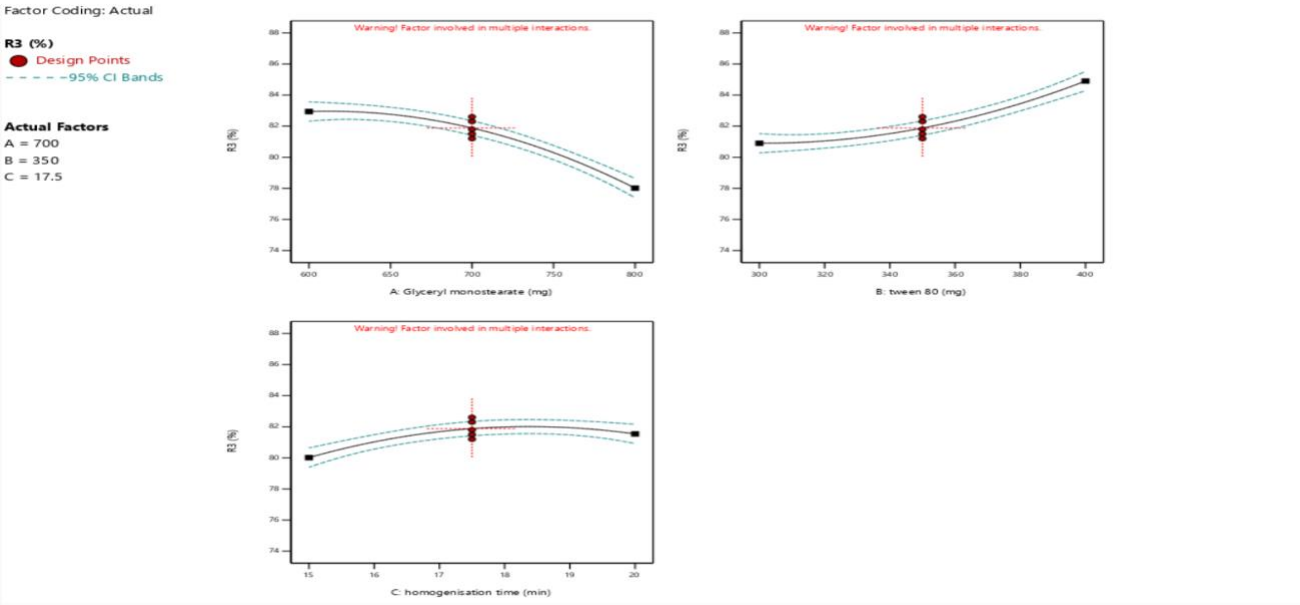
Response 3: R3

	Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
	Linear	< 0.0001	0.0377	0.7464	0.6023	
	2FI	0.6331	0.0265	0.7202	0.2413	
	Quadratic	**0.0002**	**0.9946**	**0.9716**	**0.9776**	**Suggested**
	Cubic	0.9946		0.9512		**Aliased**

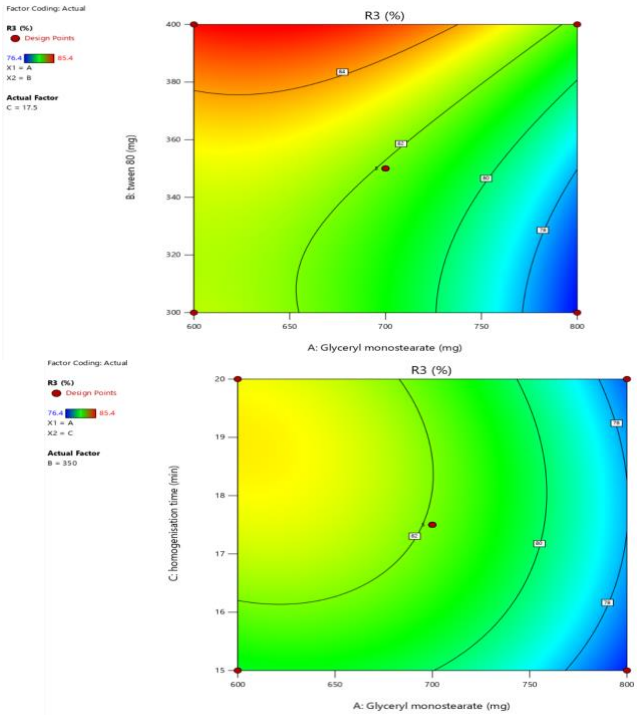
The resulting polynomial Equation (3), can be used to illustrate the total impact of independent variables on %CDR:

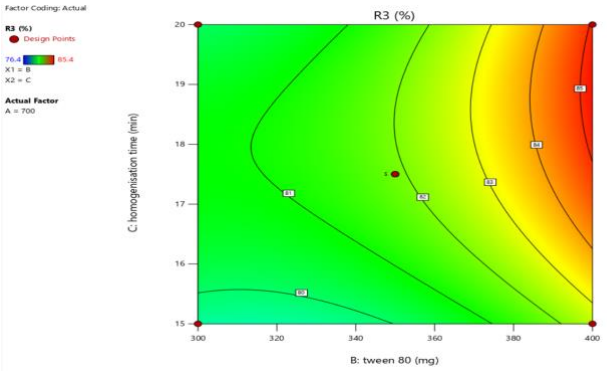
%CDR = 37.76 + 0.163A − 0.400B + 6.409C + 0.00012AB − 0.0019AC + 0.004BC − 0.00014A² + 0.00041B² − 0.1764C²

Model Graphs obtained from Box-Behnken Design

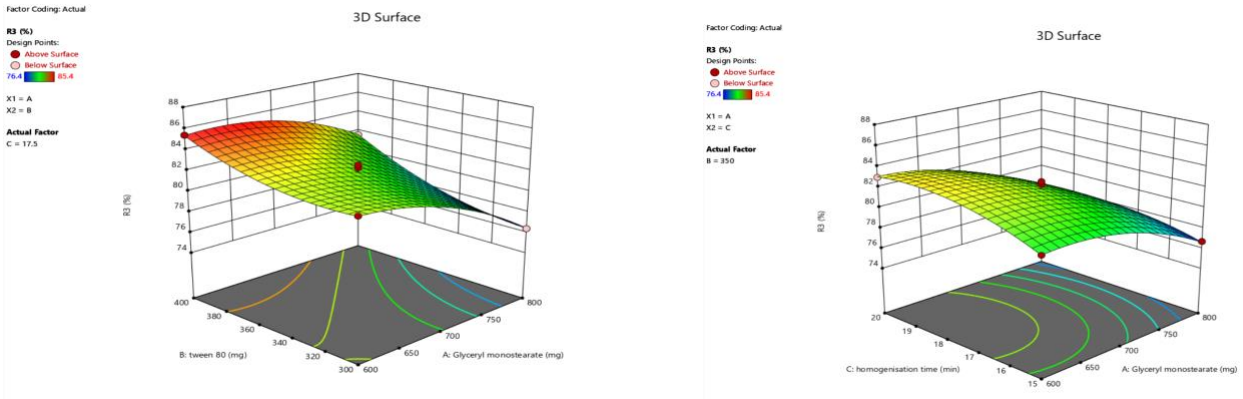


One factor plot: Effect of [a] GMS, [b] Tween 80 and [c] Homogenization time on Percentage CDR.





Contour surface plots on percentage CDR of THC-NLCs [a] GMS & Tween 80, [b] GMS & Homogenization time and [c] Tween 80 & Homogenization Time



3D-Response surface plots on percentage CDR of THC-NLCs

[a] GMS& Tween 80, [b] GMS & Homogenization time and [c] Tween 80 & Homogenization Time

Particle Size and PDI

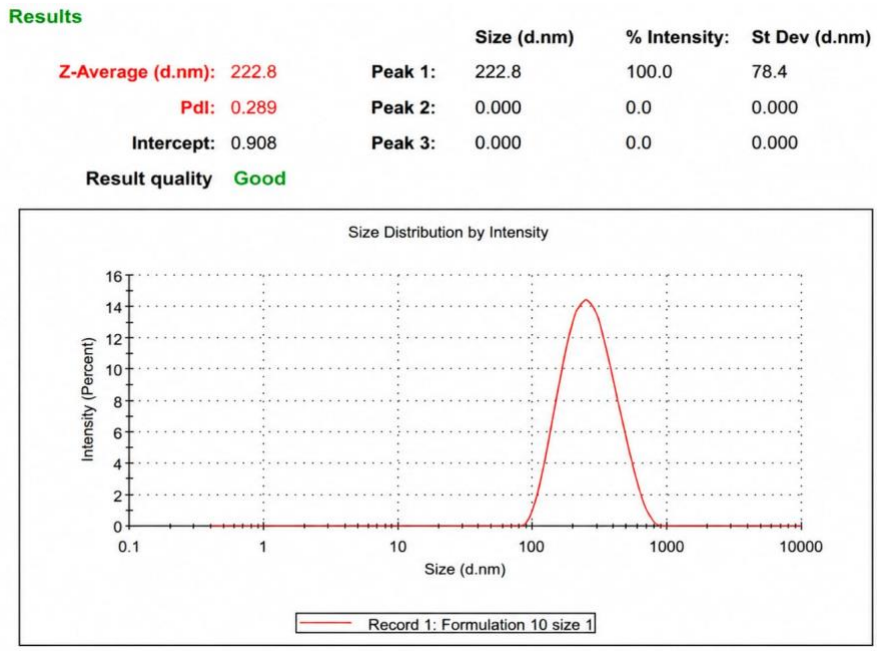


Figure 6: Particle size of Optimized Formulation

Zeta potential measurement

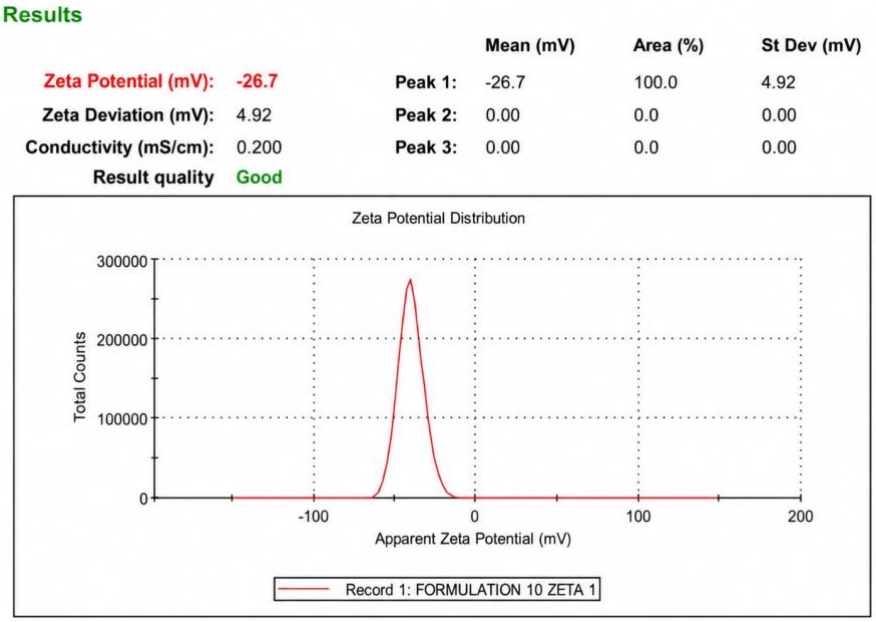


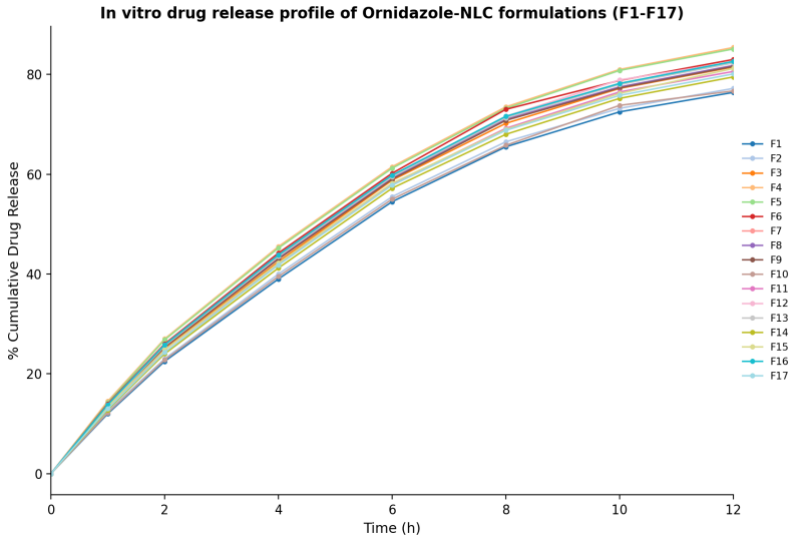
Figure 7: Zeta Potential of Optimized Formulation

In vitro Drug release studies

Table 5: Data of drug release study of 17 formulations (% CDR)

Formulation	0 h	1 h	2 h	4 h	6 h	8 h	10 h	12 h
F1	0.0	12.0	22.5	39.0	54.5	65.5	72.5	76.4
F2	0.0	12.5	23.0	40.0	55.5	66.5	73.2	77.2
F3	0.0	13.5	25.0	42.5	58.8	70.2	77.2	81.5
F4	0.0	14.5	27.0	45.5	61.5	73.5	81.0	85.4
F5	0.0	14.2	26.8	45.2	61.2	73.2	80.8	85.1

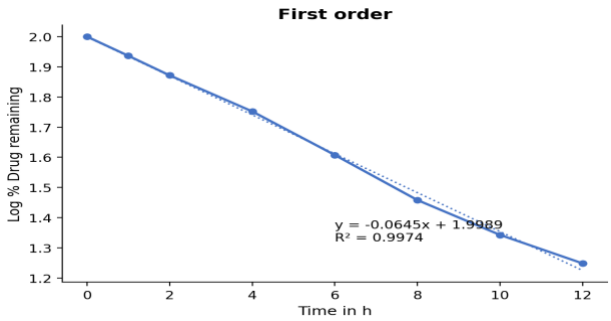
F6	0.0	14.0	26.0	44.2	60.2	73.0	78.8	83.0
F7	0.0	13.8	25.8	43.8	59.8	71.6	78.2	82.6
F8	0.0	13.6	25.5	43.2	59.2	71.0	77.5	81.8
F9	0.0	13.5	25.3	43.0	59.0	70.8	77.3	81.6
F10	0.0	12.2	22.8	39.5	55.0	65.8	73.8	76.7
F11	0.0	13.2	24.8	42.0	58.0	69.2	76.5	80.6
F12	0.0	13.8	25.8	43.8	59.8	71.6	78.9	82.5
F13	0.0	13.6	25.6	43.5	59.5	71.3	78.0	82.3
F14	0.0	12.8	24.0	41.2	57.2	68.0	75.2	79.5
F15	0.0	13.4	24.8	42.2	58.2	69.0	76.2	81.2
F16	0.0	13.8	25.8	43.8	59.8	71.6	78.2	82.6
F17	0.0	13.0	24.3	41.8	57.8	68.8	75.8	80.1



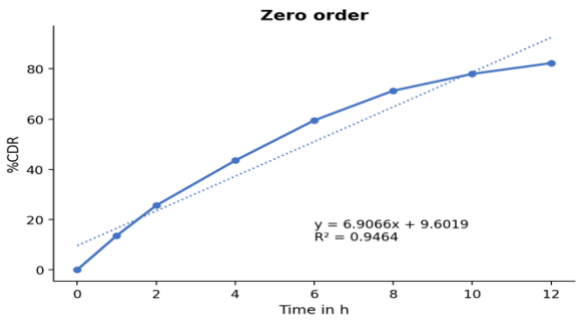
The optimized particle size of 222.8 nm was within the nanoscale range described in the study. The PDI of 0.289 indicates a relatively narrow particle-size distribution. The zeta potential was −26.7 mV; the thesis associates the negative surface charge with formulation stability. Entrapment efficiency was 83.6%, indicating incorporation of a substantial fraction of the drug into the lipid carrier. Drug content was 91.0%.

In vitro release and release kinetics

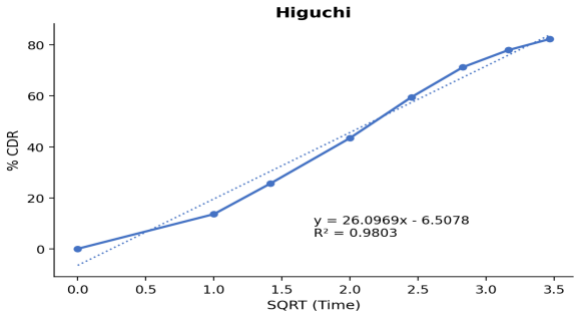
The NLC dispersion of optimized formulation F13 sustained-release phase. The thesis attributes The release data was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations F13 could be best expressed by First-order equation, as the plots showed the highest linearity (R^2: 0.9974) than zero-order release kinetics (R^2: 9464).The n values obtained from the Korsmeyer–Peppas plots ranged from 0.0.7356, indicating that the mechanism of drug release from formulations F13 was anomalous (non-Fickian) diffusion.



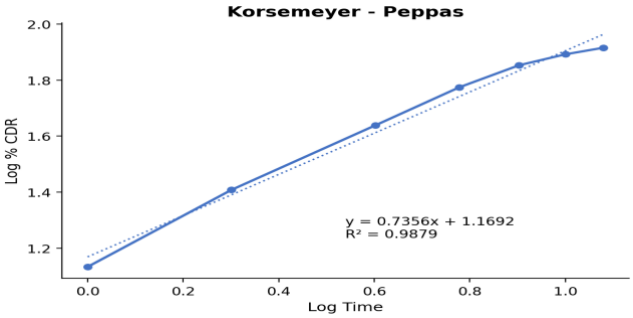
Zero-order kinetics plot



First-order kinetics plot



Higuchi plot



Korsmeyers Peppas model

Table 6: Release-kinetic parameters reported for optimized F13.

Model	Regression equation	R^2
Zero order	y = 6.9066x + 9.6019	0.9464
First order	y = −0.0645x + 1.9989	0.9974
Higuchi	y = 26.0969x − 6.5078	0.9803
Korsmeyer–Peppas	y = 0.7356x + 1.1692	0.9879

Topical gel evaluation

Table 7: Physicochemical properties of the ornidazole NLC topical gels.

Formulation	pH	Spreadability (g·cm/s)	Viscosity (cP)
F1	5.82 ± 0.03	6.42 ± 0.18	5420 ± 85
F2	5.91 ± 0.02	6.75 ± 0.21	5680 ± 92
F3	6.02 ± 0.04	7.18 ± 0.16	6120 ± 88
F4	5.76 ± 0.03	6.35 ± 0.20	5210 ± 76
F5	5.88 ± 0.02	6.82 ± 0.19	5760 ± 81
F6	6.08 ± 0.03	7.26 ± 0.17	6340 ± 95
F7	6.12 ± 0.02	7.42 ± 0.15	6520 ± 87
F8	5.79 ± 0.04	6.58 ± 0.22	5350 ± 79
F9	5.96 ± 0.03	6.94 ± 0.18	5890 ± 90
F10	6.15 ± 0.02	7.35 ± 0.20	6280 ± 84
F11	5.85 ± 0.03	6.61 ± 0.17	5480 ± 82
F12	6.05 ± 0.02	7.08 ± 0.19	6050 ± 91
F13	5.73 ± 0.03	6.28 ± 0.21	5080 ± 78
F14	5.99 ± 0.04	6.87 ± 0.16	5820 ± 86
F15	6.18 ± 0.03	7.15 ± 0.18	6610 ± 94
F16	5.92 ± 0.02	6.72 ± 0.20	5620 ± 80
F17	6.10 ± 0.03	7.31 ± 0.17	6380 ± 89

The gel formulations showed pH values from 5.73 ± 0.03 to 6.18 ± 0.03, spreadability from 6.28 ± 0.21 to 7.42 ± 0.15 g·cm/s in the tabulated results, and viscosity from 5080 ± 78 to 6610 ± 94 cP. These values indicate that the formulations possessed the physical consistency and spreadability required for topical application within the experimental study.

Surface morphology by SEM analysis

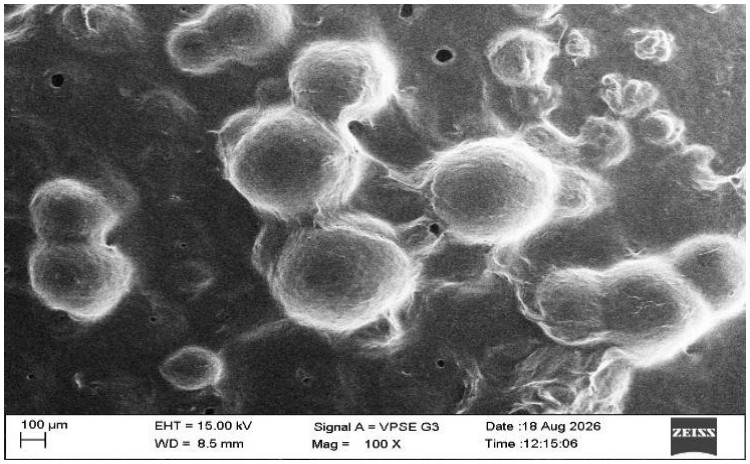


Figure 8: SEM image

SEM analysis of optimized Ornidazole

SEM image of the optimized formulation revealed that there was segregation, and the particles were spherical in shape and they are within nanoscale range

Stability of optimized formulation

Table 8: Stability findings for the optimized formulation.

Parameter	0 day	30 days	60 days
Physical appearance	Milky white	Milky white	Milky white
Phase separation	None	None	None
Drug content (%)	95.33 ± 0.017	96.39 ± 0.085	97.93 ± 0.103
Cumulative drug release (%)	90.03 ± 0.08	92.24 ± 0.116	92.50 ± 0.106

No phase separation was reported during the 60-day observation period and the physical appearance remained milky white. The reported drug content and cumulative drug release values did not show a marked deterioration during storage.

DISCUSSION

The formulation strategy combined a solid lipid (GMS) and a liquid lipid (oleic acid) to form an NLC matrix, with Tween 80 serving as surfactant. This composition was selected to produce a lipid carrier with nanoscale dimensions and the potential to modulate release. The BBD approach provided a structured means of examining the effects of lipid concentration, surfactant concentration and homogenization time on the critical formulation responses.

The optimized F13 formulation showed a particle size of 222.8 nm and PDI of 0.289. The relatively low PDI is consistent with a comparatively uniform dispersion. The negative zeta potential of −26.7 mV indicates electrostatic repulsion between particles, although the thesis itself describes this value as corresponding to limited-to-moderate stability rather than a highly stabilized system. Entrapment efficiency of 83.6% indicates effective incorporation of ornidazole into the lipid matrix.

The response-surface analysis suggests that formulation composition and processing conditions jointly controlled drug entrapment and release. The significant interaction terms for entrapment efficiency indicate that the effect of one factor cannot be interpreted independently of the levels of the other factors. For drug release, increasing GMS was associated with reduced release, whereas Tween 80 and homogenization time increased release in the fitted model. These effects are consistent with the role of lipid matrix density, interfacial stabilization and particle surface area in controlling drug diffusion from lipid carriers.

The NLC was incorporated into a Carbopol 934 hydrogel to obtain a formulation suitable for topical administration. The gel pH remained in the reported 5.73–6.18 range, and the spreadability and viscosity values indicated a balance between ease of application and formulation retention. The stability observations further indicate that the optimized system retained its reported physical appearance without phase separation over the 60-day study period.

The study has limitations that should be considered before journal submission. The thesis contains some internal numerical differences: the abstract reports 80.1% release at 12 h, the optimization section reports 82.3% at 12 h, while the summary reports 90.24 ± 1.94% and refers to release over 24 h. The particle-size range is also described differently in different thesis sections. These values should be reconciled against the original release and particle-size datasets before submission to a journal.

CONCLUSION

Ornidazole-loaded nanostructured lipid carriers were successfully developed using GMS as solid lipid, oleic acid as liquid lipid and Tween 80 as surfactant by hot homogenization followed by ultrasonication. A 17-run Box–Behnken design was used to optimize the formulation variables. F13 was identified as the optimized formulation, showing a particle size of 222.8 nm, PDI 0.289, zeta potential −26.7 mV, entrapment efficiency 83.6% and drug content 91.0%. The formulation demonstrated sustained drug release and the optimized dispersion was successfully incorporated into a Carbopol 934-based topical gel. The gel showed suitable pH, spreadability and viscosity and remained physically stable over the reported 60-day period. Overall, the findings support further

investigation of ornidazole NLC gel as a topical delivery platform, particularly through skin permeation, irritation/safety and in vivo efficacy studies.

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