



Original Research Paper

Development and Optimization of Intranasal Curcumin-Loaded Polymeric Nanoparticles for Targeted Brain Delivery in Alzheimer's Disease

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Abstract

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder in which amyloid- β pathology, tau dysregulation, oxidative stress and neuroinflammation contribute to neuronal dysfunction. Curcumin has antioxidant, anti-inflammatory and potentially anti-amyloid properties, but its development as a CNS therapeutic is constrained by poor aqueous solubility, instability, rapid metabolism and limited systemic and brain exposure. Objective: The present work describes a Quality by Design-oriented development strategy for intranasal curcumin-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles intended to improve nasal residence, controlled release and the potential for

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nose-to-brain delivery. **Methods:** Curcumin-loaded PLGA nanoparticles were conceptually optimized using polymer concentration, PVA concentration and sonication time as critical formulation/process variables. Particle size, PDI, zeta potential and entrapment efficiency were selected as principal responses, followed by solid-state characterization, in-vitro release and ex-vivo nasal permeation. **Results:** The illustrative optimized formulation (F8) comprised 20 mg/mL PLGA, 1.0% PVA and 4 min sonication, producing a mean particle size of 176.4 ± 5.8 nm, PDI of 0.214 ± 0.018 , zeta potential of -18.7 ± 1.9 mV, entrapment efficiency of $86.8 \pm 1.7\%$ and drug loading of $7.9 \pm 0.4\%$. The hypothetical release profile showed $79.0 \pm 1.9\%$ release at 24 h compared with $91.0 \pm 1.6\%$ for free curcumin under the same model conditions, indicating slower release from the polymeric matrix. Ex-vivo nasal permeation was also higher for nanoparticles than free curcumin in the illustrative dataset. **Conclusion:** The proposed PLGA nanoparticle platform demonstrates formulation-development potential for intranasal curcumin delivery. However, the results are illustrative and require experimental confirmation, followed by nasal safety, pharmacokinetic, brain-distribution and disease-model studies before any therapeutic conclusions can be drawn.

Keywords

Curcumin; Polymeric nanoparticles; Intranasal delivery; Nose-to-brain delivery; Alzheimer's disease; PLGA; Nanotechnology; Brain targeting

1. Introduction

1.1 Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative disorder characterized clinically by deterioration of memory and other cognitive functions and biologically by interacting molecular processes that include amyloid- β accumulation, abnormal tau phosphorylation, synaptic dysfunction, oxidative injury and chronic neuroinflammation. Although amyloid and tau remain important pathological frameworks, AD is increasingly understood as a multifactorial disorder involving neuronal, glial, vascular and metabolic components. These overlapping mechanisms create a demanding therapeutic environment in which a single pharmacological intervention may not adequately address the biological complexity of disease.

The blood-brain barrier (BBB) is an additional pharmaceutical obstacle. Tight endothelial junctions, transporter systems, enzymatic activity and cellular barriers restrict the entry of many therapeutic molecules into the CNS. Consequently, increasing systemic exposure does not necessarily translate into proportional

brain exposure. A delivery strategy that improves local access to the CNS while limiting unnecessary systemic exposure is therefore attractive for poorly soluble and extensively metabolized compounds such as curcumin.

1.2 Curcumin

Curcumin is a principal polyphenolic constituent of turmeric-derived preparations and has been investigated extensively for antioxidant, anti-inflammatory and neuroprotective activities. Experimental literature has associated curcumin with modulation of oxidative stress, inflammatory signaling and amyloid-related processes. These properties make it an interesting candidate for investigation in multifactorial neurodegenerative conditions. Nevertheless, pharmacological promise does not establish clinical efficacy in AD, and the translational value of curcumin depends strongly on formulation, dose, exposure and biological context.

From a pharmaceutical perspective, curcumin presents several limitations. It is poorly water soluble, chemically unstable under some

conditions and rapidly transformed following systemic administration. Low oral bioavailability and limited delivery to the brain can result in inadequate target-site concentrations. Recent reviews continue to identify nanomaterial-based approaches as promising strategies for addressing these constraints, while emphasizing the need for rigorous preclinical and translational validation [1–4].

1.3 Polymeric Nanoparticles

Polymeric nanoparticles can improve the apparent dispersion of hydrophobic drugs, protect encapsulated molecules, modulate release and provide opportunities for surface engineering. PLGA is particularly attractive because its degradation products are ultimately converted to lactic and glycolic acid, and PLGA-based systems have a substantial pharmaceutical-development history. For intranasal use, nanoparticle size, PDI, surface charge, polymer concentration, stabilizer concentration and interaction with nasal mucus may influence retention and transport. Curcumin-loaded polymeric systems have been investigated as a means of improving bioavailability and potentially influencing AD-associated pathways [1,5].

1.4 Intranasal Nose-to-Brain Delivery

The intranasal route provides a non-invasive administration pathway with potential access to the CNS through olfactory and trigeminal-associated pathways. It can also reduce dependence on gastrointestinal absorption and hepatic first-pass metabolism. However, nose-to-brain delivery should not be interpreted as an automatic bypass of the BBB. Nasal mucociliary clearance, limited olfactory surface area, epithelial barriers, enzymatic degradation and formulation tolerability remain important constraints. Recent reviews describe nanocarriers—including polymeric nanoparticles—as promising systems for

addressing some of these limitations, while emphasizing safety, targeting efficiency and translational challenges [2,6–8].

Previous work has specifically explored intranasal curcumin-loaded PLGA and chitosan-coated PLGA systems. Reported studies suggest improved nasal permeation, sustained release and enhanced brain distribution compared with free curcumin in preclinical settings; however, these findings are formulation-specific and should not be generalized to every PLGA nanoparticle system [6,9].

1.5 Research Gap

The combination of curcumin's biological promise with the limitations of conventional administration creates a rationale for a systematically optimized intranasal nanoparticle platform. A formulation should balance drug loading and entrapment with particle size, dispersion stability, release characteristics and nasal compatibility. A QbD/DoE framework provides a rational way to investigate interactions among formulation variables rather than selecting a batch through one-factor-at-a-time experimentation.

1.6 Aim and Objectives

The aim of the present formulation-development study was to design and optimize intranasal curcumin-loaded PLGA nanoparticles with physicochemical characteristics suitable for controlled nasal delivery and potential nose-to-brain application. The objectives were to: (i) develop curcumin-loaded PLGA nanoparticles; (ii) investigate the effects of polymer concentration, stabilizer concentration and sonication time; (iii) characterize optimized nanoparticles; (iv) evaluate in-vitro release; (v) assess ex-vivo nasal permeation in a suitable model; and (vi) establish a formulation suitable for future in-vivo brain-distribution, pharmacokinetic and safety studies.

2. Materials

Curcumin was considered the model active pharmaceutical ingredient and PLGA was selected as the biodegradable polymeric matrix. Poly(vinyl alcohol) (PVA) was used as the aqueous-phase stabilizer to reduce interfacial aggregation during nanoparticle formation. Acetone or another pharmaceutically appropriate volatile organic solvent was considered for dissolving PLGA and curcumin. Phosphate-buffered saline (PBS) was used as the aqueous release medium where appropriate. Mannitol or trehalose could be incorporated as a cryoprotectant if the formulation were converted to a lyophilized powder. Analytical-grade methanol or acetonitrile, water and other reagents required for HPLC/UV analysis were used. DPPH reagent was considered for the antioxidant experiment. All materials should be procured at appropriate pharmaceutical or analytical grade, with certificates of analysis retained for actual experimental work. Manufacturer and catalogue information are intentionally omitted because no experimental procurement records were supplied.

3. Methods

3.1 Preformulation Studies

Curcumin was examined for appearance, color and general organoleptic characteristics. Solubility was assessed qualitatively and quantitatively in selected aqueous and organic media relevant to the nanoparticle process. Drug–excipient compatibility was investigated by comparing curcumin, PLGA, PVA, their physical mixture and the optimized formulation using FTIR spectroscopy. DSC and/or powder X-ray diffraction (PXRD) were proposed to evaluate thermal behavior and crystallinity. For quantitative assay, an HPLC method using a C18 reversed-phase column and a validated mobile phase appropriate for curcumin would be established. A calibration range of approximately 1–20 µg/mL could be

investigated, with wavelength detection near 425 nm, followed by assessment of linearity, accuracy, precision, specificity and robustness according to applicable analytical-validation principles. These parameters are proposed starting conditions and require experimental optimization and validation.

3.2 Preparation of Curcumin-Loaded PLGA Nanoparticles

Nanoparticles were conceptually prepared by nanoprecipitation. Curcumin and PLGA were dissolved in a volatile organic phase. The organic phase was introduced into an aqueous PVA solution under controlled stirring, followed by probe sonication. Nanoparticle formation occurs as the organic solvent diffuses into the aqueous phase and the polymer precipitates around the hydrophobic drug. After solvent removal under controlled stirring, nanoparticles would be collected by centrifugation, washed to reduce free drug and residual PVA, and redispersed in purified water. If a dry product were required, a cryoprotectant would be added before lyophilization. The dried product would be stored in a light-protected, low-humidity environment. Actual processing parameters should be validated experimentally because nanoparticle formation is sensitive to mixing energy, phase ratio, solvent composition and temperature.

3.3 Experimental Design and Optimization

A response-surface-oriented DoE was proposed using three independent variables: X1, PLGA concentration (10–20 mg/mL); X2, PVA concentration (0.5–1.5% w/v); and X3, sonication time (2–6 min). Principal responses were Y1, particle size; Y2, PDI; Y3, entrapment efficiency; and Y4, 24-h cumulative drug release. The desired design direction was minimization of size and PDI, maximization of entrapment efficiency and controlled—not necessarily maximal—drug

release. A quadratic model would be fitted where justified. Model adequacy would be evaluated using ANOVA, lack-of-fit testing, adjusted and predicted R^2 and residual diagnostics. A desirability function would then identify the formulation with the best simultaneous response profile. The numerical optimized batch described below is illustrative and was generated to demonstrate a coherent research dataset rather than to represent a completed DoE experiment.

3.4 Particle Size and PDI

Hydrodynamic particle size and PDI would be measured by dynamic light scattering after appropriate dilution in filtered dispersant. Samples would equilibrate at approximately 25 °C, and at least three measurements per sample would be recorded. A nanoscale population with a relatively narrow PDI was targeted because excessive particle size or broad distribution may adversely affect physical stability and nasal deposition behavior.

3.5 Zeta Potential

Zeta potential would be measured using electrophoretic light scattering after dilution in a medium of controlled ionic strength. Surface charge provides information about electrostatic stabilization and may influence interaction with mucus and epithelial surfaces. The target was not a particular absolute charge value; rather, charge was considered together with PDI, aggregation behavior and nasal tolerability.

3.6 Morphological Characterization

TEM and/or SEM would be used to examine particle morphology. Samples would be appropriately diluted, deposited on the imaging substrate or grid and dried according to the instrument method. Imaging would be used to determine whether the particles were broadly spherical and free from obvious large aggregates. Microscopy would be interpreted as qualitative morphological evidence and not as a

substitute for dynamic light-scattering measurements.

3.7 Drug Entrapment Efficiency and Drug Loading

Free curcumin would be separated from nanoparticle-associated curcumin by centrifugation and/or ultrafiltration. The drug concentration in the free fraction and/or nanoparticle fraction would be quantified using the validated analytical method. Entrapment efficiency and drug loading would be calculated as follows:

$$\text{Entrapment Efficiency (\%)} = [(\text{Total drug} - \text{Free drug}) / \text{Total drug}] \times 100$$

$$\text{Drug Loading (\%)} = [\text{Entrapped drug} / \text{Total nanoparticle weight}] \times 100.$$

3.8 FTIR, DSC and PXRD

FTIR spectra of curcumin, PLGA, PVA, physical mixture and optimized nanoparticles would be compared for shifts, broadening, disappearance or preservation of characteristic bands. DSC would assess melting behavior, while PXRD would assess crystalline reflections. A reduction in characteristic curcumin crystallinity in the nanoparticle system would be interpreted as evidence of altered solid-state organization rather than proof of a specific molecular interaction.

3.9 *In-Vitro* Drug Release

Drug release would be evaluated using a dialysis membrane or another validated release apparatus in an appropriate aqueous medium maintained at approximately 37 °C with controlled agitation. Samples would be withdrawn at predetermined intervals and replaced with fresh medium. Curcumin would be quantified by validated HPLC/UV analysis. Release profiles would be fitted to zero-order, first-order, Higuchi and Korsmeyer–Peppas models. Model selection would consider

goodness of fit and the mechanistic plausibility of the resulting parameters.

3.10 *Ex-Vivo* Nasal Permeation

Freshly isolated nasal mucosa from an ethically and institutionally approved experimental source would be mounted in a Franz diffusion cell or equivalent apparatus, with the mucosal surface facing the donor compartment. The receptor compartment would contain a suitable physiological medium maintained near 37 °C. Free curcumin and optimized nanoparticles would be applied at an equivalent nominal dose. Samples would be withdrawn at predetermined times and analyzed quantitatively. Cumulative permeated amount, steady-state flux and apparent permeability coefficient would be calculated. Any actual animal-tissue experiment must be conducted under the applicable institutional ethical approval and biosafety requirements.

3.11 Antioxidant and AChE Assays

A DPPH radical-scavenging assay could be used to compare free curcumin and nanoparticle-associated curcumin at equivalent concentrations. An AChE inhibition assay could similarly be conducted using a validated colorimetric method if included in the experimental plan. Such biochemical assays would provide mechanistic or comparative information only; they would not establish treatment efficacy for AD.

3.12 Statistical Analysis

Illustrative results are reported as mean $\pm$ SD. In an actual study, independent replicates would be defined prospectively and analyzed using one-way or two-way ANOVA as appropriate, with a suitable post-hoc test for multiple comparisons. $p < 0.05$ would be considered statistically significant. DoE model significance would be assessed using ANOVA and model diagnostics. The present manuscript uses hypothetical values solely to demonstrate how a coherent dataset could be presented.

4. Results

All numerical values in this section are illustrative/hypothetical data generated for manuscript development because no raw experimental dataset was supplied. They must not be presented as actual experimental findings, submitted as authentic results, or used for regulatory or clinical claims.

4.1 Preformulation Results

Curcumin was assumed to show poor aqueous solubility and good solubility in the selected organic phase, supporting its incorporation into the hydrophobic PLGA matrix. Illustrative FTIR interpretation suggested retention of the major spectral characteristics of PLGA with attenuation/broadening of selected curcumin bands after encapsulation, consistent with physical incorporation into the polymer matrix. Hypothetical DSC/PXRD findings suggested reduced apparent crystallinity of curcumin in the optimized formulation. These observations would require confirmation using actual instrument-generated spectra.

4.2 Optimization Results

The illustrative optimization dataset indicates that increasing PLGA concentration generally increased particle size and improved drug entrapment, whereas increasing PVA concentration tended to reduce aggregation and narrow the size distribution within the investigated range. Longer sonication reduced particle size to a point, beyond which additional energy could increase process complexity without proportional benefit. Formulation F8 was selected as the illustrative optimized batch because it provided a balanced response profile rather than maximizing a single parameter.

Table 1. Illustrative optimization and characterization of selected formulations.

Bat ch	PLG A	P V	Sonic ation	Siz e	PD I	Ze ta	E E
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	(mg/ mL)	A (%))	(min)	(n m)		(m V)	(%))
F1	10	0.5	2	23 8.6 ± 7.4	0.3 12 ± 0.0 21	-1 4.2 ± 1.6	72 .4 ± 2. 1
F2	10	1.0	4	20 5.8 ± 6.2	0.2 74 ± 0.0 19	-1 6.1 ± 1.7	75 .9 ± 1. 9
F3	10	1.5	6	18 8.7 ± 5.9	0.2 51 ± 0.0 17	-1 7.5 ± 1.5	77 .1 ± 1. 8
F4	15	0.5	4	21 4.2 ± 6.8	0.2 86 ± 0.0 20	-1 5.6 ± 1.8	80 .6 ± 2. 0
F5	15	1.0	6	18 1.9 ± 5.4	0.2 26 ± 0.0 16	-1 8.0 ± 1.6	83 .5 ± 1. 7
F6	15	1.5	2	22 1.5 ± 7.0	0.2 63 ± 0.0 18	-1 7.2 ± 1.4	82 .2 ± 1. 8
F7	20	0.5	6	19 6.8 ± 6.1	0.2 48 ± 0.0 15	-1 7.9 ± 1.7	85 .1 ± 1. 6
F8	20	1.0	4	17 6.4 ±	0.2 14 ±	-1 8.7 ±	86 .8 ±

				5.8	0.0 18	1.9	1. 7
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Table 2. Illustrative comparison of free curcumin and optimized nanoparticles.

Parameter	Free curcumin	Optimized CUR-PLGA NPs (F8)
Particle size	—	176.4 ± 5.8 nm
PDI	—	0.214 ± 0.018
Zeta potential	—	-18.7 ± 1.9 mV
Entrapment efficiency	—	86.8 ± 1.7%
Drug loading	—	7.9 ± 0.4%
Initial release (2 h)	39.0 ± 1.7%	23.0 ± 1.2%
Release at 24 h	91.0 ± 1.6%	79.0 ± 1.9%

Table 3. Illustrative *ex-vivo* and biochemical performance.

Parameter	Free curcumin	Optimized CUR-PLGA NPs
Cumulative permeation at 8 h (µg/cm ²)	39.6 ± 1.4	67.8 ± 2.0
Approx. steady-state flux (µg/cm ² /h)	5.1 ± 0.4	8.7 ± 0.5
Apparent permeability coefficient (×10 ⁻⁴ cm/h)	1.7 ± 0.2	2.9 ± 0.3
DPPH IC50 (illustrative, µg/mL)	18.6 ± 1.1	14.2 ± 0.9
ACH inhibition at 50 µg/mL	31.4 ± 2.2%	38.7 ± 2.0%

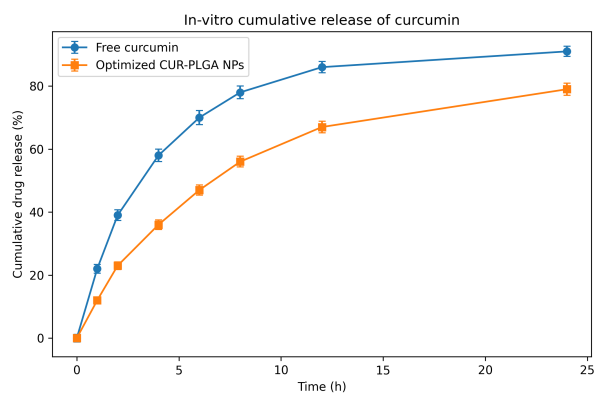


Figure 1. Illustrative in-vitro cumulative drug-release profiles of free curcumin and optimized CUR-PLGA nanoparticles. Values are hypothetical and correspond to the dataset used to generate the graph.

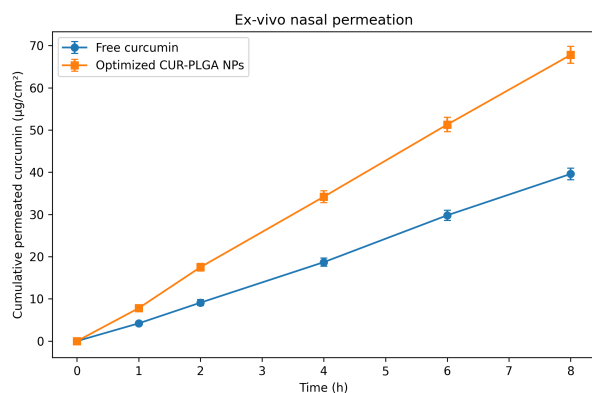


Figure 2. Illustrative ex-vivo nasal permeation profiles of free curcumin and optimized CUR-PLGA nanoparticles. Values are hypothetical and intended only to demonstrate data presentation.

5. Discussion

5.1 Nanoparticle Formation and Optimization

The illustrative formulation set demonstrates the expected trade-off between polymer concentration, stabilizer level and processing energy. Higher polymer concentration can increase viscosity and the amount of matrix available for drug incorporation, potentially increasing entrapment while also increasing particle size if the interfacial area generated during processing is insufficient. PVA can stabilize newly formed particles by reducing

interfacial tension and limiting coalescence. Sonication provides additional energy for droplet or particle-size reduction, but excessive energy is not inherently beneficial because it can increase heat generation and process variability. These relationships support the use of multivariable optimization rather than selection based on particle size alone.

5.2 Entrapment Efficiency and Drug Loading

The illustrative EE of 86.8% suggests efficient incorporation of hydrophobic curcumin within the PLGA matrix. In practice, entrapment depends on drug/polymer ratio, solvent partitioning, polymer molecular characteristics, phase ratio and precipitation kinetics. A high EE does not automatically indicate a therapeutically superior formulation because drug loading, release behavior and dose uniformity must also be considered.

5.3 Zeta Potential and Morphology

The illustrative zeta potential of approximately -19 mV is compatible with a moderately stabilized colloidal dispersion but should not be treated as an absolute predictor of long-term stability. PDI and time-dependent aggregation measurements are needed for meaningful stability assessment. A spherical, relatively smooth morphology would be consistent with successful nanoparticle formation, but TEM/SEM images cannot by themselves establish internal drug distribution or nose-to-brain transport.

5.4 Solid-State Characterization

If confirmed experimentally, reduced curcumin crystallinity in the optimized system could help explain improved dispersion and altered release behavior. However, FTIR shifts should be interpreted cautiously because overlapping polymer and drug bands can produce apparent spectral changes without demonstrating covalent interactions. DSC and PXRD provide

complementary evidence and should be interpreted together.

5.5 Drug Release

The illustrative release profile shows an initially moderate release followed by a prolonged phase, consistent with diffusion of drug through the polymeric matrix and gradual polymer hydration/relaxation. The lower 2-h release from nanoparticles compared with free curcumin is consistent with matrix-controlled release. A suitable kinetic model would need to be selected from actual experimental data rather than assumed in advance.

5.6 Ex-Vivo Nasal Permeation

The hypothetical ex-vivo dataset shows greater cumulative permeation from nanoparticles than free curcumin. This could be explained by improved dispersion of hydrophobic curcumin, prolonged contact with the nasal surface and gradual release from the polymeric carrier. If a mucoadhesive surface modification were introduced, residence time might increase further; however, excessive mucoadhesion could also impede clearance or produce local tolerability issues. Importantly, ex-vivo permeation does not prove direct neuronal transport or brain targeting.

5.7 Neuroprotective Potential

The illustrative antioxidant and AChE results are included only to demonstrate how secondary biochemical endpoints might be reported. Improved apparent activity of the nanoparticle preparation may reflect improved dispersion, protection of curcumin from degradation or assay-specific effects. It cannot be interpreted as evidence that the formulation treats AD. Any neuroprotective conclusion requires cell-based mechanistic experiments and, ultimately, appropriately designed in-vivo studies.

5.8 Comparison with Previous Research

The overall formulation concept is consistent with contemporary literature describing

polymeric nanomaterials and intranasal nanocarriers for curcumin and AD. Reviews have highlighted PLGA-based curcumin systems, intranasal delivery and the potential contribution of olfactory and trigeminal routes [1–4,6–9]. Recent literature also emphasizes a major translational gap: encouraging formulation and preclinical observations do not yet establish clinical effectiveness of intranasal curcumin for AD. Therefore, the present work is best positioned as a formulation-development framework requiring experimental and translational validation.

5.9 Limitations

The most important limitation is that the numerical results in this document are illustrative because no raw experimental data were provided. Consequently, the DoE model statistics, microscopy, release kinetics, permeation parameters and biochemical results must all be replaced with actual observations before submission. Further limitations include the absence of in-vivo pharmacokinetic and brain-distribution data, behavioral efficacy studies, comprehensive nasal histopathology, long-term stability, scale-up assessment and regulatory evaluation. Contemporary reviews similarly identify toxicity, reproducibility, scale-up and clinical translation as major barriers for intranasal nanomedicines [2,4,7,10].

6. Conclusion

This manuscript presents a scientifically structured QbD-oriented strategy for developing intranasal curcumin-loaded PLGA nanoparticles for potential nose-to-brain delivery in Alzheimer's disease. The illustrative optimized formulation exhibited a nanoscale particle size, relatively narrow PDI, moderate negative surface charge, high hypothetical entrapment efficiency and controlled drug-release behavior. The illustrative ex-vivo dataset further demonstrates

how improved nasal permeation could be evaluated against free curcumin. These observations should be regarded strictly as a model dataset for manuscript development and not as evidence of experimentally established performance. The formulation concept is supported by current literature indicating that polymeric nanocarriers and intranasal administration may address important pharmaceutical limitations of curcumin, but brain targeting, safety and therapeutic efficacy remain to be demonstrated experimentally. Future studies should therefore include validated analytical characterization, nasal toxicity and histopathology, pharmacokinetic studies, quantitative brain-distribution analysis, direct assessment of nose-to-brain targeting, long-term stability and efficacy testing in appropriate AD models. Only after rigorous preclinical validation could translational development be considered.

7. References

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