

Solid Lipid Nanoparticle Gel for Controlled Topical Delivery of Ketoprofen

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ABSTRACT

Background and Objective: Ketoprofen is a non-steroidal anti-inflammatory drug commonly used for the management of pain and inflammation. Conventional topical formulations may have limitations in providing controlled drug release at the site of application. The present study aimed to develop and optimize ketoprofen-loaded solid lipid nanoparticles (K-SLNs) and incorporate the optimized nanoparticles into a topical gel to achieve controlled drug delivery. **Methods:** K-SLNs were prepared by modified high-speed homogenization followed by ultrasonication using glycerol monostearate, Span 60, and Tween 80. A three-factor, three-level Box–Behnken design was employed to optimize the formulation based on particle size and entrapment efficiency. The optimized K-SLNs were characterized for particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, drug loading, morphology, drug–excipient compatibility, and in vitro drug release. The optimized nanoparticles were incorporated into a Carbopol 934/HPMC K100M gel and evaluated for physicochemical properties, in vitro drug diffusion, release kinetics, and short-term stability. **Results:** The optimized K-SLN showed a particle size of 152.6 nm, PDI of 0.262, entrapment efficiency of 90.16%, zeta potential of –30.3 mV, and drug loading of 14.91%. The formulation exhibited gradual drug release with diffusion-associated behaviour. The optimized K-SLN gel showed suitable topical properties, with a pH of 5.74, viscosity of 12,121 cP, and spreadability of 8.29 mm². Compared with plain and marketed ketoprofen gels, the nanoparticle gel demonstrated slower drug diffusion and the closest fit to zero-order kinetics. **Conclusion:** The developed K-SLN gel exhibited favourable physicochemical characteristics and controlled drug release, indicating its potential as a promising topical delivery system for ketoprofen.

Keywords: Ketoprofen; Solid-lipid nanoparticle; Topical gel; Homogenization, Box-Behnken design.

I. INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis among adults and is primarily associated with chronic joint pain, stiffness, and impaired physical function. Globally, OA affected approximately 595 million individuals in 2020, corresponding to about 7.6% of the adult population. Its prevalence increases considerably with advancing age, with nearly 73% of affected individuals being above 55 years. Women account for approximately 60% of OA cases, indicating a higher disease burden compared with men.¹ OA is a progressive joint disorder involving deterioration of articular cartilage and synovial inflammation resulting from the complex influence of mechanical stress, cellular alterations, aging, and persistent low-grade inflammation. The knees, hips, and hands are among the joints most commonly affected.²

Several pharmacological and non-pharmacological approaches are employed for arthritis management, with treatment selected according to disease severity and individual patient requirements. Available formulations include oral, topical, and parenteral preparations of various therapeutic agents. NSAIDs are commonly administered as tablets, capsules, topical gels, or injections, whereas disease-modifying antirheumatic drugs such as methotrexate may be given orally or by injection.³

Management of OA generally incorporates lifestyle modification and exercise before pharmacological intervention. NSAIDs such as ibuprofen, ketoprofen, diclofenac, and naproxen are frequently used for symptomatic pain relief. Nevertheless, prolonged or high-dose systemic NSAID therapy may produce gastrointestinal complications, cardiovascular adverse events, and renal impairment. Parenteral administration may additionally cause discomfort. Therefore, OARSI guidelines emphasize using the lowest effective NSAID dose for the shortest feasible duration and avoiding unnecessary long-term therapy. Topical NSAIDs are recommended by National Institute for Health and Care Excellence as first- or second-line options for mild-to-moderate knee or hand OA because they can provide local therapeutic effects while reducing systemic exposure.⁴

Ketoprofen is a propionic acid derivative that exerts analgesic and anti-inflammatory effects primarily through reversible inhibition of cyclooxygenase enzymes (COX-1 and COX-2), thereby reducing prostaglandin synthesis. It belongs to BCS Class II, exhibiting poor aqueous solubility with high membrane permeability, while its oral absolute bioavailability exceeds 90% in humans.⁵ Topical ketoprofen 2.5% gel offers an alternative to oral administration for localized musculoskeletal pain and inflammation, providing therapeutic activity at the application site with reduced systemic exposure. Compared with oral ketoprofen, topical administration can substantially reduce gastrointestinal adverse effects associated with systemic NSAID exposure.⁶

Nanotechnology-based topical delivery systems have gained considerable attention for improving drug deposition and permeation through the skin.⁷ Among these systems, solid lipid nanoparticles (SLNs) are submicron carriers composed of physiologically compatible lipids that remain solid at room and body temperatures. They offer advantages including controlled drug release, improved stability, substantial drug-loading potential, and protection of incorporated drugs.⁸ Nanogel-based systems can further enhance topical drug delivery by promoting skin interaction and providing sustained drug release. Their nanoscale dimensions and hydrated structure enable incorporation and delivery of drugs with different physicochemical characteristics.⁹

Therefore, the present study aimed to develop and evaluate a ketoprofen-loaded solid lipid nanoparticle gel for topical delivery, with the objective of achieving controlled drug release, reducing systemic exposure, and providing a potentially improved approach for managing pain and inflammation associated with OA.

II. MATERIALS AND METHODS

Chemicals

Ketoprofen, received as a pure gift sample from Infinity Laboratories Pvt Ltd., Punjab. Glycerol monostearate, GMS (Rolex Chemical Industries, Mumbai). Tween 80 and Polyethylene glycol, PEG 400 (Merck Ltd., Mumbai). Span 60, stearic acid, palmitic acid, and cetyl alcohol (Sisco Research Laboratories Pvt Ltd., Maharashtra). Carbopol 934 (Loba Chemie Pvt Ltd., Mumbai) and Hydroxypropyl methylcellulose, HPMC K100M (Central Drug House Pvt Ltd., Mumbai). Ethanol (Bio Liqua Research Pvt Ltd., Bengaluru) and methanol (Qualigens Fine Chem Ltd., Mumbai). Triethanolamine (T.V. Industrial estate, Mumbai). Potassium dihydrogen phosphate, cholesterol, and beeswax (S.D. Fine Chem Ltd., Mumbai). Sodium

hydroxide pellets (Chem Pure Specialty Chemicals, Mumbai). Dialysis membrane-110 (HiMedia Laboratories Pvt Ltd., Mumbai). All the chemicals with reagents were of analytical grade.

Equipment

UV-Visible Spectrophotometer UV-1800, 240 V (Shimadzu, Japan), and FTIR Spectrophotometer 1700S (Shimadzu, Japan) equipped with Spectra Manager software. T25 digital Ultra Turrax VGST-GRD178 (IKA India Pvt Ltd., Bengaluru). Nanoparticle Analyzer SZ 100 (Horiba Scientific, China). Eutech pH 700 Digital pH meter (Thermo Fisher Scientific Pvt Ltd., Mumbai, Maharashtra). Bath Sonicator (PCI Analytics, Thane, Maharashtra). Brightfield Digital Microscope (Labomed, India).

Screening of Lipids

A modified lipid screening method was used to identify a suitable lipid based on ketoprofen solubility. Glycerol monostearate (GMS), stearic acid, palmitic acid, cetyl alcohol, beeswax, and cholesterol representing different lipid classes were evaluated. Each lipid (50 mg) was placed separately in a test tube and mixed with ketoprofen (10 mg). The mixtures were heated gently until complete lipid melting and stirred for 10 min to facilitate drug incorporation. After cooling to room temperature, the samples were examined visually for uniformity, undissolved drug, and crystallization. The lipid providing the highest apparent drug solubility without visible crystallization was selected for SLN development.¹⁰⁻¹²

Preliminary Trials

Preliminary trials were performed using different lipid and surfactant concentrations and varying homogenization speeds under ultra turrex for 30 min. Formulations were assessed for particle size and entrapment efficiency. Based on these preliminary findings, formulations showing smaller particle size and higher drug entrapment were selected for further optimization using the experimental design.¹²

Drug–Excipient Compatibility Study

Ketoprofen (10 mg) was mixed with physical mixture of GMS, Span 60, Tween 80, Carbopol 934, and HPMC K100M. The mixture was blended with dried KBr (100 mg), compressed into a pellet at 10 tons, and scanned from 4000–400 cm^{-1} by FTIR analysis. The spectra were compared with pure ketoprofen to identify possible interactions.¹³

Preparation of Ketoprofen loaded SLN

K-SLNs were prepared using modified high-speed homogenization followed by ultrasonication. GMS and Span 60 were separately melted above their melting points and mixed with ethanol. Ketoprofen (50 mg) was dissolved in ethanol (10 mL) and incorporated into the molten lipid phase with continuous stirring. Tween 80 was dissolved in distilled water (40 mL) and heated to the same temperature as the lipid phase. The lipid phase was gradually added to the aqueous phase through a 23-gauge syringe while homogenizing with an Ultra-Turrax at 10,000 rpm for 20 min. Ice was then added to promote rapid cooling, and homogenization was continued for another 10 min. The resulting dispersion was ultrasonicated for 15 min to obtain K-SLNs. The experimental setup is shown in **Fig. 1**. The prepared nanoparticles were subsequently characterized for relevant formulation and physicochemical properties.^{10,14}

Design of Experiment

Stat-Ease 360 software (version 25.0.1.0) was used for statistical analysis and formulation optimization. A three-factor, three-level Box–Behnken design was applied using GMS, Span 60, and Tween 80 as independent variables. Based on preliminary trials, suitable experimental ranges were selected and coded as low (−1), middle (0), and high (+1) levels. The design comprised 15 experimental runs, including three centre-point replicates. Formulations were prepared according to the design matrix presented in **Table X**,

and the obtained responses were statistically analyzed to determine the influence of formulation variables and identify the optimized K-SLN formulation.¹⁵

Characterization of Ketoprofen-loaded SLN

Particle Size and Polydispersity Index

Particle size and Polydispersity Index (PDI) were measured by dynamic light scattering using a Horiba SZ-100 analyzer at 90° and 25°C. The sample (1 mL) was diluted to 10 mL with double-distilled water, sonicated for 15 min, vortex-mixed, and analyzed in polystyrene cuvettes.¹⁶

Zeta Potential

Zeta potential (ZP) was determined using a Horiba SZ-100 analyzer. The sample (1 mL) was diluted to 10 mL with double-distilled water and sonicated for 15 min. The diluted dispersion was transferred into an electrode cuvette and analyzed to determine the zeta potential.¹⁷

Entrapment Efficiency

Entrapment efficiency (EE%) was determined indirectly by quantifying the untrapped ketoprofen in the supernatant. The SLN dispersion (1 mL) was centrifuged at 15,000 rpm for 30 min at 25°C. The supernatant was diluted with phosphate buffer (pH 7.4), and absorbance was measured at 257 nm using a UV-visible spectrophotometer.^{15,18}

Entrapment efficiency was calculated using the following equation:

$$EE (\%) = \frac{W_{\text{total drug}} - W_{\text{drug in supernatant}}}{W_{\text{total drug}}} \times 100$$

where, W_{total} - total amount of drug used; W_{free} - amount of untrapped (free) drug in the dispersion medium.

Percentage Drug Loading

Drug loading was calculated from the quantity of ketoprofen entrapped within the SLNs relative to the total formulation weight of drug, lipid, and surfactants.¹⁹ The entrapped drug amount was obtained from the entrapment efficiency, and DL was expressed as a percentage using the following equation:

$$\%DL = \frac{W_{\text{entrapped drug}}}{(W_{\text{total drug}} + W_{\text{total lipid}} + W_{\text{total surfactants}})} \times 100$$

where, W - weight in mg

Numerical Optimization

Optimization was performed to identify formulation conditions that best satisfied the predefined objectives. Depending on the desired outcome, responses may be minimized, maximized, targeted, or restricted within specified limits, while formulation variables can be adjusted to suitable levels to obtain the required formulation characteristics.¹²

Studies on Optimized Formulation

Numerical optimization was carried out using the desirability approach in Stat-Ease 360. The formulation was selected according to predefined criteria of minimum particle size and maximum entrapment efficiency. The optimized formulation presented in Table X was subsequently subjected to detailed characterization using relevant evaluation parameters.¹²

Formulation Compatibility Study

The optimized SLN dispersion was analyzed by FT-IR using the KBr pellet method. A small sample was mixed with dried KBr (100 mg), compressed at 10 tons, dried under an incandescent bulb, and scanned from 4000–400 cm^{-1} . The spectrum was compared with pure ketoprofen and the drug–excipient mixture to assess possible interactions.^{13,20}

Microscopic Imaging

A small quantity of optimized K-SLN dispersion was placed on a clean glass slide, covered with a coverslip, and examined using a bright-field digital microscope with S-EYE 2.0 image-analysis software. The dispersion was viewed at 10× and 40× magnifications, and representative images were captured from different fields.^{8,21}

In vitro Drug Release and Kinetics Study

In vitro drug release from optimized K-SLN was assessed using a dialysis membrane bag method. A hydrated cellulose membrane (mol.wt.cutoff 12,000–14,000 Da; pore size 2.4nm) containing K-SLN equivalent to 5 mg ketoprofen was immersed in 200 mL phosphate buffer (pH 7.4) at 37 ± 0.5°C and stirred at 100 rpm. At predetermined intervals, 5 mL samples were withdrawn and replaced with fresh buffer. Samples were analyzed at 260 nm in triplicate (n = 3). Release data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models, with R² values used to identify the best-fitting release model.^{15,22}

Preparation of Topical Gel

Preparation of Plain Gel: Carbopol 934 and HPMC K100M were dispersed in 50 mL distilled water and hydrated overnight. The polymers were then mixed with continuous stirring, followed by gradual addition of triethanolamine for neutralization and gel formation. The gel was kept overnight to remove air bubbles and achieve uniformity after incorporating the required humectant and preservative.^{22,23}

Preparation of K-SLN-Gel: The optimized K-SLN dispersion was incorporated into a gel base containing Carbopol 934 and HPMC K100M, which were dispersed in distilled water and hydrated overnight. The dispersion was stirred the next day, followed by dropwise addition of triethanolamine and PEG 400 for neutralization and consistency. A preservative was added, and the gel was mixed thoroughly to ensure uniformity.²²⁻²⁴

Evaluation of K-SLN-Gel

Physical Appearance

The gel was visually assessed for color, uniformity, and foreign particles.²⁵

pH

The pH was measured using a calibrated digital pH meter after dispersing 1 g of gel in 30 mL distilled water and immersing the electrode.²³

Viscosity Measurement

Gel viscosity was determined using a Brookfield viscometer equipped with a CPE-63 spindle at an optimized rotational speed of 10 rpm.²⁶

Spreadability

Spreadability was evaluated by the parallel-plate method. The gel sample (1 g), prepared 48 h before testing, was placed between two glass plates. A 100 g weight was applied for 1 min, and the diameter of the spread sample was measured.²⁷ Spreadability was calculated using the following formula: $S_i = d^2 \times (\pi / 4)$ where, 'S_i' represents the spreading area (mm²) depending on mass, and 'd' symbolizes the spreading area diameter (mm).

Drug Content

Drug content was determined by dissolving 1 g gel in 10 mL ethanol, followed by filtration through Whatman No. 1 filter paper. The filtrate (1 mL) was diluted to 10 mL with phosphate buffer (pH 7.4), and absorbance was measured in triplicate ($n = 3$) at 260 nm using a UV-visible spectrophotometer.²⁸

***In vitro* Drug Diffusion & Kinetics Study**

In vitro drug diffusion of the SLN-loaded, plain ketoprofen, and marketed gels was evaluated using a Franz diffusion cell with a pre-soaked dialysis membrane. The receptor compartment contained 135 mL phosphate buffer (pH 7.4) and was maintained at $37 \pm 0.5^\circ\text{C}$ with stirring at 100 rpm. Samples were withdrawn at predetermined intervals, replaced with fresh buffer, analyzed at 260 nm in triplicate. Diffusion data were fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to determine the best-fitting kinetic model and probable release mechanism.^{22,29-31}

Stability Study

The stability of optimized K-SLN dispersion and SLN gel was assessed for 3 months following ICH Q1C guidelines. The dispersion was refrigerated, while the gel was stored at $25 \pm 2^\circ\text{C}$ in aluminium foil-covered containers. Samples were evaluated initially and after 1 and 3 months. K-SLN was assessed for particle size, PDI, zeta potential, and EE%, whereas the gel was evaluated for drug content and 24-h drug release.³²

III. RESULTS AND DISCUSSION

Screening of Lipid

Lipid screening identified suitable lipids for K-SLN development. GMS, cetyl alcohol, and palmitic acid formed clear drug–lipid mixtures without visible crystallization, indicating good ketoprofen solubilization. Based on these observations, the three lipids were selected for further preliminary formulation trials.



Fig. 2: Visual observation of screened lipids.

Preliminary Trials

Preliminary trials showed that formulation composition and processing conditions markedly affected particle size, size distribution, surface charge, and drug entrapment. Among the tested batches, T10 and T11 produced small particles (152.6 and 131.1 nm) with high entrapment efficiencies (90% and 88%, respectively). Based on this combination of desirable characteristics, GMS was selected as the most suitable solid lipid for K-SLNs. These findings provided a rational basis for defining the formulation region for subsequent DoE-based optimization. Importantly, selection based on both particle size and entrapment efficiency minimized the risk of optimizing a single response at the expense of overall formulation performance.^{2,75}



Fig. 1: Experimental setup for K-SLN preparation by high-speed homogenization.

Table X: Preliminary formulation trials with results of evaluated parameters.

Batch codes	GMS (mg)	Palmitic acid (mg)	Cetyl alcohol (mg)	Span 60 (mg)	Tween 80 (%w/v)	Speed x 1000 (rpm)	PS (nm)	PDI	ZP (mV)	EE (%)
T1	50	-	-	50	0.2	7.5	191.1	0.48	-26.4	88
T2	50	-	-	100	0.4	7.5	219.4	0.42	-28.2	82
T3	50	-	-	25	0.6	7.5	261.9	0.68	-30.6	84
T4	-	50	-	50	0.2	7.5	221.8	0.56	-29.2	79
T5	-	50	-	100	0.4	7.5	326.8	0.63	-28.1	80
T6	-	50	-	25	0.6	7.5	358.9	0.69	-26.4	76
T7	-	-	50	50	0.2	7.5	316.8	0.62	-30.5	81
T8	-	-	50	100	0.4	7.5	366.5	0.68	-28.2	79
T9	-	-	50	25	0.6	7.5	461.7	0.61	-26.6	77
T10	50	-	-	50	0.4	10	152.6	0.44	-28.4	90
T11	50	-	-	100	0.6	10	131.1	0.42	-28.8	88
T12	-	50	-	50	0.4	10	259.7	0.63	-27.2	80
T13	-	50	-	100	0.6	10	221.2	0.68	-30.3	81
T14	-	-	50	50	0.4	10	259.2	0.58	-25.8	79
T15	-	-	50	100	0.6	10	256.6	0.66	-26.3	78

Drug–Excipient Compatibility Study

FT-IR analysis of the drug–excipient mixture showed retention of ketoprofen’s characteristic absorption bands with only minor wavenumber shifts. No significant peak disappearance or new peak formation was observed, indicating the absence of notable drug–excipient interactions and confirming compatibility with GMS, Span 60, Tween 80, Carbopol 934, and HPMC K100M.^{75,76}

Preparation and Characterization of Ketoprofen-loaded SLN

The prepared batches were characterized, and the results are presented in Table X.

Table 1. Formulation and evaluation results of K-SLN using a 3-factor BBD.

Batch codes	GMS (mg)	Span 60 (mg)	Tween 80 (%w/v)	PS (nm)	EE (%)	PDI	ZP (mV)	DL (%)
S1	75	100	0.2	214.8	87.13	0.67	-30.6	17.08
S2	75	62.5	0.4	155.1	91.96	0.44	-28.4	15.45
S3	75	62.5	0.4	149.6	90.38	0.49	-26.6	15.18
S4	75	25	0.6	175.4	84.35	0.48	-28.8	12.40
S5	75	25	0.2	225.1	82.21	0.49	-25.7	22.83
S6	75	100	0.6	165.2	87.89	0.43	-28.1	10.58
S7	50	100	0.4	170.6	86.22	0.47	-26.1	13.90
S8	75	62.5	0.4	158.3	91.30	0.41	-26.2	15.34
S9	50	25	0.4	185.3	80.61	0.49	-26.5	17.15
S10	100	25	0.4	219.2	87.60	0.59	-28.4	15.36
S11	100	62.5	0.2	244.9	84.12	0.67	-28.9	17.34
S12	50	62.5	0.2	194.7	81.11	0.55	-29.4	21.06
S13	100	62.5	0.6	184.7	89.22	0.54	-28.2	11.08
S14	50	62.5	0.6	145.3	82.03	0.48	-26.6	11.63
S15	100	100	0.4	234.8	91.77	0.61	-30.3	12.74

Table : ANOVA results for particle size (Y1) and entrapment efficiency (Y2).

Source	Sum of squares		df		Mean square		F-value		p-value		
	Y ₁	Y ₂	Y ₁	Y ₂	Y ₁	Y ₂	Y ₁	Y ₂	Y ₁	Y ₂	
Model	14683.86	225.65	9	9	1631.54	25.07	68.98	26.39	0.0001	0.0011	significant
A - GMS	4403.91	66.12	1	1	4403.91	66.12	186.19	69.61	<0.0001	0.0004	
B - Span 60	48.02	50.00	1	1	48.02	50.00	2.03	52.63	0.2135	0.0008	
C - Tween 80	5454.90	10.12	1	1	5454.90	10.12	230.62	10.66	<0.0001	0.0223	
AB	229.52	2.25	1	1	229.52	2.25	9.70	2.37	0.0264	0.1844	
AC	29.16	4.00	1	1	29.16	4.00	1.23	4.21	0.3174	0.0954	
BC	0.0025	0.2500	1	1	0.0025	0.2500	0.0001	0.2632	0.9922	0.6298	
A ²	1904.01	39.00	1	1	1904.01	39.00	80.50	41.05	0.0003	0.0014	
B ²	2388.39	14.77	1	1	2388.39	14.77	100.98	15.55	0.0002	0.0109	
C ²	870.94	51.92	1	1	870.94	51.92	36.82	54.66	0.0018	0.0007	
Residual	118.26	4.75	5	5	23.65	0.9500					
Lack of Fit	79.54	2.75	3	3	26.51	0.9167	1.37	0.9167	0.4485	0.5595	not significant
Pure Error	38.73	2.00	2	2	19.36	1.0000					
Cor Total	14802.12	230.40	14	14							
Quadratic Model	R²		Adjusted R²		Predicted R²		Adeq Precision		SD		%CV
Y₁ (PS)	0.9920		0.9776		0.9081		24.9687		4.86		2.58
Y₂ (%EE)	0.9794		0.9423		0.7895		14.2934		0.9747		1.13

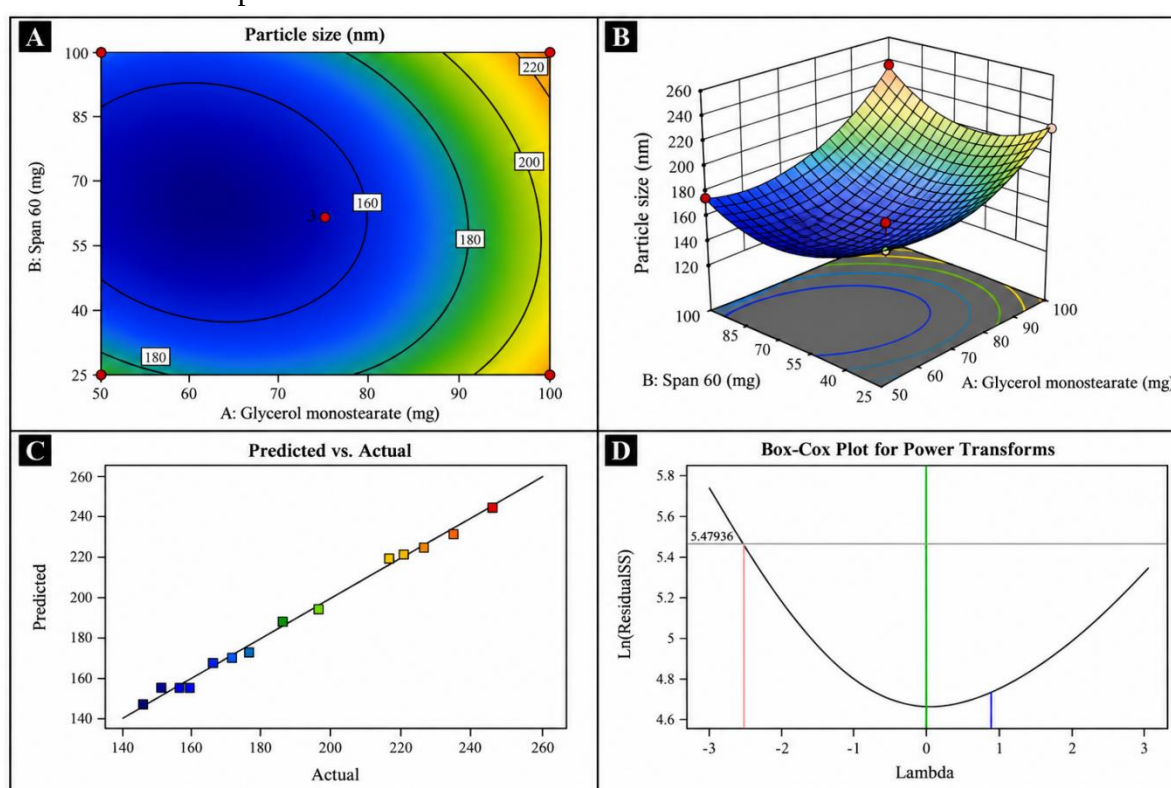
Particle Size and Polydispersity Index

Particle size is an important parameter for characterizing nanoparticles, as it influences their physical properties and performance. PDI indicates the uniformity of particle size distribution and overall formulation consistency. The prepared SLNs (S1–S15) showed particle sizes ranging from 145.3 to 244.9 nm, with PDI values between 0.41 and 0.67.

The experimental data fit a significant quadratic model ($F = 68.98$, $p < 0.0001$) that can be seen in **Table** , with high R^2 (0.9920), adjusted R^2 (0.9776), and predicted R^2 (0.9081), indicating good model fit and predictive capability. The non-significant lack of fit ($F = 1.37$, $p = 0.4485$) confirmed the model's adequacy. GMS and Tween 80 showed significant linear effects ($p < 0.0001$), whereas Span 60 was non-significant linearly ($p = 0.2135$). Final Equation in Terms of Coded Factors:

$$\text{Particle size} = 154.33 + 23.46*A - 2.45*B - 26.11*C + 7.58*AB - 2.70*AC + 0.0250*BC + 22.71*A^2 + 25.43*B^2 + 15.36*C^2$$

The positive coefficient for GMS (+23.46) indicated an increase in particle size with increasing GMS concentration, while the negative coefficient for Tween 80 (−26.11) indicated a reduction in particle size. Although the linear effect of Span 60 was non-significant, its quadratic term (B^2) was significant ($p = 0.0002$), indicating a nonlinear effect. Significant quadratic effects were also observed for GMS (A^2 ; $p = 0.0003$) and Tween 80 (C^2 ; $p = 0.0018$). Among the interaction terms, only the GMS–Span 60 interaction (AB) was significant ($p = 0.0264$), indicating that the effect of GMS on particle size depended on the concentration of Span 60.



The contour plot indicated that particle size was influenced mainly by GMS and Span 60, with the lowest values observed around 70–75 mg GMS and 55–65 mg Span 60. Increasing either component beyond this region increased particle size. The 3D response surface confirmed a nonlinear relationship, showing a minimum particle-size region at intermediate factor levels. The predicted-versus-actual plot showed close agreement between experimental and predicted values, supporting the adequacy of the developed model. Box–Cox analysis suggested an optimum lambda of approximately 0.2, indicating that the selected transformation was appropriate for model analysis. The significant quadratic model confirmed that formulation variables influenced particle size. High model fit, close adjusted and predicted performance, and non-significant lack of fit demonstrated reliable prediction within the studied formulation range.

Zeta Potential

Zeta potential reflects nanoparticle surface charge and serves as an important indicator of colloidal stability during storage. The K-SLNs exhibited ZP values between -25.7 and -30.6 mV, indicating good colloidal stability. These values were within the commonly reported range of -20 to -40 mV for SLN formulations.

ZP represents the electrical charge on the surface of nanoparticles and is an important indicator of the physical stability of a colloidal dispersion during storage. The ZP of the ketoprofen-loaded SLNs ideally ranged from -25.7 to -30.6 mV. The consistent negative surface charge may enhance colloidal stability by promoting electrostatic repulsion and reducing particle association and aggregation.^{80, 81}

Entrapment Efficiency

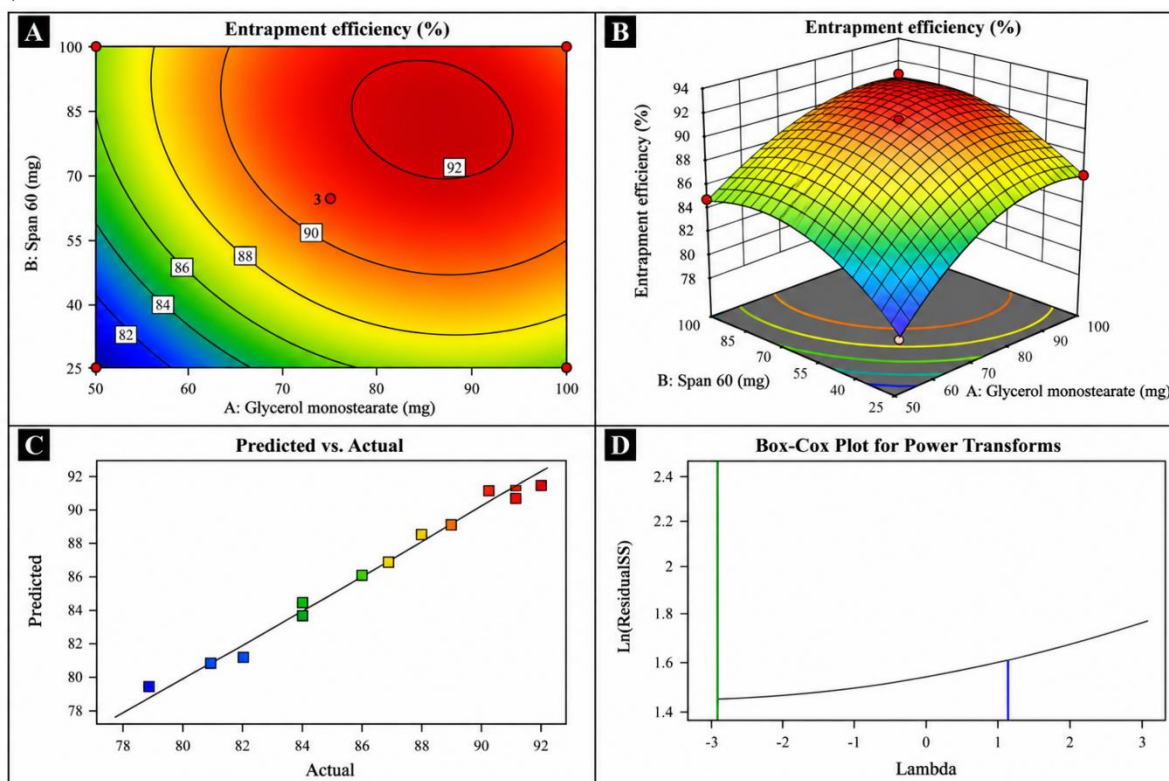
High entrapment efficiency ensures effective drug incorporation within the lipid matrix, maximizing drug loading and minimizing drug loss during formulation. The K-SLNs showed 80.61–91.96% entrapment efficiency, confirming effective incorporation of ketoprofen within the lipid matrix.

A significant quadratic model tabulated in **Table**, was obtained ($F = 26.39$, $p = 0.0011$), with $R^2 = 0.9794$, adjusted $R^2 = 0.9423$, and predicted $R^2 = 0.7895$, indicating a satisfactory model fit. The lack of fit was non-significant ($F = 0.9167$, $p = 0.5595$), confirming model adequacy, which can be seen in **Table**.

Final Equation in Terms of Coded Factors:

$$\% EE = 91.00 + 2.87*A + 2.50*B + 1.13*C - 0.7500*AB + 1.0000*AC - 0.2500*BC - 3.25*A^2 - 2.00*B^2 - 3.75*C^2$$

GMS, Span 60, and Tween 80 showed significant linear effects on entrapment efficiency, with p-values of 0.0004, 0.0008, and 0.0223, respectively. Their positive coefficients (+2.87, +2.50, and +1.13, respectively) indicated that increasing the levels of these variables generally enhanced entrapment efficiency. Significant quadratic effects were observed for GMS (A^2 ; $p = 0.0014$), Span 60 (B^2 ; $p = 0.0109$), and Tween 80 (C^2 ; $p = 0.0007$), indicating nonlinear effects. None of the two-factor interactions (AB, AC, and BC) were significant ($p > 0.05$).



The contour plot showed that entrapment efficiency increased with GMS and Span 60 concentration, reaching above 90% at intermediate-to-high levels. The 3D response surface confirmed a nonlinear

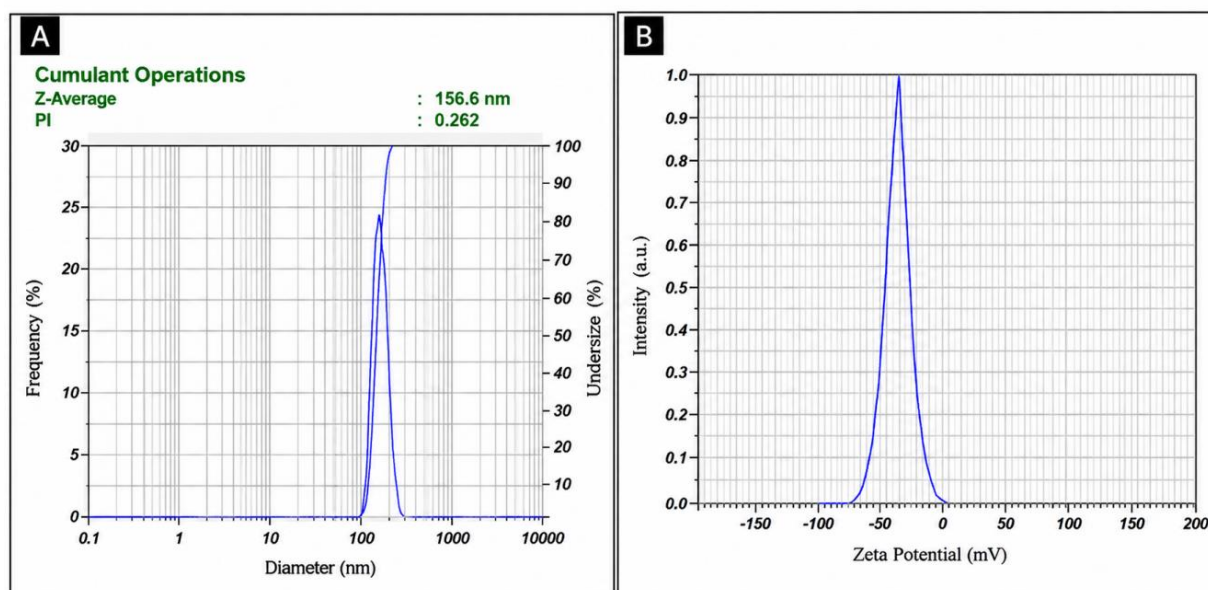
relationship, with maximum entrapment observed around 80–90 mg GMS and 70–90 mg Span 60, followed by a slight decline at higher levels. The predicted-versus-actual plot showed close agreement between experimental and predicted values, supporting good model fit. Box–Cox analysis indicated an optimum lambda near -3 , suggesting that response transformation improved model adequacy. Overall, GMS and Span 60 substantially influenced ketoprofen entrapment, with an optimum region identified for efficient drug incorporation.

Percentage Drug Loading

Drug loading indicates the amount of drug incorporated per unit mass of nanoparticles, reflecting formulation efficiency and therapeutic payload capacity. Drug loading of ketoprofen-loaded SLNs ranged from 10.58–22.83%. Differences in drug loading indicate that entrapment efficiency and drug loading are related but distinct parameters. High entrapment does not necessarily imply high drug loading, as greater lipid and excipient proportions can reduce the drug fraction within the nanoparticles.⁸¹

Evaluation of Optimized K-SLN

The optimized K-SLN exhibited nanoscale size, low PDI, high entrapment efficiency, and negative zeta potential. Experimental responses closely matched DoE predictions and were comparable to batch S2. The low PDI indicated a relatively uniform particle distribution. Overall, the combination of nanoscale size, controlled distribution, efficient drug entrapment, and negative surface charge demonstrated a favourable physicochemical profile for further development.^{2, 80}



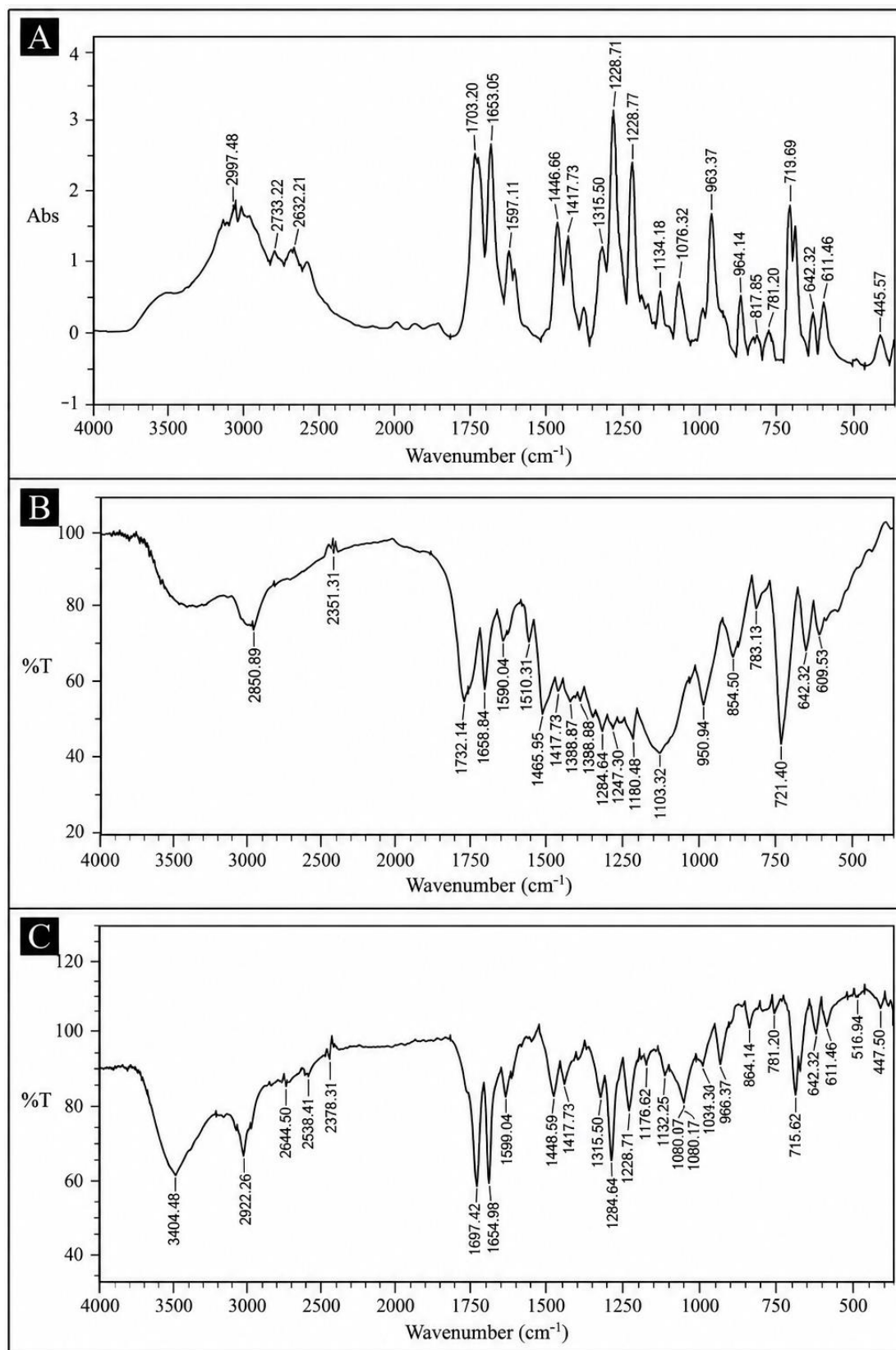
Parameter	Optimized K-SLN	DOE Predicted	Closest Matching Batch (S2)
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PS (nm)	152.6	147.59	155.1
EE (%)	90.16	91.36	91.96
PDI	0.262	-	-
ZP (mV)	-30.3	-	-
DL (%)	14.91	-	-

Formulation Compatibility Study

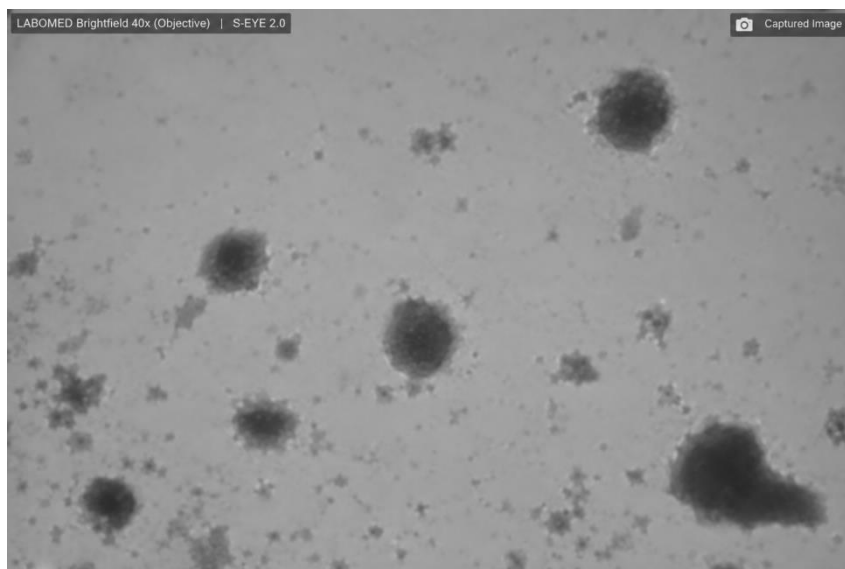
The optimized K-SLN retained characteristic ketoprofen peaks with minor wavenumber shifts, indicating preservation of drug identity without major chemical alteration indicating no significant drug–excipient interaction or chemical incompatibility and supporting physical incorporation within the lipid–surfactant matrix.²

SL. No.	Functional group	Standard values of Ketoprofen (cm ⁻¹)	Observed peak values of pure Ketoprofen (cm ⁻¹)	Observed peak values of drug + all excipients (cm ⁻¹)	Observed peak values of optimized K-SLN (cm ⁻¹)
1.	O–H stretching (carboxylic acid)	2500–3300	2997.48, 2733.22, 2652.21	2850.89	3404.48
2.	C=O stretching (carboxylic acid)	1680–1720	1703.20	1732.14	1697.42
3.	C=O stretching (ketone)	1640–1660	1653.05	1658.84	1654.98
4.	Aromatic C=C stretching	1500–1600	1597.11	1590.04, 1510.31	1599.04
5.	C–O stretching (carboxylic acid)	1210–1320	1282.71	1284.64	1284.64
6.	Aromatic C–H bending	700–750	731.39	721.40	715.62



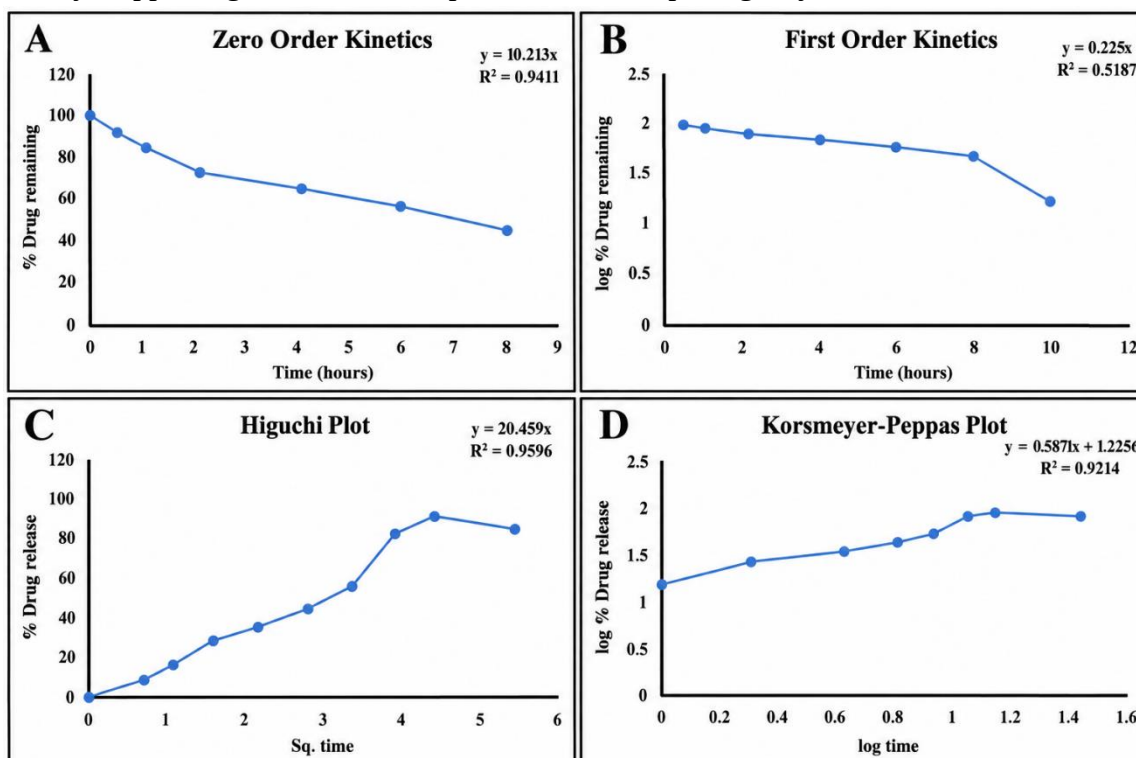
Microscopic Imaging

Microscopic examination at 40× magnification showed predominantly spherical to rounded K-SLN particles with compact, relatively smooth, and well-defined surfaces. Some irregular aggregates were observed, indicating limited particle association. The predominantly rounded morphology supports formation of discrete lipid-based particles, while the compact structure suggests organized lipid matrix formation. These observations, together with instrumental particle-size analysis, confirmed successful formation of the K-SLN particulate system rather than a bulk lipid dispersion.²



***In vitro* Drug Release and Kinetics Study**

The optimized K-SLN showed a gradual ketoprofen release, increasing from 8.41% at 0.5 h to 54.25% at 8 h, followed by a marked increase to 83.67% at 10 h and 91.03% at 12 h. The recorded release at 24 h was 83.67% (Table 5.12). Among the kinetic models, the Higuchi model showed the highest correlation ($R^2 = 0.9596$), followed by zero-order ($R^2 = 0.9411$) and Korsmeyer–Peppas ($R^2 = 0.9214$), whereas first-order showed the lowest fit ($R^2 = 0.5187$). The Higuchi model therefore indicated that diffusion through the lipid matrix was a major determinant of drug release. The Korsmeyer–Peppas exponent ($n = 0.5871$) indicated anomalous, non-Fickian transport, suggesting that release involved both drug diffusion and matrix-related changes. The gradual release pattern may be attributed to the lipid matrix acting as a barrier to rapid drug diffusion, with surface-associated drug contributing initially and matrix-entrapped drug being released progressively. Overall, the findings confirm that SLN incorporation modulated ketoprofen release and provided sustained drug availability, supporting its further incorporation into a topical gel system.



Preparation of K-SLN-Gel

Carbopol 934 and HPMC K100M were combined to provide suitable gel structure and viscosity. Carbopol contributed gel strength, while HPMC enhanced viscosity, adhesion, film formation, and drug-release control. Their complementary properties improved the gel's physical stability, spreadability, and skin residence, supporting effective topical delivery of K-SLN.^{90,91}

Six plain gel formulations (G1–G6) were prepared using varying Carbopol 934 and HPMC K100M concentrations. Based on transparency, texture, and thickness, G5 and G6 were selected for K-SLN incorporation. SLN-G1 and SLN-G2 were prepared using 25 mL optimized K-SLN dispersion and subjected to further evaluation.

Table 4.7: Formulation table of plain gel.

Name of excipient	Quantity					
	G1	G2	G3	G4	G5	G6
Carbopol 934 (% w/v)	0.25	0.5	1.0	0.125	0.25	0.5
HPMC K100M (% w/v)	0.25	0.5	1.0	0.25	0.5	1.0
Distilled water (mL)	50	50	50	50	50	50
Triethanolamine (mL)	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation of K-SLN-Gel

Both SLN gel formulations showed acceptable physical appearance and pH, with measurable viscosity and spreadability. The drug-content values indicated satisfactory incorporation of ketoprofen into the gel formulations. Based on the preliminary evaluation, SLN-G1 was selected as the optimized K-SLN-G formulation.

Formulation composition	SLN-G1	SLN-G2
Carbopol 934 (% w/v)	0.25	0.5
HPMC K100M (% w/v)	0.5	1.0
Distilled water (mL)	50	50
Optimized SLN (mL)	25	25
Triethanolamine (mL)	q.s.	q.s.
PEG 400 (mL)	0.2	0.2
Methylparaben (g)	0.2	0.2
Evaluation parameters	SLN-G1	SLN-G2
Color & texture	White and homogeneous	White and homogeneous
pH	5.74	5.56
Viscosity (cP)	12121	10132
Spreadability (mm ²)	8.29	9.13
Drug content (%)	89.58	88.26

***In vitro* Drug Diffusion & Kinetics Study**

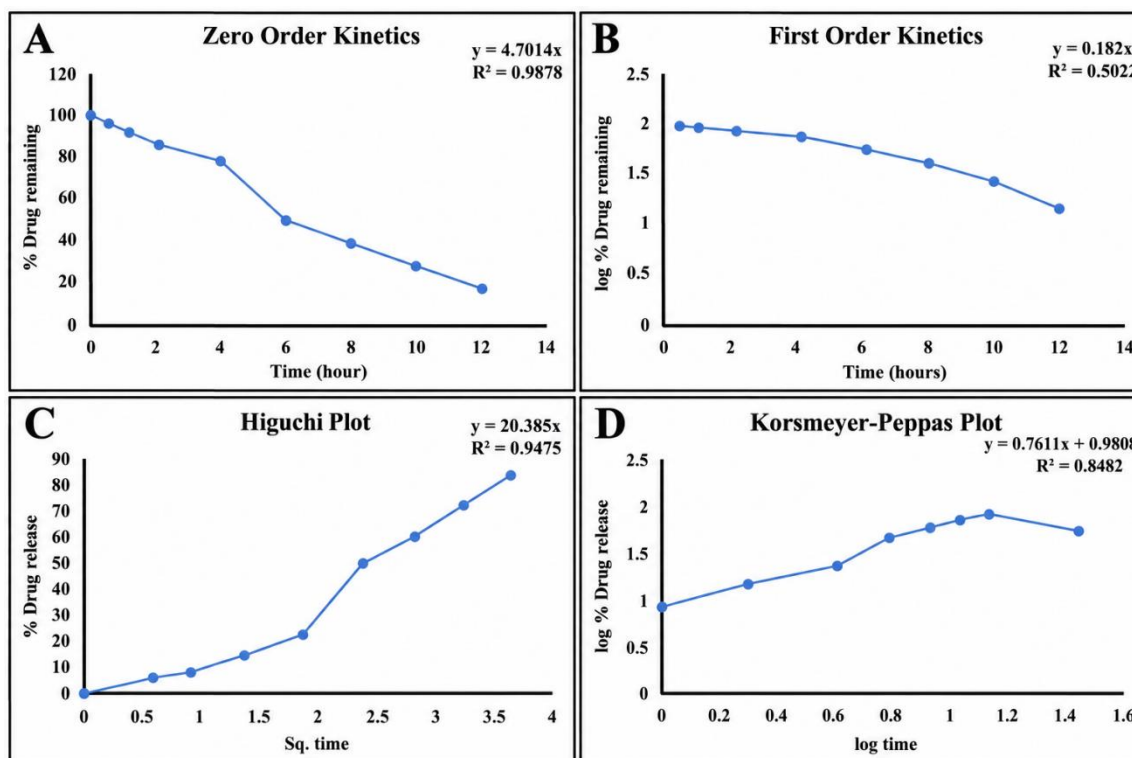
The *in vitro* drug diffusion study compared K-SLN-G, Drug + Plain Gel, and Marketed K-Gel over 24 h, with results presented in Table 5.12 and Fig. 5.17. K-SLN-G showed a gradual increase in drug diffusion from 4.94% at 0.5 h to 83.21% at 12 h. In comparison, Drug + Plain Gel showed faster diffusion, increasing from 20.15% to 98.39%, while Marketed K-Gel increased from 23.58% to 99.31% over the same period. Thus, K-SLN-G exhibited comparatively slower drug diffusion, indicating a sustained-release effect.

Time (hour)	K-SLN	K-SLN-G	K-Plain Gel	Marketed K-Gel
0.5	8.41 ±0.13	4.94 ±0.10	20.15 ±0.30	23.58 ±0.35
1.0	15.54 ±0.23	8.32 ±0.15	22.41 ±0.34	27.51 ±0.41
2.0	27.31 ±0.41	14.27 ±0.25	30.58 ±0.46	36.13 ±0.54
4.0	35.03 ±0.53	22.73 ±0.39	39.45 ±0.59	47.51 ±0.71
6.0	43.86 ±0.66	49.65 ±0.74	70.45 ±1.06	77.24 ±1.16
8.0	54.25 ±0.81	60.22 ±0.90	82.47 ±1.24	86.89 ±1.30
10.0	83.67 ±1.26	72.41 ±1.09	91.03 ±1.37	93.10 ±1.40
12.0	91.03 ±1.37	83.21 ±1.25	98.39 ±1.48	99.31 ±1.49
24.0	83.67 ±1.26	57.47 ±0.86	88.27 ±1.32	90.34 ±1.36

The slower diffusion from K-SLN-G can be attributed to the combined effects of the lipid nanoparticle matrix and polymeric gel network. In the plain gel and marketed formulation, ketoprofen was more readily available for diffusion through the hydrated gel matrix. In contrast, K-SLN-G required drug release from the lipid carrier followed by diffusion through the gel network. This sequential pathway provided an additional barrier to drug movement and effectively prolonged drug release. The findings indicate that the sustained diffusion was mainly associated with SLN incorporation rather than the gel vehicle alone. Overall, the K-SLN-G demonstrated controlled drug diffusion and provided a suitable formulation approach for sustained topical delivery of ketoprofen.^{3, 75, 87}

Drug Release Kinetics for K-SLN-Gel

The release kinetics of K-SLN-Gel showed the highest correlation with the zero-order model ($R^2 = 0.9878$), followed by Higuchi ($R^2 = 0.9475$), Korsmeyer–Peppas ($R^2 = 0.8482$), and first-order models ($R^2 = 0.5022$). Thus, the release profile was best described by zero-order kinetics, indicating a relatively consistent drug-release rate over the studied period. The Korsmeyer–Peppas exponent ($n = 0.7611$) indicated anomalous, non-Fickian transport, suggesting involvement of more than one release mechanism.



Formulation	Zero order	First order	Higuchi	Korsmeyer-peppas	
	R^2	R^2	R^2	R^2	n
K-SLN	0.9411	0.5187	0.9596	0.9214	0.5871
K-SLN-Gel	0.9878	0.5022	0.9475	0.8482	0.7611

The close fit to zero-order kinetics indicates that drug availability from K-SLN-Gel was relatively independent of the amount of drug remaining in the formulation, supporting its controlled-release potential. The comparatively high Higuchi correlation further confirmed that diffusion contributed substantially to drug transport. The anomalous release behaviour suggests a combined influence of drug diffusion and structural changes or relaxation within the lipid-polymer matrix. Notably, incorporation of K-SLNs into the gel shifted the release behaviour from predominantly Higuchi-type release in the nanoparticle dispersion toward zero-order kinetics in the final gel. This change may be attributed to the additional resistance provided by the polymeric gel network, which regulates drug movement after release from the lipid nanoparticles. Overall, the K-SLN-Gel functioned as a combined release-control system, with the SLN regulating drug availability from the lipid matrix and the gel matrix further controlling its subsequent diffusion.^{3, 75}

Stability Study

The optimized K-SLN and K-SLN-G showed satisfactory short-term stability over 3 months, with only minor changes in their evaluated parameters. Refrigerated K-SLN maintained nanoscale particle size, negative zeta potential, and relatively high entrapment efficiency, indicating good physical stability. The K-SLN-G stored at room temperature showed minimal changes in pH, viscosity, spreadability, and drug content. The drug diffusion profile also remained satisfactory, at 12 h during the stability study. Overall, the limited changes in physicochemical properties and drug-release behaviour indicated acceptable short-term stability of both formulations under the studied storage conditions.

Time	K-SLN					K-SLN-Gel			
	ZP (mV)	EE (%)	PS (nm)	PDI	EE (%)	pH	Viscosity (cP)	Spread ability (mm ²)	Drug content (%)
Initial	-30.3	90.16	152.6	0.262	90.16	5.74	12121	8.29	89.58
1 month	-30.6	89.75	157.2	0.414	89.75	5.62	12452	8.41	88.94
3 months	-28.8	88.64	164.4	0.442	88.64	5.69	12610	8.68	86.28

IV. CONCLUSION

The present study successfully developed and optimized a ketoprofen-loaded solid lipid nanoparticle gel (K-SLN-Gel) as a topical drug delivery system intended to provide controlled drug release and suitable topical application. A systematic formulation approach was followed, including preformulation studies, lipid and excipient screening, Box–Behnken design-based optimization, nanoparticle characterization, gel development, in vitro drug release and diffusion studies, and short-term stability evaluation.

Preformulation and compatibility studies supported the suitability of ketoprofen and the selected formulation components. Optimization using the Box–Behnken design demonstrated that variations in lipid and surfactant concentrations influenced the nanoparticle characteristics. The optimized K-SLN exhibited suitable nanoscale particle size, relatively uniform size distribution, high drug entrapment, and satisfactory negative surface charge, confirming successful formation of the lipid-based nanoparticulate system. The experimental responses were reasonably comparable with the predicted values, supporting the suitability of the optimization model.

The optimized K-SLN was successfully incorporated into a Carbopol 934–HPMC K100M polymeric gel. The resulting K-SLN-Gel showed acceptable physicochemical properties, including suitable pH, viscosity, spreadability, homogeneity, and drug content, indicating its suitability for topical application. The incorporation of K-SLN into the gel provided an additional barrier to drug diffusion, with the lipid matrix regulating drug release and the polymeric network further controlling diffusion. Accordingly, K-SLN-Gel showed slower and more controlled drug diffusion than the plain ketoprofen gel and marketed gel under the experimental conditions. Release-kinetic analysis indicated the involvement of diffusion along with matrix-related effects in drug transport.

The stability study showed that the optimized K-SLN and K-SLN-Gel maintained their major evaluated characteristics during the investigated storage period, with only limited changes in physicochemical properties and drug-release behaviour. These findings support satisfactory short-term stability under the studied conditions. However, long-term and accelerated stability studies are necessary to establish the shelf life and overall stability profile.

Overall, the study demonstrates that combining ketoprofen-loaded SLNs with a topical polymeric gel is a rational approach for modulating drug release and diffusion. The developed K-SLN-Gel represents a promising platform for controlled topical delivery of ketoprofen. Further studies involving long-term stability, comparative permeation, dermatokinetic evaluation, safety assessment, and in vivo investigations are required to establish its therapeutic potential and facilitate further development.

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