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Development and Evaluation of Solid Lipid Nanoparticle-Loaded Oral Films for Enhanced Delivery of a BCS Class IV Drug

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ABSTRACT: Curcumin, a polyphenol derived from *Curcuma longa*, possesses well-established anti-inflammatory, antioxidant, antimicrobial, and neuroprotective properties. However, its clinical translation is severely constrained by its Biopharmaceutical Classification System (BCS) Class IV designation. This designation confers simultaneously poor aqueous solubility (< 0.1 mg/mL) and low membrane permeability, yielding oral bioavailability below 1%. Additional barriers including first-pass glucuronidation, alkaline pH instability, and photodegradation further impede therapeutic application. This study developed curcumin-loaded Solid Lipid Nanoparticles (SLNs) incorporated into Rapidly Disintegrating Oral Films (RDOFs) as a dual-phase oral delivery platform designed to overcome these limitations simultaneously. SLNs prepared by solvent emulsification–evaporation using Glyceryl Monostearate (drug:lipid 1:5 w/w; Tween 80:Span 80 4:1; HLB 12.9) achieved entrapment efficiency of 99.85%, mean particle size of 187.4 nm (PDI 0.182), and zeta potential of -27.84 mV, confirming near-quantitative encapsulation and adequate colloidal stability. A Quality by Design (QbD)-guided Design of Experiments (DoE) approach employing HPMC E15 and MCC 101 as Critical Material Attributes produced statistically validated polynomial models for disintegration time ($R^2 = 0.979$) and drug release ($R^2 = 0.875$). Numerical desirability optimization identified F5* (HPMC E15 = 2.64% w/v; MCC 101 = 1.71% w/v; desirability D = 1.000), which exhibited disintegration in 17.5 seconds, drug content of 93.6%, and a characteristic biphasic release profile reaching 81.7% cumulative drug release at 6 hours, following Non-Fickian anomalous transport (Korsmeyer–Peppas model; $n = 0.687$). Accelerated stability studies conducted over 3 months at 40°C/75% RH (ICH Q1A(R2)) confirmed retention of all critical quality attributes within acceptance limits. These findings establish the curcumin SLN-loaded oral film as a bio-pharmaceutically rational, patient-friendly, and scalable platform with significant translational potential for the management of oral diseases and neurodegenerative disorders.

INTRODUCTION

Curcumin ($C_{21}H_{20}O_6$; MW = 368.38 g/mol) is the principal polyphenol of *Curcuma longa* (Zingiberaceae), exhibiting diverse pharmacological activities including anti-inflammatory, antioxidant, antimicrobial, anticancer, and neuroprotective effects relevant to oral diseases and neurodegenerative disorders (Sharifi-Rad et al., 2020; Peng et al., 2021). Despite this broad

therapeutic profile, curcumin is classified as a BCS Class IV drug is characterized by simultaneously poor aqueous solubility (< 0.1 mg/mL) and low membrane permeability yielding oral bioavailability below 1% in humans even at doses of 8–12 g/day (Stohs et al., 2020). First-pass glucuronidation and sulphation in the intestinal wall and liver, alkaline pH-induced degradation, and rapid photodegradation in solution further compound the challenge of clinical translation. These combined barriers have prevented curcumin from realizing its considerable therapeutic potential despite decades of research, making it an important candidate for advanced drug delivery system development. Solid Lipid Nanoparticles (SLNs) are physiologically compatible, surfactant-stabilised colloidal carriers (50–1000 nm) that simultaneously enhance drug solubility through nanometric size reduction, provide physicochemical degradation protection through solid lipid matrix encapsulation, and enable sustained controlled release via diffusion through the lipid core (Akbari et al., 2025). Compared to alternative nanocarrier systems such as polymeric nanoparticles, liposomes, and nanosuspensions, SLNs offer distinct advantages including use of GRAS-listed excipients, large-scale manufacturability by high-pressure homogenization or solvent emulsification–evaporation, and inherent biocompatibility. Recent curcumin-SLN studies using glyceride lipids report entrapment efficiencies above 90% with sub-200 nm particle sizes, substantially improving oral bioavailability relative to free curcumin (Rahman et al., 2023; Liu et al., 2022; Ban et al., 2020). Glyceryl Monostearate (GMS), a GRAS-listed biocompatible monoglyceride with a melting point of 55–65°C, provides an effective solid lipid matrix for lipophilic actives such as curcumin. Rapidly Disintegrating Oral Films (RDOFs) dissolve within seconds of salivary contact, offering water-free administration, improved mucosal absorption through prolonged buccal contact, and superior patient compliance for paediatric, geriatric, and dysphagic patients who have difficulty swallowing conventional tablets or capsules (Takeuchi et al., 2025). The thin-film platform also eliminates the first-pass hepatic metabolism concern to a degree, as pre-gastric buccal absorption can be facilitated. Incorporating SLNs into RDOFs creates a dual-phase drug delivery architecture: an initial burst phase driven by rapid film dissolution upon salivary contact, followed by a sustained nanoparticle-mediated release phase as the dispersed SLN particles gradually release curcumin through diffusion across the solid GMS matrix. This biphasic profile is therapeutically superior to either a conventional film (which would give burst release without sustaining therapeutic concentrations) or a standalone SLN dispersion (which lacks the patient-friendly film dosage form). Quality by Design (QbD) as defined by ICH Q8(R2) provides a systematic, prospective, and risk-based framework for optimizing such multi-component formulations through Design of Experiments (DoE). This approach enables quantitative understanding of formulation variable interactions and their effects on Critical Quality Attributes (Shah et al., 2022; Suryawanshi et al., 2021; Ubgade et al., 2026). Despite the growing body of literature on curcumin Nanoformulations and on oral films separately, reports integrating curcumin-SLN systems into QbD - optimized RDOFs with comprehensive biphasic release characterization remain limited. The present study addresses this gap by reporting the formulation, DoE-based optimization, and comprehensive in vitro evaluation of curcumin SLN-loaded RDOFs targeting a biphasic release profile to overcome BCS Class IV limitations (Takeuchi et al., 2025 Yu et al., 2023).

MATERIALS AND METHODS

Materials

Curcumin (purity $\geq 98\%$), Glyceryl Monostearate (GMS), Tween 80, Span 80, Hydroxypropyl Methylcellulose E15 (HPMC E15), Microcrystalline Cellulose PH 101 (MCC 101), Glycerol, Mannitol, Citric acid, and Mint flavour were procured from Roots Formulations, MIDC Ambad, Nashik, Maharashtra, India. Acetone (HPLC grade), Methanol, Ethanol, KBr, and Phosphate Buffer pH 6.8 were of analytical grade. All materials were used as received.

Ethical Statement

This study is an entirely in vitro physicochemical investigation. No animals or human subjects were used at any stage of the research. Accordingly, ethical approval from an Institutional Animal Ethics Committee (IAEC) or Institutional Review Board (IRB) was not required. All experimental procedures were conducted in accordance with standard laboratory safety guidelines.

Preformulation Studies

Curcumin was characterized for organoleptic properties, melting point, and aqueous solubility. UV spectrophotometry established λ_{max} and validated calibration curves at 425 nm in methanol ($y = 0.0195x + 0.0074$, $R^2 > 0.999$) and ethanol ($y = 0.0503x + 0.0560$, $R^2 > 0.999$) over 2–10 $\mu\text{g/mL}$. FTIR (KBr pellet; 4000–400 cm^{-1}) confirmed molecular identity and drug–excipient compatibility. DSC (40–400°C; 10°C/min; N_2) characterized thermal behavior (Shahare et al., 2026; Daga et al., 2026).

Preparation of Curcumin SLNs

SLNs were prepared by solvent emulsification–evaporation. GMS (1.000 g) and curcumin (200 mg; 1:5 w/w drug: lipid) were dissolved in acetone (10 mL; 65°C) as the organic phase. A binary surfactant blend of Tween 80: Span 80 (4:1; HLB = 12.9; 1.0% w/v total) in purified water (45 mL; 40°C) formed the aqueous phase. The organic phase was added dropwise under homogenization (15,000 rpm; 10 min); acetone was removed by continuous stirring followed by bath ultrasonication (15 min; ice bath). Preliminary screening of four solid lipids, five drug: lipid ratios, and four surfactant concentrations identified the optimum composition (baste et al., 2024; Shahare et al., 2026).

Characterization of Curcumin SLNs

Entrapment efficiency (EE%) was determined indirectly by ultracentrifugation (15,000 rpm; 30 min); free drug in supernatant was quantified by UV spectrophotometry at 425 nm. $EE\ (%) = [(Total\ drug - Free\ drug) / Total\ drug] \times 100$. Particle size and PDI were measured by Dynamic Light Scattering (NanoPlus analyzer; 25°C); zeta potential by electrophoretic light scattering (Bhowmick et al., 2024; Shahare et al., 2026). In vitro release from SLN dispersion was studied using a Franz diffusion cell (area 3.14 cm²; pH 6.8 phosphate buffer; 37 ± 0.5°C; 100 rpm; 1–6 hr).

Excipient Screening and DoE Optimization of Oral Films

Nine preliminary film batches screened three polymers (HPMC E5, HPMC E15, Chitosan) and two plasticizers (Glycerol, PEG 400) for disintegration time and folding endurance, selecting HPMC E15 and glycerol (0.70% w/v). MCC 101 was selected as superdisintegrant. Drug–excipient compatibility was confirmed by FTIR (Verma et al., 2026, Shahare et al., 2025). A QbD-guided Optimal Design (Design Expert v13.0; nine runs, F1–F9) used HPMC E15 concentration (X₁: 2.35–2.75% w/v) and MCC 101 concentration (X₂: 1.60–2.00% w/v) as Critical Material Attributes, with disintegration time and drug release as Critical Quality Attributes. Numerical desirability optimization identified F5*.

Film Preparation and Characterization

Films were prepared by solvent casting: HPMC E15 gel, MCC 101 dispersion, SLN dispersion (45 mL batch), glycerol, mannitol (2.0% w/v), citric acid (0.5% w/v), and mint flavour (0.2% v/v) were combined sequentially. Degassed casting solution was cast and dried; films were cut to 3 × 3 cm units (5.28 mg curcumin each). Films were evaluated for thickness, weight variation, surface pH, folding endurance, and disintegration time. In vitro release was studied by Franz diffusion cell in two phases: film dissolution (5–30 min) and NP sustained release (1–6 hr). Release data were fitted to five kinetic models. Accelerated stability of F5* was evaluated at 40°C ± 2°C / 75% RH ± 5% for 3 months (ICH Q1A(R2)).

RESULTS AND DISCUSSION

Preformulation Characterization

Curcumin appeared as a bright yellow-orange crystalline powder with a characteristic earthy aroma and bitter taste. The experimentally determined melting point of 183°C was in agreement with the Indian Pharmacopoeia (IP) reference range of 183–186°C, thereby confirming pharmacopeial purity and the absence of significant impurities or polymorphic variants. Solubility studies confirmed practical insolubility in water (< 0.1 mg/mL at 25°C), consistent with the BCS Class IV classification, and good solubility in ethanol, methanol, and acetone, the latter solvents being selected for SLN preparation. UV spectrophotometric characterization established a maximum absorption wavelength (λ_{max}) of 425 nm in both methanol and ethanol, consistent with the conjugated dienone chromophore of curcumin. Calibration curves constructed over the analytical range of 2–10 µg/mL were strictly linear in both solvents (methanol: $y = 0.0195x + 0.0074$, $R^2 > 0.999$; ethanol: $y = 0.0503x + 0.0560$, $R^2 > 0.999$), validating the spectrophotometric method for subsequent quantification of entrapment efficiency and drug release.

FTIR spectroscopy confirmed molecular identity through ten characteristic absorption peaks (Figure 1A). The diagnostic C–O–C ether stretch at 1149.37 cm^{−1}, phenolic O–H stretching at 3510.77 cm^{−1}, aromatic C–H at 3009.94 cm^{−1}, and conjugated C=O at 1590.99 cm^{−1} represent the defining spectral fingerprint of curcumin. Critically, all ten peaks appeared at identical wavenumbers (within ±5 cm^{−1}) in the curcumin–GMS physical mixture (Figure 1B) and the curcumin–HPMC E15–MCC 101 ternary blend (Figure 1C). Minor shifts within this tolerance range are attributable to physical mixing effects not chemical

interaction confirming complete physicochemical compatibility of curcumin with all excipients selected for both the SLN and film formulations (Rahman et al., 2023). DSC thermography revealed a single, sharp endothermic melting peak at 183°C (Figure 2). The sharpness and temperature of this endotherm confirm highly crystalline purity of the starting material; this high lattice energy is itself a primary contributor to poor aqueous solubility that SLN encapsulation through partial amorphization of the drug within the lipid core during rapid solidification is intended to address.

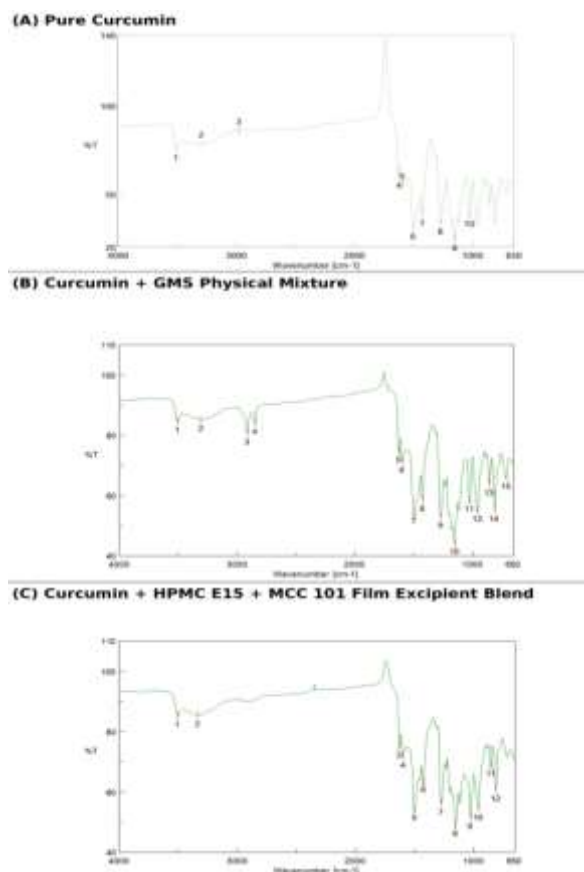


Figure 1. FTIR spectra: (A) Pure Curcumin; (B) Curcumin + GMS physical mixture; (C) Curcumin + HPMC E15 + MCC 101 film excipient blend — all showing retention of diagnostic peaks confirming excipient compatibility.

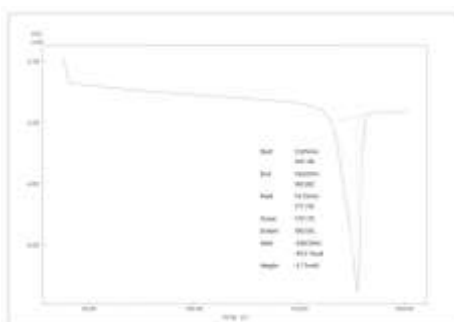


Figure 2. DSC thermogram of pure curcumin showing a sharp endothermic melting peak at 183°C, confirming crystalline nature.

Optimization and Characterization of Curcumin SLNs

Lipid screening identified GMS as optimal: it achieved complete curcumin solubilization at 1:5 drug: lipid ratio and the highest entrapment efficiency (99.85%), consistent with its strong hydrophobic affinity for curcumin ($\log P \approx 3.29$). Stearic acid,

beeswax, and cetyl alcohol were rejected due to inferior EE (65–78%) or incomplete drug dissolution. A Tween 80: Span 80 binary surfactant blend at 1.0% w/v (HLB = 12.86 $\approx$ 12.9) provided optimal particle size, PDI, and physical stability consistent with reported HLB requirements for stable o/w nanoemulsion formation (Akbari et al., 2025).

The optimized SLN formulation (Table I) achieved EE of 99.85%, drug loading of 11.32%, and drug content of 99.07% confirming near-quantitative encapsulation with minimal processing loss. The exceptional EE reflects the strong thermodynamic affinity of curcumin ($\log P \approx 3.29$) for the hydrophobic GMS core.

During the solvent-evaporation step, curcumin preferentially partitions into the solidifying lipid phase, leaving negligible free drug in the aqueous supernatant. This mechanism is supported by the FTIR compatibility data, which confirmed physical encapsulation without chemical conjugation.

Dynamic light scattering confirmed a mean particle size of 187.4 nm and PDI of 0.182 (Figure 3). PDI below 0.3 indicates a monodisperse colloidal system, a prerequisite for reproducible in vitro and in vivo performance. The nanometric size range (< 200 nm) is associated with enhanced mucosal and epithelial permeation, offering a mechanistic rationale for the anticipated bioavailability improvement over conventional curcumin oral formulations.

A minor secondary DLS peak at 1.7 nm is attributable to free surfactant micelles rather than drug-loaded nanoparticles. Zeta potential of -27.84 mV (Figure 4) reflects adequate electrostatic repulsion from the adsorbed Tween 80/Span 80 surfactant layer, providing sufficient stability against particle aggregation during storage.

This value is consistent with the -20 to -35 mV range reported for stable curcumin-SLN dispersions prepared by emulsification methods (Rahman et al., 2023; Liu et al., 2022). In vitro release from the SLN dispersion reached 47.3% at 6 hr, confirming sustained, diffusion-controlled release from the solid GMS matrix at physiological temperature.

Table 1. Characterization summary of the optimized curcumin SLN formulation, listing entrapment efficiency, drug loading, drug content, mean particle size, polydispersity index, zeta potential, and 6-hour in vitro release against their respective acceptance specifications

Parameter	Result	Specification / Remark
Entrapment Efficiency	99.85%	Near-quantitative encapsulation
Drug Loading	11.32%	Within 5–20% range for SLNs
Drug Content	99.07%	Minimal processing loss confirmed
Mean Particle Size (DLS)	187.4 nm	Nanometric; < 200 nm
Polydispersity Index (PDI)	0.182	Monodisperse; PDI < 0.3
Zeta Potential	-27.84 mV	Stable; $ \zeta > 20$ mV
In vitro Release at 6 hr	47.3%	Sustained matrix-diffusion release

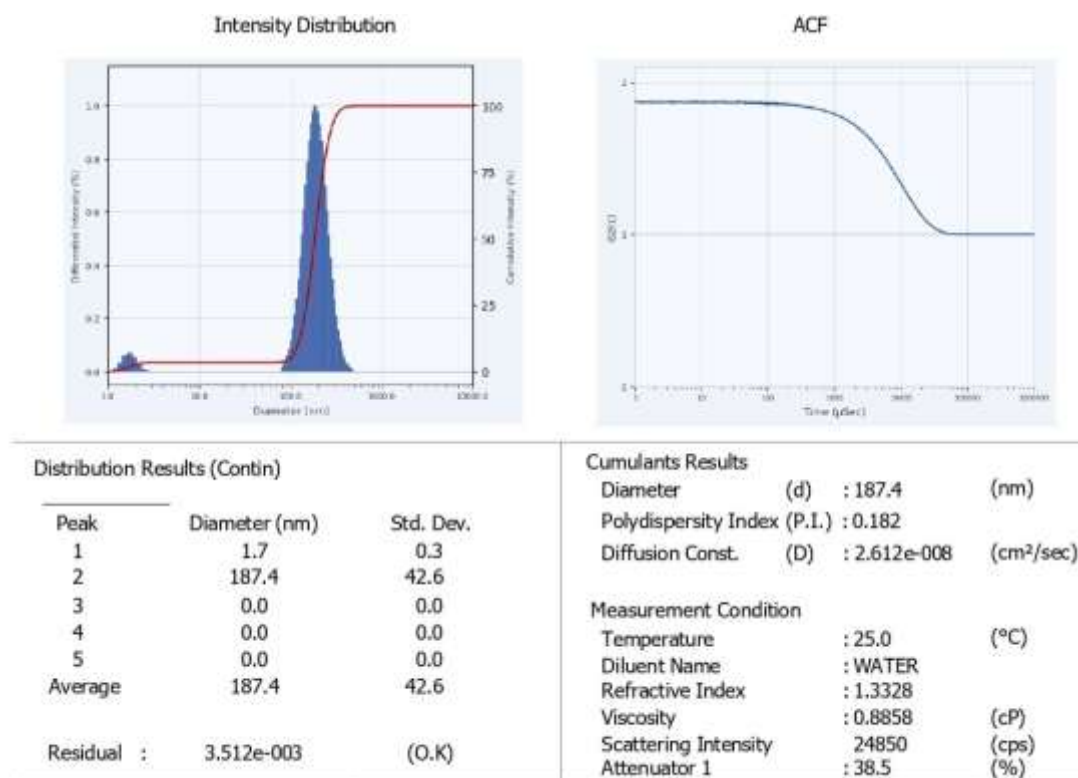


Figure 3. Particle size distribution (DLS) of optimized curcumin SLN formulation: mean particle size 187.4 nm, PDI 0.182.

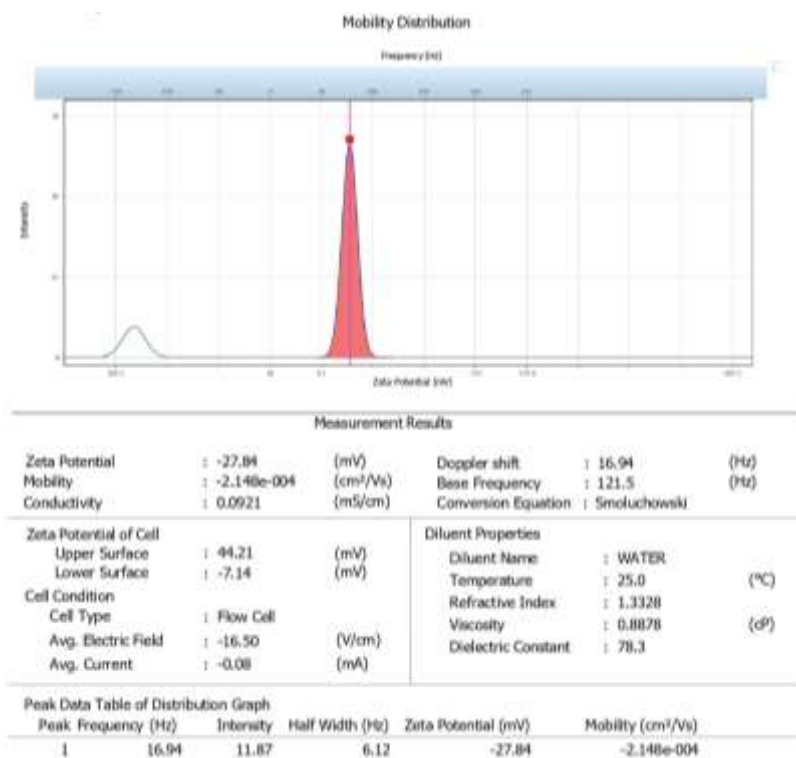


Figure 4. Zeta potential distribution of optimized curcumin SLN formulation: -27.84 mV confirming adequate colloidal stability.

DoE Optimization of SLN-Loaded Oral Films

Preliminary polymer screening selected HPMC E15 as optimal: it achieved the lowest disintegration time (36 ± 1.2 sec) and highest folding endurance (210 counts) among the three polymers evaluated, attributable to its intermediate viscosity (15 cPs) which provides adequate mechanical strength while enabling rapid hydration. Glycerol at 0.70% w/v was selected as plasticiser: it lowers the glass transition temperature (T_g) of HPMC E15 by disrupting inter-chain hydrogen bonds, increasing chain mobility and film flexibility without compromising disintegration performance. FTIR analysis confirmed complete absence of chemical interaction between curcumin, HPMC E15, and MCC 101 in the ternary blend (Figure 1C), validating the excipient selection for the film formulation.

Nine DoE film batches (F1–F9) were comprehensively characterized. All batches met acceptance criteria: DT 11.0–27.8 sec (< 30 sec), folding endurance 201–261 (> 200), drug content 92.2–93.6% (90–110%), surface pH 5.85–5.90 (within 5.5–7.0 for oral mucosal compatibility), and thickness 0.030–0.054 mm. Surface pH values reflect the presence of citric acid (0.5% w/v), which stimulates salivary secretion to facilitate film wetting while maintaining oral mucosal compatibility. All batches appeared smooth, uniform, pale yellow, and flexible, with no whiteness or oiliness. ANOVA yielded statistically significant first-order polynomial models:

$$Y_1 \text{ (Disintegration Time, sec)} = 17.39 + 2.04 \times X_1 - 1.81 \times X_2 \quad (R^2 = 0.979; F = 138.6; p < 0.0001)$$

$$Y_2 \text{ (Drug Release, \%)} = 93.41 - 0.093 \times X_1 - 0.305 \times X_2 \quad (R^2 = 0.875; F = 21.0; p = 0.002)$$

Both HPMC E15 and MCC 101 exerted significant opposing effects on disintegration time ($p < 0.0001$ each): increasing HPMC E15 prolonged disintegration by forming a denser gel barrier, while increasing MCC 101 accelerated it through capillary wicking and swelling — consistent with reported polymer–super disintegrant interactions in DoE-optimized oral films (Shah et al., 2022). A mechanistically significant finding: HPMC E15 was non-significant for drug release ($p = 0.107$), while MCC 101 was the sole significant factor ($p = 0.0008$). This confirms that curcumin release is governed by diffusion through the GMS SLN lipid matrix, not film polymer concentration the SLN solid lipid core acts as the primary rate-controlling membrane. Numerical optimization identified F5* (HPMC E15 = 2.64% w/v; MCC 101 = 1.71% w/v; D = 1.000).

In vitro Dual-Phase Drug Release and Kinetics

All batches exhibited the designed biphasic release profile characteristic of a nanoparticle-in-film dual-phase system. In the film dissolution phase (5–30 min), cumulative release across all batches ranged from 9–23%, attributable to two concurrent processes: rapid dissolution of the HPMC E15 film matrix upon salivary contact, releasing the dispersed SLN particles into the receptor medium; and surface-layer dissolution of curcumin from the outermost SLN lipid layers. The moderate initial release fraction ($< 25\%$ rather than near-complete burst) directly reflects the rate-controlling role of the solid GMS matrix, which remains solid at 37°C due to its elevated melting point ($55\text{--}65^\circ\text{C}$) and thereby restricts rapid drug diffusion even after film dissolution. In the subsequent nanoparticle-mediated sustained-release phase (1–6 hr), cumulative release progressed steadily, reaching 76.7–87.3% at 6 hr across all batches. The characteristic deceleration of release rate with time is consistent with progressive depletion of the curcumin concentration gradient within the GMS lipid core driving diffusion a pattern analogous to that reported for other curcumin SLN-in-film systems (Hosny et al., 2023). Batches with higher MCC 101 concentrations (F7–F9) showed slightly higher 6-hr release (84–87%) compared to lower MCC 101 batches (F1–F3; 77–80%), reflecting facilitated receptor medium accessibility to the SLN matrix through the more rapidly disintegrating film. The optimized F5* achieved 81.7% at 6 hr, representing the targeted balance between initial film-mediated and sustained SLN-mediated release. Kinetic modelling of the sustained phase confirmed the Korsmeyer–Peppas model as best fit for F1–F8 ($R^2 = 0.993\text{--}0.997$), outperforming zero-order (0.777–0.803), first-order (0.915–0.991), Higuchi (0.890–0.909), and Hixson–Crowell (0.876–0.964). The release exponent n ranged 0.662–0.718 ($0.45 < n < 0.89$), diagnostic of Non-Fickian anomalous transport — simultaneous Fickian diffusion through the lipid core and polymer chain relaxation from the film matrix. Batch F9 uniquely followed first-order kinetics ($R^2 = 0.999$), suggesting concentration-dependent release at maximum excipient loading.

Accelerated Stability Optimized Batch F5*

All critical quality attributes of F5* remained within specification over 3 months at $40^\circ\text{C}/75\% \text{ RH}$ (Table II). Drug content declined by only 0.74% (93.58% $\rightarrow$ 92.84%), and drug release at 6 hr decreased by 1.12% (81.66% $\rightarrow$ 80.54%), both within the $\leq 2\%$ deviation specification. No degradation, discoloration, cracking, or brittleness was observed, confirming GMS matrix

protection against curcumin degradation and HPMC E15 film mechanical integrity under accelerated conditions (Akbari et al., 2025).

Table 2. Accelerated stability data for the optimized batch F5* over 3 months at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ / $75\% \text{ RH} \pm 5\%$ (ICH Q1A(R2)), showing appearance, thickness, folding endurance, surface pH, disintegration time, drug content, and 6-hour drug release at the initial, 1-month, and 3-month time points against specification

Parameter	Initial	1 Month	3 Months	Specification
Appearance	Pale yellow	No change	No change	No change
Thickness (mm)	0.046 ± 0.005	0.046 ± 0.005	0.047 ± 0.005	≤ 0.06
Folding Endurance	242 ± 3	240 ± 3	238 ± 4	> 200
Surface pH	5.854 ± 0.008	5.857 ± 0.007	5.860 ± 0.009	$5.5-7.0$
Disintegration (sec)	17.53 ± 0.577	18.10 ± 0.577	18.65 ± 0.577	$< 30 \text{ sec}$
Drug Content (%)	93.58 ± 0.117	93.21 ± 0.134	92.84 ± 0.152	$90-110\%$
Release at 6 hr (%)	81.66 ± 0.85	81.12 ± 0.92	80.54 ± 1.08	$< 2\% \Delta$

All values Mean $\pm$ SD (n = 3). RH = Relative Humidity.

The collective results from Preformulation characterization, SLN optimization, film DoE, biphasic drug release profiling, and accelerated stability studies demonstrate the scientific rationale and technical feasibility of curcumin SLN-loaded rapidly disintegrating oral films as a dual-phase BCS Class IV drug delivery platform. Each component of the formulation was deliberately designed to address a specific barrier to curcumin's oral delivery: the SLN encapsulates the drug within a biocompatible solid lipid matrix to overcome aqueous insolubility and protect against first-pass degradation, while the RDOF ensures rapid pre-gastric delivery with minimum patient compliance barriers. Together, these two architectures produce a release profile that neither component can achieve independently.

The near-quantitative entrapment efficiency of 99.85% is particularly noteworthy and warrants mechanistic discussion. The thermodynamic affinity of curcumin ($\log P \approx 3.29$) for the hydrophobic GMS core is the primary driving force, but the selection of the binary Tween 80: Span 80 surfactant system at an optimized HLB of 12.9 appears to be equally critical. HLB values near 12–13 are characteristic of systems that form stable oil-in-water nanoemulsions, and this interfacial stability during the solvent-evaporation step prevents drug migration to the aqueous phase before solidification is complete. The combined effect of strong lipid–drug affinity and optimal interfacial surfactant coverage explains the superior EE relative to single-surfactant formulations reported in the literature. The particle size of 187.4 nm and PDI of 0.182 further reflect the efficiency of this interfacial stabilization: a monodisperse colloidal system of this size is associated with enhanced mucosal and epithelial permeability, providing a mechanistic basis for the anticipated bioavailability improvement over free curcumin suspensions.

The DoE findings reveal an important mechanistic insight about the relative roles of the film polymer and the nanoparticle carrier in governing drug release. The non-significance of HPMC E15 concentration for drug release ($p = 0.107$), contrasted with the high significance of MCC 101 ($p = 0.0008$), confirms that the SLN lipid matrix not the film polymer matrix is the rate-controlling element for curcumin release. This is a critical distinction: in conventional oral films without nanoparticle loading, the film polymer concentration is typically the primary determinant of drug release rate. The inversion of this relationship in the present system validates the dual-phase design principle and demonstrates that SLN encapsulation introduces an additional, dominant diffusion barrier that operates independently of the film formulation variables. This finding has practical significance for scale-up and product development: once the SLN parameters are fixed, film composition optimization can focus primarily on disintegration performance and patient acceptability (surface pH, folding endurance, taste masking) rather than drug release rate control.

The three-month accelerated stability data provide particularly strong evidence for the translational readiness of the F5* formulation. A drug content decline of only 0.74% and a drug release change of 1.12% over 90 days at $40^{\circ}\text{C}/75\% \text{ RH}$ conditions considerably more stressful than standard storage demonstrate that the GMS lipid matrix provides effective protection against

curcumin's known degradation pathways (alkaline pH instability, oxidative degradation, and photodegradation). The maintenance of mechanical properties (folding endurance: 242 $\rightarrow$ 238, well above the >200 specification) and rapid disintegration (17.53 $\rightarrow$ 18.65 sec, well within the <30 sec limit) over the stability period further confirms that the HPMC E15 film matrix retains its structural integrity without plasticizer migration or polymer chain scission under accelerated conditions. Collectively, these stability data satisfy the ICH Q1A(R2) requirements for shelf-life prediction studies and support the claim that the curcumin SLN-loaded oral film is a stable, shelf-viable pharmaceutical product candidate.

Comparison with Reported Literature

The characterization results for the optimized SLN formulation compare favourably with recently published curcumin-SLN studies. Rahman et al. (2023) reported EE of 87–94% and particle sizes of 150–250 nm for GMS-based curcumin SLNs prepared by analogous emulsification methods; the present study achieved EE of 99.85% and 187.4 nm. This improvement suggests that the binary Tween 80: Span 80 surfactant system, at its optimized HLB value of 12.9, provided superior interfacial coverage and drug retention compared to single-surfactant systems. Liu et al. (2022) reported zeta potentials of -18 to -25 mV for similar formulations; the -27.84 mV achieved here indicates marginally better colloidal stability, consistent with the use of the anionic contribution from the Span 80 head group at the nanoparticle surface.

For the oral film component, the DoE- optimized disintegration time of 17.5 sec for F5* is consistent with QbD- optimized HPMC-based fast-dissolving films reported by Shah et al. (2022) and Suryawanshi et al. (2021), which similarly achieved sub-20-second disintegration through polymer–superdisintegrant concentration optimization. The Non-Fickian release exponent ($n = 0.662$ – 0.718) observed in the present study is mechanistically comparable to values reported by Hosny et al. (2023) for lipid nanoparticle-in-film systems ($n = 0.61$ – 0.74), supporting the interpretation that anomalous transport in such systems arises from the simultaneous contribution of lipid matrix diffusion and polymer chain relaxation a mechanistic distinction not observed in conventional oral films where Fickian diffusion or first-order kinetics typically dominate. Taken together, these comparisons confirm that both the SLN and film components of the present formulation perform competitively relative to the current state of the art, while their combined dual-phase architecture delivers a release profile not achievable from either component alone.

Scale-Up and Clinical Applicability Considerations

From a translational standpoint, both unit operations employed here are amenable to industrial scale-up: the solvent emulsification– evaporation process used for the SLNs can be transferred to continuous high-pressure homogenization, while solvent casting of the films is readily adapted to roll-to-roll continuous coating. The exclusive use of GRAS-listed excipients (GMS, HPMC E15, MCC 101, glycerol, and mannitol) further supports regulatory and manufacturing feasibility for large-scale production. Realizing clinical applicability will, however, require in vivo pharmacokinetic confirmation of the bioavailability enhancement, buccal permeation and mucosal-irritation assessment, and pilot-scale process validation under ICH Q8–Q10 guidance. Together, these steps define a practical roadmap toward a clinically deployable, patient-friendly curcumin dosage form.

CONCLUSION

This study demonstrates the successful QbD based development of curcumin SLN-loaded rapidly disintegrating oral films as a dual-phase BCS Class IV delivery platform. Curcumin SLNs (GMS; drug: lipid 1:5; Tween 80: Span 80 4:1; HLB 12.9) achieved near-quantitative encapsulation (EE 99.85%), nanometric size (187.4 nm; PDI 0.182), and colloidal stability ($\zeta = -27.84$ mV). DoE-based optimization yielded statistically significant models confirming that SLN lipid matrix diffusion not film polymer governs drug release kinetics. The optimized F5* ($D = 1.000$) exhibited $DT = 17.5$ sec, $FE = 242$, drug content = 93.6%, and biphasic release reaching 81.7% at 6 hr following Non-Fickian transport ($n = 0.662$ – 0.718). Three-month accelerated stability confirmed integrity of all critical quality attributes. The curcumin SLN-loaded oral film represents a scientifically rational, patient-friendly platform with significant translational potential for oral diseases and neurodegenerative disorders. Future work will focus on in vivo pharmacokinetic and oral bioavailability evaluation in a suitable animal model to confirm the anticipated enhancement in curcumin absorption, followed by pilot-scale process validation to support clinical translation.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this manuscript. The authors have no financial, professional or personal relationships that could have influenced the reported work.

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