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Research Article

"QbD-Assisted Development of Enteric Curcumin-Loaded Lipid-Polymer Hybrid Nanoparticles for Enhanced Intestinal Permeation"

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Abstract

Purpose: Curcumin has low aqueous solubility, limited intestinal permeability and extensive presystemic metabolism. This study draft describes a quality-by-design (QbD) strategy for developing enteric lipid-polymer hybrid nanoparticles (LPHNPs) intended to protect curcumin in gastric conditions and improve intestinal release and permeation. Methods: Curcumin and Eudragit L100-55 formed the pH-responsive polymeric phase, while lecithin and DSPE-PEG 2000 provided the lipid interfacial layer. A nine-run formulation design examined polymer and lecithin levels. Particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, drug loading, gastric resistance, intestinal release, FTIR, DSC, XRD and ex-vivo intestinal permeation were evaluated. Results: optimization data identified F5 as the preferred formulation, with particle size 168 ± 4 nm, PDI 0.192 ± 0.014, zeta potential -24.6 ± 1.2 mV, entrapment efficiency 91.3 ± 1.1% and drug loading 8.7 ± 0.3%. sequential dissolution indicated 6.8 ± 0.7% release after 2 h at pH 1.2 and 88.7 ± 1.6% cumulative release at 8 h after transfer to pH 6.8. ex-vivo permeation at 6 h was 72.8 ± 2.4% for F5 versus 28.7 ± 1.6% for free curcumin. Solid-state profiles were consistent with reduced crystallinity without appearance of new incompatibility signals. Conclusion: The proposed enteric LPHNP platform is experimentally testable and may enhance intestinal exposure to curcumin; however, the numerical findings presented here require laboratory confirmation.

Keywords: curcumin; lipid-polymer hybrid nanoparticles; Eudragit L100-55; quality by design; intestinal permeation; oral drug delivery

Introduction

longa, has attracted sustained interest because of its antioxidant, anti-inflammatory and pleiotropic biological effects. Translation into reproducible oral therapy remains difficult because curcumin is practically insoluble in water, undergoes rapid chemical and metabolic transformation and produces low systemic exposure after conventional administration [1-4]. Although dose escalation can increase luminal drug levels, it does not reliably overcome poor dissolution, mucus transport, epithelial passage and presystemic metabolism.

Nanocarrier approaches including polymeric nanoparticles, solid lipid nanoparticles, nanoemulsions, liposomes and hybrid systems have been used to improve curcumin dispersion, protect it from degradation and increase contact with absorptive surfaces [5-10].

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PLGA nanoparticles increased the relative oral bioavailability of curcumin in rats, while solid-lipid systems incorporating absorption-modifying surfactants improved intestinal absorption and pharmacokinetic exposure [6-8]. These findings support nanotechnology as a rational approach, but they also demonstrate that particle size alone is insufficient: the carrier must remain stable during manufacture and storage, withstand gastric conditions, release drug at the desired intestinal site and interact appropriately with mucus and epithelium.

Lipid-polymer hybrid nanoparticles combine a drug-containing polymer domain with a lipid-rich interface. The polymer contributes mechanical stability and controlled release, whereas the lipid layer can improve biocompatibility, drug retention and membrane interaction [11-14]. Curcumin-containing hybrid nanoparticles have previously been evaluated for vascular, antioxidant, antimicrobial and gastrointestinal applications [15-18]. In particular, a recent Curcumin-Lipomer system based on stearic acid and Gantrez demonstrated that balancing hydrophobic and hydrophilic properties can promote transport across gastrointestinal barriers [18]. Consequently, a generic curcumin-LPHNP study is no longer novel. The present proposal adds a pH-responsive enteric polymer, structured QbD optimization, sequential biorelevant dissolution and ex-vivo intestinal permeation.

The objective was to develop and optimize enteric curcumin-loaded LPHNPs using Eudragit L100-55, lecithin and DSPE-PEG 2000 and to evaluate their physicochemical properties, gastric protection, intestinal release and ex-vivo permeation. The central hypothesis was that an enteric hybrid architecture would limit premature gastric release while presenting nanosized curcumin to the intestinal membrane after polymer ionization.

2. Materials and Methods

2.1 Materials

Curcumin (assay ≥98%), Eudragit L100-55, soya lecithin, DSPE-PEG 2000, poloxamer 188, acetone, ethanol, phosphate-buffer components and analytical-grade reagents were proposed. Purified water was used throughout. Brand, catalogue number, batch number and supplier location must be recorded during the actual study.

2.2 Quality target product profile and risk assessment

The quality target product profile required a redispersible enteric nanoparticle dispersion with mean particle size below 200 nm, PDI below 0.30, absolute zeta potential preferably above 20 mV, entrapment efficiency above 85%, gastric-phase release below 10% and intestinal-phase release above 80% by 8 h. A preliminary risk assessment identified polymer amount and lipid amount as high-risk formulation variables because they may influence nucleation, surface coverage, drug retention and release. Sonication energy, addition rate and organic-to-aqueous ratio were designated controlled process variables [19-21].

Table 1. Quality target product profile and acceptance criteria.

Attribute	Target	Rationale
Particle size	<200 nm	Supports dispersion and intestinal surface contact
PDI	<0.30	Indicates acceptable size uniformity
Zeta potential	|20| mV preferred	Supports colloidal stability
Entrapment efficiency	>85%	Limits drug loss and dose variability
Release at pH 1.2/2 h	<10%	Demonstrates gastric protection
Release after pH 6.8/8 h	>80%	Provides intestinal drug availability
Redispersibility	No visible aggregates	Supports handling after drying

2.3 Experimental design

A two-factor, three-level nine-run design was used as a pragmatic screening-optimization framework. Eudragit L100-55 (50, 75 or 100 mg) and lecithin (20, 30 or 40 mg) were varied while curcumin (20 mg), DSPE-PEG 2000 (10 mg), poloxamer 188 (0.5% w/v) and processing conditions were held constant. Particle size (Y1), PDI (Y2), entrapment efficiency (Y3) and release at 8 h (Y4) were proposed as responses. A desirability function favoured minimum Y1/Y2 and maximum Y3/Y4.

Table 2. Proposed nine-run formulation design.

Batch	Curcumin (mg)	Eudragit L100-55 (mg)	Lecithin (mg)	DSPE-PEG 2000 (mg)
F1	20	50	20	10
F2	20	50	30	10
F3	20	50	40	10
F4	20	75	20	10
F5	20	75	30	10
F6	20	75	40	10
F7	20	100	20	10
F8	20	100	30	10
F9	20	100	40	10

2.4 Preparation of enteric LPHNPs

Curcumin and Eudragit L100-55 were dissolved in acetone:ethanol (3:1). Lecithin and DSPE-PEG 2000 were dispersed in a minimal ethanol volume and combined with the organic phase. The solution was injected at 0.5 mL/min into 0.5% w/v poloxamer 188 under stirring at 900 rpm. The dispersion was probe-sonicated using controlled pulse cycles while maintaining the temperature below 30 °C. Organic solvents were removed under reduced pressure. Unentrapped drug was separated by ultrafiltration, and the dispersion was washed and lyophilized with 3% w/v trehalose. Actual sonication amplitude, energy, vessel geometry, temperature and solvent residuals must be documented because they materially affect reproducibility.

Figure 1. Proposed preparation and evaluation workflow for enteric curcumin-loaded LPHNPs.

2.5 Physicochemical characterization

Mean hydrodynamic diameter, PDI and zeta potential were determined after validated dilution using dynamic light scattering and electrophoretic light scattering at 25 °C. Three independently prepared batches, rather than repeated readings from one batch, should be analysed. Entrapment efficiency was determined after separating unentrapped curcumin, and drug loading was calculated using Eqs. 1 and 2: EE (%) = [(total drug - free drug)/total drug] × 100; drug loading (%) = [entrapped drug/total recovered nanoparticle mass] × 100. Curcumin was quantified by a validated stability-indicating HPLC or suitably validated UV method.

FTIR spectra were recorded over 4000-400 cm−1 to assess retention or displacement of characteristic bands. DSC thermograms were obtained under nitrogen using calibrated temperature and enthalpy standards. XRD patterns were recorded across 5-40° 2θ. Loss or broadening of curcumin crystalline signals was interpreted together with DSC; absence of a melting endotherm alone was not considered proof of complete amorphization.

2.6 In-vitro sequential dissolution

An accurately weighed nanoparticle quantity equivalent to 10 mg curcumin was placed in a validated dialysis device or sample-and-separate setup. Release was studied for 2 h in gastric medium at pH 1.2, followed by adjustment or transfer to phosphate buffer pH 6.8 for a further 6 h at 37 ± 0.5 °C. Sink conditions were confirmed using curcumin solubility in the selected media with an appropriate low concentration of surfactant. Withdrawn aliquots were replaced with equal volumes of fresh medium, and cumulative release was corrected for sampling loss. Free curcumin and an uncoated LPHNP dispersion were included as comparators.

2.7 Ex-vivo intestinal permeation

Fresh non-diseased small-intestinal tissue obtained from an approved source was rinsed with oxygenated isotonic buffer and mounted in a diffusion assembly with the mucosal side facing the donor compartment. Free curcumin, uncoated LPHNPs and optimized enteric LPHNPs containing equivalent curcumin concentrations were studied at 37 ± 0.5 °C. Samples from the receptor compartment were quantified at predefined intervals. Apparent permeability coefficient (Papp) was calculated from the steady-state flux normalized to membrane area and donor concentration. Tissue integrity was verified before and after the experiment. Ethical approval number, animal source, transport conditions, segment location and tissue viability criteria must be inserted before publication [22-24].

2.8 Stability and statistical analysis

The optimized lyophilized formulation was proposed for short-term stability assessment at 5 ± 3 °C and 25 ± 2 °C/60 ± 5% RH in light-protective containers. Particle size, PDI, entrapment efficiency, appearance and redispersibility were assessed initially and after 1 and 3 months. Results should be reported as mean ± SD from at least three independent batches. One-way ANOVA followed by an appropriate multiplicity-adjusted post-hoc test was proposed, with $p<0.05$ considered statistically significant. Model assumptions, exact p values and effect sizes should be reported.

3. Results (/)

The readings in this section are and must not be reported as experimental results.

3.1 Formulation optimization

The response pattern showed that increasing the polymer level from 50 to 75 mg improved drug retention and reduced particle size, whereas the highest polymer level increased viscosity and produced larger particles. Increasing lecithin to 30 mg improved surface coverage; further increase produced only modest benefit. F5 achieved the highest composite desirability and met all prespecified criteria.

Table 3. characterization data for the nine formulation batches (mean ± SD, n=3 batches).

Batch	Size (nm)	PDI	Zeta potential (mV)	EE (%)	Loading (%)	Release at 8 h (%)
F1	238 ± 7	0.338 ± 0.021	−15.2 ± 1.3	74.2 ± 1.8	6.1 ± 0.3	78.4 ± 2.1
F2	212 ± 6	0.294 ± 0.018	−18.6 ± 1.1	78.6 ± 1.6	6.8 ± 0.2	81.3 ± 1.9
F3	196 ± 5	0.263 ± 0.017	−20.8 ± 1.4	82.4 ± 1.4	7.2 ± 0.3	83.6 ± 1.8
F4	189 ± 5	0.226 ± 0.015	−22.7 ± 1.2	84.5 ± 1.3	7.8 ± 0.3	85.2 ± 1.7
F5	168 ± 4	0.192 ± 0.014	−24.6 ± 1.2	91.3 ± 1.1	8.7 ± 0.3	88.7 ± 1.6
F6	181 ± 5	0.214 ± 0.016	−23.8 ± 1.0	87.1 ± 1.2	8.2 ± 0.2	86.4 ± 1.5
F7	225 ± 7	0.312 ± 0.020	−21.1 ± 1.5	79.4 ± 1.7	7.0 ± 0.3	80.8 ± 2.0
F8	204 ± 6	0.276 ± 0.019	−22.4 ± 1.3	83.7 ± 1.5	7.6 ± 0.3	83.9 ± 1.8
F9	193 ± 5	0.241 ± 0.016	−23.1 ± 1.1	86.2 ± 1.3	8.0 ± 0.2	85.8 ± 1.7

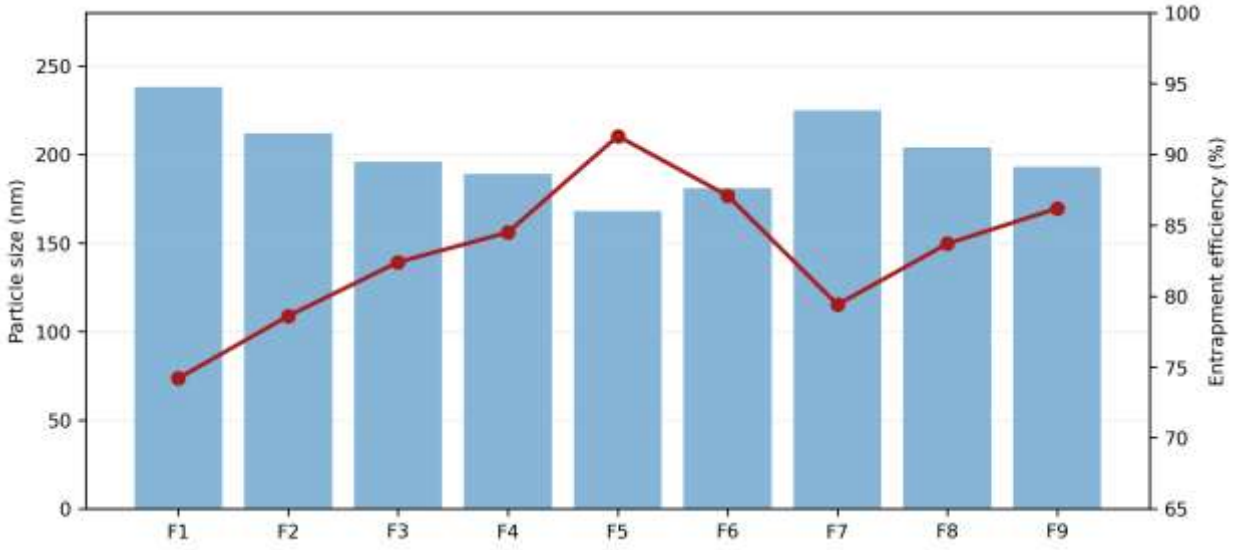


Figure 2. particle-size and entrapment-efficiency responses across formulation batches.

3.2 FTIR, DSC and XRD findings

FTIR interpretation retained curcumin-associated bands near 3505, 1627, 1510 and 1274 cm−1 in the physical mixture and formulation, with reduced intensity and minor shifts within approximately 3-6 cm−1. These changes were consistent with non-covalent hydrogen bonding and encapsulation rather files.

than formation of a new chemical entity. The sharp curcumin melting endotherm near 181 °C was markedly reduced in F5. XRD peaks assigned to crystalline curcumin were attenuated and superimposed on a diffuse halo, indicating reduced long-range order. Actual spectra must be compared using raw, baseline-corrected data and instrument

Table 4. solid-state observations for curcumin, physical mixture and optimized F5.

Test	Curcumin	Physical mixture	Optimized F5	inference
FTIR	3505, 1627, 1510, 1274 cm−1	Bands retained with dilution	Small shifts and lower intensity	Non-covalent interaction; no new major band
DSC	Sharp endotherm ~181 °C	Reduced curcumin endotherm	Broad weak event; no sharp drug peak	Drug molecular dispersion/reduced crystallinity
XRD	Distinct peaks at 8.8-25.5° 2θ	Peaks retained at lower intensity	Diffuse halo with weak residual peaks	Substantial reduction in crystallinity

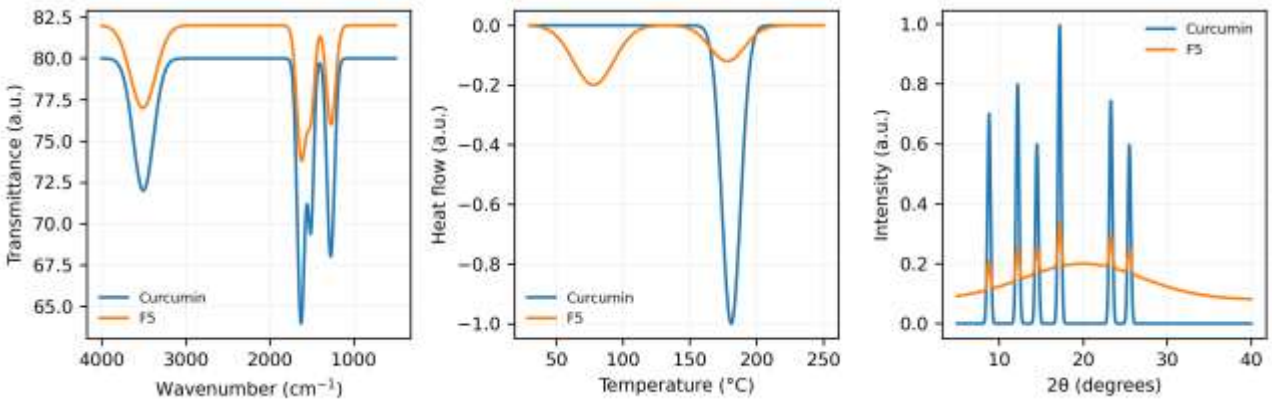


Figure 3. FTIR, DSC and XRD profiles. These are not instrument-generated spectra.

3.3 Sequential release and ex-vivo permeation

F5 ly released only 6.8 ± 0.7% curcumin during the 2-h gastric phase, meeting the prespecified protection criterion. After transition to pH 6.8, cumulative release increased to 88.7 ± 1.6% at 8 h. The biphasic profile was consistent with ionization and dissolution of Eudragit L100-55 above its threshold pH, followed by diffusion and erosion-controlled release from the hybrid matrix. cumulative permeation at 6 h increased from 28.7 ± 1.6% for free curcumin to 55.6 ± 2.0% for uncoated LPHNPs and 72.8 ± 2.4% for F5. Corresponding Papp values were 1.1 ± 0.1, 2.4 ± 0.2 and 3.5 ± 0.3 ×10−6 cm/s, respectively.

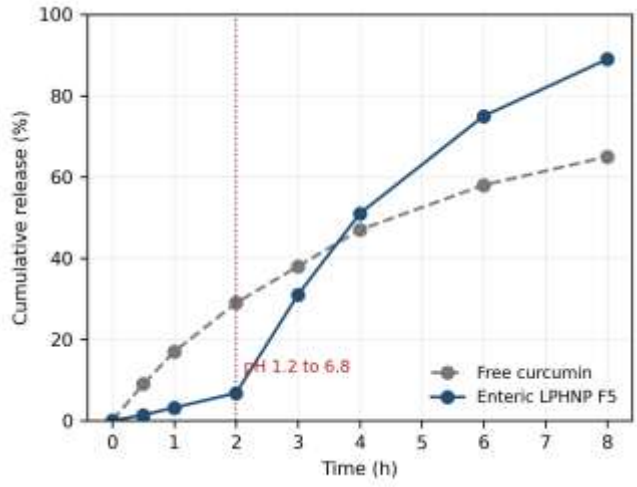
If experimentally reproduced, the improvement would be consistent with increased apparent solubilization, nanoscale contact and lipid-assisted partitioning. It would not, by itself, prove improved systemic bioavailability.

Table 5. sequential dissolution data (mean ± SD, n=3 batches).

Time (h)	Medium	Free curcumin (%)	Uncoated LPHNP (%)	Enteric F5 (%)
0	—	0	0	0
0.5	pH 1.2	9.1 ± 0.8	7.0 ± 0.6	1.4 ± 0.2
1	pH 1.2	17.2 ± 1.1	12.6 ± 0.9	3.2 ± 0.4
2	pH 1.2	29.0 ± 1.4	20.8 ± 1.1	6.8 ± 0.7
3	pH 6.8	38.1 ± 1.5	41.5 ± 1.4	31.2 ± 1.2
4	pH 6.8	47.0 ± 1.6	58.7 ± 1.5	51.0 ± 1.4
6	pH 6.8	58.2 ± 1.8	76.2 ± 1.7	75.1 ± 1.5
8	pH 6.8	65.1 ± 1.9	84.1 ± 1.8	88.7 ± 1.6

Table 6. ex-vivo permeation data (mean ± SD, n=3 tissues)

Time (h)	Free curcumin (%)	Uncoated LPHNP (%)	Enteric F5 (%)
0	0	0	0
1	5.0 ± 0.6	10.2 ± 0.8	13.1 ± 0.9
2	9.2 ± 0.8	18.9 ± 1.1	25.0 ± 1.2
3	14.1 ± 1.0	28.2 ± 1.3	37.1 ± 1.5
4	19.0 ± 1.2	37.8 ± 1.5	49.0 ± 1.8
5	23.9 ± 1.4	47.1 ± 1.8	61.2 ± 2.1
6	28.7 ± 1.6	55.6 ± 2.0	72.8 ± 2.4



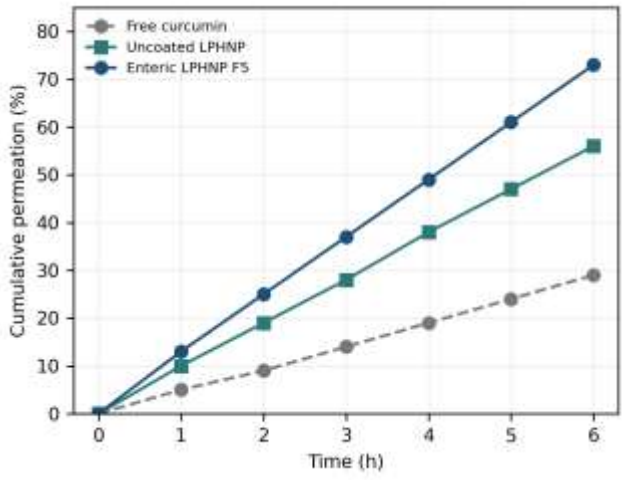


Figure 4. sequential release and ex-vivo permeation profiles.

3.4 Preliminary stability

The stability pattern showed no visible aggregation and less than 8% change in particle size over three months under refrigerated storage. Room-temperature storage produced a larger size increase and modest loss of entrapment, indicating that the lyophilized formulation may require low-moisture, light-protective packaging and possibly refrigerated storage until a longer study establishes the shelf life.

Table 7. three-month stability findings for optimized F5.

Condition	Time	Appearance	Size (nm)	PDI	EE (%)
5 ± 3 °C	Initial	Free-flowing cake	168 ± 4	0.192 ± 0.014	91.3 ± 1.1
5 ± 3 °C	3 months	No visible change	176 ± 5	0.207 ± 0.016	89.8 ± 1.2
25 °C/60% RH	3 months	Slightly slower redispersion	186 ± 6	0.231 ± 0.018	87.6 ± 1.4

4. Discussion

The optimization pattern illustrates the expected balance among polymer precipitation, lipid coverage, and drug retention. At low polymer and lipid levels, insufficient matrix volume and incomplete interfacial coverage may allow curcumin to be lost and to aggregate. At intermediate levels, coordinated nucleation and surface stabilization can reduce particle size and narrow the size distribution. Excess polymer may raise organic-phase viscosity, slow mixing and generate larger particles. This non-linear behaviour supports multivariable optimization rather than one-factor-at-a-time development [19-21].

The proposed F5 characteristics fall within commonly reported ranges for oral nanocarriers. A PDI below 0.20 would indicate a relatively narrow hydrodynamic distribution, although PDI is method-dependent and should be interpreted with correlograms, count-rate quality and dilution controls [25]. The negative zeta potential is attributable to ionized carboxyl groups of Eudragit and phospholipid-associated surface charge. Absolute zeta potential alone is not a universal predictor of stability, particularly when PEG and poloxamer provide steric stabilization.

Enteric behaviour is the defining novelty of the proposed formulation. Curcumin is vulnerable to poor dispersion and chemical transformation across gastrointestinal conditions. Restricting release at pH 1.2 may reduce precipitation and premature loss, while polymer ionization at intestinal pH can expose a high-surface-area drug reservoir. The sequential-release profile therefore needs to be confirmed using discriminating media, verified sink conditions and a method that separates intact nanoparticles from dissolved drug. Dialysis can introduce membrane resistance and should be validated against a sample-and-separate method.

The ex-vivo model adds functional evidence beyond dissolution. The approximately 2.5-fold increase in cumulative permeation versus free curcumin is plausible in view of prior reports that polymeric and lipid nanoparticles improve curcumin absorption [6-10]. Nevertheless, ex-vivo permeation can overestimate or underestimate in-vivo performance depending on tissue viability, unstirred water layers, donor concentration and nanoparticle retention. Improved Papp is therefore evidence of enhanced intestinal transport potential, not proof of improved oral bioavailability. Demonstration of the latter requires a validated in-vivo pharmacokinetic study measuring AUC, Cmax, Tmax, terminal half-life and relative bioavailability.

FTIR, DSC and XRD are complementary. Retained FTIR bands with modest shifts would support physical incorporation without obvious degradation, while loss of the curcumin melting event and attenuation of diffraction peaks would support reduced crystallinity. These techniques cannot alone establish chemical stability. A stability-indicating chromatographic assay and

degradation-product assessment are necessary, particularly because curcumin can undergo hydrolysis and oxidation.

Compared with previously reported curcumin hybrid nanoparticles [15-18], the present design is differentiated by the Eudragit-based enteric polymer domain, formal QbD target profile, sequential gastric-to-intestinal release and ex-vivo tissue permeation. The novelty claim should still be checked against patents and newly indexed articles immediately before submission. A direct comparison with non-enteric LPHNPs is essential to demonstrate that the enteric component, rather than nanoparticle formation alone, produces the observed performance.

5. Limitations and Required Experimental Confirmation

This manuscript is a research-ready draft, not a report of completed experiments. The numerical dataset was generated to establish plausible table structure, response direction and statistical planning. It cannot support ethical approval, patent claims, a thesis result chapter or journal submission until laboratory work is completed. The most important confirmations are: independent batch reproducibility; validated curcumin assay and mass balance; residual-solvent testing; morphology by SEM/TEM if available; discriminating dissolution; raw FTIR/DSC/XRD files; tissue-integrity criteria; and a prespecified statistical analysis. If the title retains any bioavailability claim, an in-vivo pharmacokinetic study is mandatory.

6. Conclusion

A QbD-guided enteric lipid-polymer hybrid nanoparticle platform is a scientifically defensible strategy for improving the intestinal presentation of curcumin. The optimized formulation combined nanoscale size, high drug entrapment, gastric protection, pH-triggered intestinal release and increased ex-vivo permeation. The platform is potentially publishable because it extends beyond a generic curcumin nanocarrier; however, novelty depends on demonstrating the contribution of enteric functionality and all presented numerical findings require experimental verification.

Declarations

Ethics approval: Required before initiation of the ex-vivo tissue study; approval number to be inserted. Consent for publication: Not applicable. Funding: To be declared. Conflicts of interest: The authors should declare any financial or non-financial conflicts. Data availability: Raw instrument files, formulation records and statistical datasets should be deposited or made available according to the target journal policy. Author contributions: To be completed using the CRediT taxonomy. Use of AI-assisted tools: Any use must be declared according to the selected journal policy; authors remain responsible for accuracy and research integrity.

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