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Polymer Selection Governs Nanocarrier Performance in Nose-to-Brain Delivery: A Unified Box–Behnken Comparison of Chitosan, Polycaprolactone and PLGA Systems for Two Antidepressants

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Abstract

Carrier polymer is routinely chosen by convention rather than by evidence in nose-to-brain nanomedicine, and the absence of matched comparisons makes the consequences of that choice difficult to judge. This work addresses the deficit directly by developing four antidepressant-loaded nanoparticulate systems under a single, identical experimental framework. Viloxazine and venlafaxine were each encapsulated in a cationic polysaccharide (chitosan) and in a synthetic aliphatic polyester (polycaprolactone for viloxazine, poly(lactide-co-glycolide) for venlafaxine), giving the systems designated VXCN, VPNS, VFCN and VPLNP. Every system was optimised through a three-factor, three-level Box–Behnken design of seventeen runs, with particle size, entrapment efficiency and polydispersity index as responses and identical characterisation applied throughout.

All four quadratic models were statistically significant ($F = 15.41\text{--}164.86$; $p \leq 0.0008$) with non-significant lack of fit, and confirmation batches prepared at the software-predicted optima agreed with prediction to within 4.8% for every response. The optimised carriers differed systematically by polymer class rather than by drug. Chitosan systems consistently produced the smallest particles (160.0 and 170.7 nm) with cationic or weakly anionic surfaces suited to mucoadhesion, but the lowest entrapment for viloxazine (70.1%). The polyesters delivered higher payloads — 78.12% for polycaprolactone and 83.61% for PLGA — with PLGA additionally furnishing the strongest electrokinetic stabilisation (-24.9 mV) at a size comparable to chitosan (172.0 nm). Polycaprolactone was the outlier, giving a particle size roughly twice that of the other three systems (323.7 nm) and falling outside the dimensional window generally regarded as favourable for transmucosal uptake. Chitosan nanoparticles were converted into Carbopol-934 in-situ gels; batches VXCN-NPG4 and VFCN-G5 combined nasal-compatible pH (5.58 and 5.71), sol–gel transition within the physiological window (31.4 and 29.8 °C) and the highest drug content of their series. Across excised goat nasal mucosa, all optimised carriers markedly exceeded the corresponding plain drug dispersions, reaching 96% cumulative permeation at 24 h

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against 60% for unformulated drug, while histopathology confirmed that mucosal architecture remained intact. Formulations were physically stable over three months.

The study demonstrates that polymer identity, not drug identity, is the dominant determinant of nanocarrier quality attributes in this delivery route, and that the trade-off between mucoadhesive potential and encapsulation capacity is systematic and predictable. These findings provide a rational, statistically grounded basis for carrier selection in intranasal CNS formulation development.

Keywords: Nose-to-brain delivery; Box–Behnken design; Quality by Design; Chitosan; Polycaprolactone; PLGA; Viloxazine; Venlafaxine; In-situ gel; Nasal mucosa.

Highlights

- Four antidepressant nanocarriers were optimised under one identical Box–Behnken framework, permitting a genuine head-to-head polymer comparison.
- Polymer class, rather than drug identity, dictated particle size, entrapment efficiency and surface charge.
- Chitosan minimised particle size and conferred mucoadhesive surface character; polyesters maximised payload.
- Viloxazine-loaded polycaprolactone nanoparticles are reported here for the first time.
- All optimised carriers raised transmucosal permeation from 60% to 96% at 24 h without compromising nasal mucosal integrity.

Graphical Abstract

The graphical abstract is arranged as a single horizontal flow. At the left, two antidepressant molecules (viloxazine and venlafaxine) feed into a central panel depicting three biodegradable polymers — chitosan, polycaprolactone and PLGA — each rendered as a distinct nanoparticle. A shared Box–Behnken cube sits beneath the central panel to signify that all four systems passed through one identical optimisation framework. The right-hand third shows a sagittal section of the nasal cavity with the olfactory and trigeminal routes indicated by arrows converging on the brain, bypassing a stylised blood–brain barrier. Four labelled callouts beneath the nasal diagram carry the defining attribute of each optimised carrier (160.0 nm, 323.7 nm, 170.7 nm, 172.0 nm and their respective entrapment efficiencies), and a single summary strip beneath the whole figure reads “permeation 60% → 96%, mucosa intact”.

1. Introduction

Depressive disorder is among the most prevalent contributors to global disability. The World Health Organization estimates that approximately 4% of the world population lives with depression, corresponding to some 332 million people, with a burden falling roughly 1.5 times more heavily on women than on men [1]. Analyses derived from the Global Burden of Disease programme document a rise from about 182 million affected individuals in 1990 to more than 290 million by 2019, an increase that outpaces population growth and signals a widening treatment deficit [2]. Even in high-income settings only around one-third of people with depression receive any form of care [1].

Pharmacotherapy remains the mainstay of management, yet the oral route imposes constraints that are pharmacokinetic rather than pharmacodynamic in origin. Antidepressants administered orally are subject to presystemic metabolism, exhibit variable and often modest absolute bioavailability, and distribute widely before a therapeutically meaningful fraction reaches the central nervous system. Venlafaxine illustrates the problem: absolute bioavailability of the extended-release form is approximately 45%, and the parent compound is converted by CYP2D6 to O-desmethylvenlafaxine with a half-life short enough to require modified-release engineering [3,4]. Viloxazine, a structurally distinct bicyclic morpholine that inhibits the norepinephrine transporter while modulating several serotonergic receptors, shares this liability and has likewise required extended-release reformulation for clinical use [5,6].

The deeper obstacle is anatomical. The blood–brain barrier excludes the overwhelming majority of therapeutic agents from the brain parenchyma; Pardridge's analysis established that essentially all large-molecule drugs

and more than 98% of small molecules fail to cross it in therapeutically useful quantities [7]. Raising the systemic dose to force a gradient across this barrier increases peripheral exposure disproportionately and is the principal driver of the adverse-effect burden that undermines adherence to antidepressant therapy.

Intranasal administration circumvents the barrier rather than attempting to breach it. Drug deposited on the olfactory region of the nasal cavity may reach the central nervous system along olfactory and trigeminal nerve pathways without first entering the systemic circulation, and recent mechanistic work has clarified the relative contribution of each route [8,9]. Evidence obtained with aggregation-caused quenching probes indicates that the trigeminal pathway predominates in the transport of intact polymeric nanoparticles, a finding of direct consequence for carrier design because it implies that particles must survive the mucosal environment as intact entities rather than merely releasing their payload at the epithelium [9]. The nasal cavity nevertheless presents its own defences: mucociliary clearance removes deposited material within minutes, and enzymatic activity in the mucosa degrades susceptible molecules. A carrier is therefore required, and its properties determine whether the anatomical opportunity is realised.

Biodegradable polymeric nanoparticles have emerged as the most versatile response to this requirement. Their appeal lies in the combination of protection from enzymatic degradation, tunable release kinetics, safe metabolic clearance of the carrier, and surface characteristics that can be adjusted to interact favourably with the nasal epithelium [10,11]. Three polymers dominate the field. Chitosan, obtained by N-deacetylation of chitin, carries protonated amino groups at physiological pH that generate a cationic surface, adhere electrostatically to the anionic sialic acid residues of nasal mucus, and reversibly loosen epithelial tight junctions to favour paracellular transport [12,13]. Its nanoparticles are conveniently formed by ionic gelation with sodium tripolyphosphate, a mild aqueous process requiring neither organic solvent nor heat [14]. Against these advantages must be set documented limitations: swelling and dissociation in isotonic media, imprecise dimensional control, and inefficient encapsulation of hydrophobic or high-molecular-weight cargo [12]. Polycaprolactone and poly(lactide-co-glycolide), by contrast, are synthetic aliphatic polyesters offering reproducible manufacture and predictable hydrolytic degradation, and both have been applied to central nervous system targets [15,16,17].

What the literature does not provide is a matched comparison. Studies of chitosan, polycaprolactone and PLGA carriers are numerous but methodologically heterogeneous, differing in preparation technique, factor ranges, characterisation protocol and statistical treatment, so that reported differences between polymers cannot be separated from differences between laboratories. The few genuine comparisons that exist are restricted to two carriers and usually to a single drug: solid lipid nanoparticles set against PLGA for intranasal insulin [18], and uncoated PLGA against chitosan-coated PLGA for ropinirole and for insulin [19,20]. Even the direction of benefit conferred by chitosan decoration has been questioned in a critical reappraisal of its capacity to promote transport into the brain [21]. Carrier selection consequently rests on precedent and convenience rather than on evidence generated under controlled conditions.

The present study was designed to remove that ambiguity. Two antidepressants with distinct physicochemical character were each formulated into a natural cationic polysaccharide and into a synthetic polyester, and all four resulting systems were developed under one identical Box–Behnken framework with matched characterisation. Where prior work from this laboratory reported the viloxazine–chitosan in-situ gel as a standalone formulation [22], the present investigation situates that system within a controlled comparison and extends it to three further carriers, of which the viloxazine–polycaprolactone system has not previously been described. The governing hypothesis is that the identity of the polymer, rather than the identity of the encapsulated drug, is the principal determinant of the critical quality attributes that decide the fate of a nose-to-brain nanocarrier.

1.1. Research gap

Comparative evidence on polymer selection for nose-to-brain nanocarriers is confounded by methodological heterogeneity. Published comparisons involve at most two carriers, are generally confined to

a single drug, and are rarely conducted within a common statistical design, leaving formulators without a defensible basis on which to choose between a mucoadhesive polysaccharide and a synthetic polyester.

1.2. Novelty statement

This is, to the authors' knowledge, the first study to develop and optimise four antidepressant-loaded nanoparticulate systems spanning three biodegradable polymers and two drugs within a single identical three-factor, three-level Box–Behnken framework, with matched characterisation, ex-vivo permeation and histopathological evaluation applied throughout. The design permits polymer effects to be distinguished from drug effects and from methodological artefact. The viloxazine–polycaprolactone nanoparticle system is additionally reported here for the first time.

1.3. Objectives

- ✓ To develop viloxazine- and venlafaxine-loaded nanoparticles from chitosan, polycaprolactone and poly(lactide-co-glycolide) using preparation routes appropriate to each polymer.
- ✓ To optimise all four systems under one identical three-factor, three-level Box–Behnken design and to validate the resulting quadratic models by point prediction.
- ✓ To characterise the optimised carriers for particle size, polydispersity index, entrapment efficiency, surface charge and morphology under matched conditions.
- ✓ To formulate the chitosan systems as Carbopol-934 in-situ nasal gels and evaluate their physicochemical suitability for intranasal administration.
- ✓ To compare transmucosal permeation across excised goat nasal mucosa and to establish mucosal biocompatibility by histopathological examination.
- ✓ To determine whether polymer class or drug identity exerts the greater influence on critical quality attributes.

2. Materials And Methods

2.1. Materials

Viloxazine hydrochloride and venlafaxine were procured from Medcent Pharma (Hyderabad, India). Chitosan was supplied by BLD Pharmatech (Hyderabad, India). Polycaprolactone, poly(lactide-co-glycolide), poly(vinyl alcohol) and Tween 20 were of pharmaceutical grade. Sodium tripolyphosphate, glacial acetic acid and Carbopol-934 were obtained from Research-Lab Fine Chem Industries (Mumbai, India), and poloxamer-407 from Yarrow Chem (Mumbai, India). Dichloromethane, acetone, ethanol, dimethyl sulfoxide and diethyl ether were purchased from S.D. Fine Chemicals (Mumbai, India). All reagents were of analytical grade and were used without further purification. Water used throughout was freshly distilled.

2.2. Preparation of chitosan nanoparticles (VXCN and VFCN)

Chitosan nanoparticles carrying either drug were generated by ionic gelation between the protonated amino groups of the polysaccharide and the polyanionic phosphate groups of sodium tripolyphosphate. Chitosan (150 mg) was hydrated in 100 mL of distilled water and allowed to stand overnight to ensure complete swelling. Glacial acetic acid was diluted to 0.5% v/v and introduced into the polymer dispersion dropwise over 30 min under continuous magnetic stirring, yielding a clear, slightly viscous solution. Drug (10 mg) was dissolved in this solution, and tripolyphosphate solution was then added at the concentration dictated by the experimental design while the system was stirred at the design-specified speed for 2–3 h at ambient temperature. Opalescence developing during addition indicated particle formation. The resulting nanosuspension was centrifuged at 12,000 rpm, the supernatant being retained for indirect quantification of encapsulated drug.

2.3. Preparation of polycaprolactone nanoparticles (VPNS)

Polycaprolactone nanoparticles were prepared by a modified emulsification–solvent evaporation procedure. Viloxazine and polycaprolactone were co-dissolved in 10 mL of acetone at the proportions specified by the design. An aqueous phase containing Tween 20 at the design concentration was prepared separately and

the organic phase was introduced into it under probe sonication for the design-specified interval, forming an oil-in-water emulsion. The organic solvent was subsequently removed under continuous stirring at reduced pressure, allowing the polymer to precipitate as discrete nanoparticles. The dispersion was recovered by centrifugation and washed to remove residual surfactant.

2.4. Preparation of PLGA nanoparticles (VPLNP)

Poly(lactide-co-glycolide) nanoparticles were produced by single-emulsion solvent evaporation with minor modification of established methodology. PLGA was dissolved in 3 mL of dichloromethane together with venlafaxine, and the organic solution was emulsified by probe sonication over an ice bath for 2 min to prevent thermal degradation. The primary emulsion was transferred into an aqueous poly(vinyl alcohol) solution and sonicated for the interval prescribed by the design. Dichloromethane was eliminated by continuous stirring at ambient pressure, and the hardened nanoparticles were collected by centrifugation, washed with distilled water and resuspended.

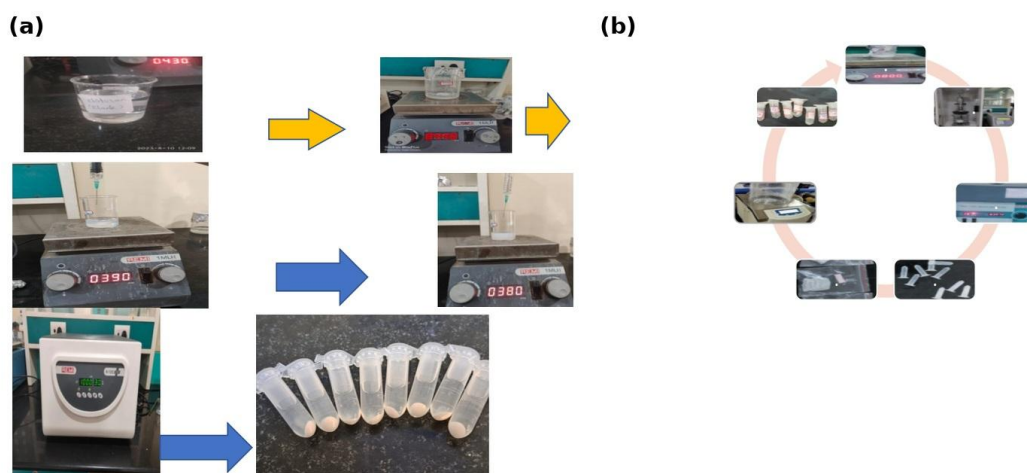


Figure 1. Preparation schemes for the two nanoparticle manufacturing routes employed in this study. (a) Ionic gelation of chitosan with sodium tripolyphosphate under magnetic stirring, used for the VXCN and VFCN systems. (b) Emulsification-solvent evaporation used for the polyester systems, illustrated for venlafaxine-loaded PLGA (VPLNP).

2.5. Experimental design

A three-factor, three-level Box-Behnken design was applied identically to all four systems using Design-Expert software. This design was selected in preference to a full factorial arrangement because it estimates quadratic terms and two-factor interactions efficiently without requiring experimental runs at the extreme corner combinations, which for nanoparticle systems frequently lie outside the manufacturable region. Each design comprised seventeen runs including five replicated centre points, providing an independent estimate of pure error.

The factors were selected on mechanistic grounds specific to each preparation route. For the chitosan systems, polymer concentration (X_1), tripolyphosphate concentration (X_2) and stirring speed (X_3) were varied, these being the determinants of crosslink density and of the shear field under which particles nucleate. For the polycaprolactone system, polymer concentration (X_1), Tween 20 concentration (X_2) and sonication time (X_3) were selected, corresponding respectively to organic-phase viscosity, interfacial stabilisation and emulsification energy. For the PLGA system the analogous factors were PLGA mass (X_1), poly(vinyl alcohol) mass (X_2) and sonication time (X_3). Factor levels are given in Table 1.

Particle size (Y_1), entrapment efficiency (Y_2) and polydispersity index (Y_3) were treated as responses for the chitosan and polycaprolactone systems; for the PLGA system zeta potential replaced polydispersity index as the third response in accordance with the electrostatically stabilised character of that carrier. Optimisation constraints were uniform: particle size minimised, entrapment efficiency maximised and polydispersity index constrained below unity. Linear, two-factor-interaction and quadratic models were fitted to each response and the best-fitting model identified by comparison of sequential sum of squares, lack-of-fit

statistics and adjusted determination coefficients. Optima were located by the desirability function, and a confirmation batch was manufactured at the predicted settings of each system to test the predictive validity of the model.

Table 1. Unified Box–Behnken factor levels and optimisation constraints applied to all four nanoparticulate systems.

System	Drug – polymer	Independent variable	Low (–1)	Mid (0)	High (+1)
VXCN	Viloxazine chitosan	X ₁ Chitosan (% w/w)	0.2	0.3	0.4
		X ₂ TPP (% w/w)	0.1	2.0	2.5
		X ₃ Stirring speed (rpm)	400	450	500
VPNS	Viloxazine – PCL	X ₁ PCL (% w/v)	2.0	3.5	5.0
		X ₂ Tween 20 (% w/v)	2.0	4.5	7.0
		X ₃ Sonication time (min)	3	4	5
VFCN	Venlafaxine chitosan	X ₁ Chitosan (% w/w)	0.1	0.2	0.3
		X ₂ TPP (% w/w)	0.10	0.15	0.20
		X ₃ Stirring speed (rpm)	350	400	450
VPLNP	Venlafaxine PLGA	X ₁ PLGA (mg)	100	150	200
		X ₂ PVA (mg)	2	3	4
		X ₃ Sonication time (min)	5	7.5	10

Responses common to all systems: particle size (Y_1 , minimised) and entrapment efficiency (Y_2 , maximised). The third response was polydispersity index (Y_3 , constrained below unity) for VXCN, VPNS and VFCN, and zeta potential for VPLNP. Each design comprised 17 runs including five replicated centre points.

2.6. Characterisation of nanoparticles

Particle size and polydispersity index were determined by dynamic light scattering at 25 °C, samples being dispersed in distilled water at 200 µg/mL. Zeta potential was obtained from electrophoretic mobility measured under an applied field of 150 mV. Each sample was analysed in triplicate and results are expressed as mean ± standard deviation.

Entrapment efficiency was determined indirectly. Unencapsulated drug was separated by centrifugation at 15,000 rpm for 40 min and its concentration in the clear supernatant was measured spectrophotometrically at 272 nm for viloxazine and 225 nm for venlafaxine against calibration curves constructed in the corresponding medium. Entrapment efficiency was calculated as the difference between the total drug added and the free drug recovered, expressed as a percentage of the total. Surface morphology was examined by field-emission scanning electron microscopy. Specimens were air-dried, sputter-coated with gold to a thickness of 200–500 Å under argon in a high-vacuum evaporator, and imaged at a range of accelerating voltages. Fourier-transform

infrared spectra of the pure drugs, the individual excipients and the optimised formulations were recorded at ambient temperature over 400–4000 cm^{-1} from potassium bromide discs, and were interpreted qualitatively for evidence of chemical interaction. Differential scanning calorimetry was performed on 5–15 mg samples sealed in aluminium pans and heated from 30 to 350 °C at 10 °C/min under nitrogen purged at 50 mL/min, against an empty reference pan.

2.7. Preparation and evaluation of in-situ nasal gels

The optimised chitosan nanoparticle dispersions were incorporated into in-situ gelling vehicles by a cold technique. Carbopol-934 was dispersed in water at 8% w/v and allowed to hydrate overnight before neutralisation with triethanolamine. Ten millilitres of optimised nanoparticle dispersion were combined with 5 g of the neutralised base under propeller homogenisation at 400 rpm until macroscopically uniform, and the preparations were refrigerated overnight to complete polymer swelling. Five batches of each drug were prepared at differing poloxamer-407 and Carbopol-934 proportions. Clarity was assessed visually against contrasting backgrounds. Gelling temperature was determined by immersing a 2 mL aliquot in a water bath raised in 1 °C increments with 5 min equilibration at each step, gelation being recorded at the temperature at which the meniscus ceased to move when the tube was inclined through 90°. pH was measured on a tenfold aqueous dilution using a calibrated digital electrode. Viscosity was measured on a Brookfield DV-II+Pro viscometer fitted with an S-94 spindle at 100 rpm. Drug content was determined after extraction of 1 mL of gel into 10 mL of phosphate buffer pH 5.5 by vortex mixing, with spectrophotometric quantification at the appropriate wavelength. Gel strength was quantified by allowing 50 g of formulation to gel at 37 °C in a 100 mL graduated cylinder, applying a 35 g weight and recording the time required for it to descend 5 cm.

2.8 Ex-vivo permeation across nasal mucosa

Permeation was studied across freshly excised goat nasal mucosa obtained from a local abattoir and transferred immediately into phosphate-buffered saline at pH 5.5. Tissue was equilibrated for 15 min under magnetic stirring before the superior nasal membrane was mounted in a Franz diffusion cell. The receptor chamber held 8 mL of diffusion medium maintained at 37 ± 2 °C and stirred at 400 rpm, with the membrane in minimal contact with the medium. Optimised formulation or the corresponding plain drug dispersion was placed in the donor compartment. Aliquots of 1 mL were withdrawn at predetermined intervals with immediate replacement of an equal volume of fresh buffer, and drug content was determined spectrophotometrically. Cumulative permeation was corrected for sampling dilution. As the tissue was obtained post-mortem from an abattoir, no live-animal procedures were undertaken and institutional animal ethics approval was not required.

2.9. Histopathological evaluation

Mucosal specimens were retrieved at the conclusion of the permeation experiments and fixed for histopathological assessment. Untreated tissue equilibrated in buffer alone served as negative control. Sections were stained with haematoxylin and eosin and examined by light microscopy for epithelial continuity, integrity of the ciliated border, submucosal architecture and the presence of inflammatory infiltrate or necrosis.

2.10. Stability studies

Optimised formulations were stored for three months in sealed amber vials under ambient conditions in accordance with International Council for Harmonisation guidance. Physical appearance, particle size, entrapment efficiency and polydispersity index were determined at monthly intervals.

2.11. Statistical analysis

Regression analysis, analysis of variance and response-surface visualisation were performed in Design-Expert. Model adequacy was judged by the significance of the model F-statistic, by the requirement that lack of fit be non-significant, and by inspection of the normal probability plot of residuals and the plot of residuals against predicted values. Individual model terms were retained where $p < 0.05$. Predictive validity was assessed by calculating the percentage bias between the point-predicted and experimentally observed value of each response. Analytical determinations were performed in triplicate and are reported as mean $\pm$ standard deviation.

3. RESULTS AND DISCUSSION

3.1. Preformulation and drug–excipient compatibility

Both drugs were confirmed against their reference characteristics before formulation. Viloxazine hydrochloride melted at 177 °C and absorbed maximally at 272–273 nm; venlafaxine gave an absorption maximum at 225 nm. Calibration curves constructed in 0.1 N hydrochloric acid and in phosphate buffers at pH 5.5, 6.4 and 7.4 were linear across the working range and were used for all subsequent quantification.

Infrared spectra of the optimised formulations retained the principal absorption bands of the respective drugs without displacement or disappearance, indicating that encapsulation proceeded by physical entrapment rather than chemical association with the polymer or the crosslinker. Differential scanning calorimetry supported this reading (Figure 2): the sharp endotherm of crystalline viloxazine, with onset at 186.92 °C and peak at 188.38 °C, was substantially attenuated in the nanoparticulate systems, a pattern consistent with conversion of the drug to a molecularly dispersed or amorphous state within the polymer matrix. Amorphisation is generally advantageous in this context because it removes the lattice energy barrier to dissolution, although it also raises the possibility of recrystallisation on storage — a concern addressed by the stability data presented below.

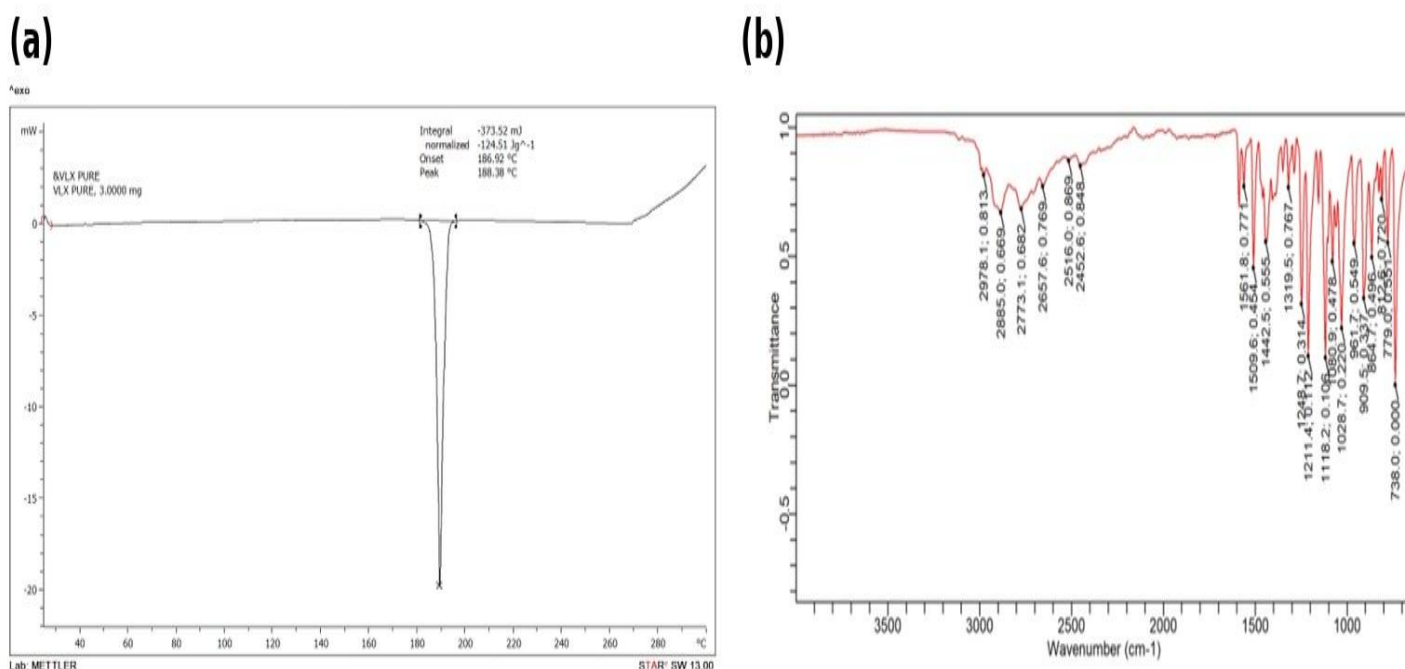


Figure 2. Thermal and spectroscopic characterisation. (a) Differential scanning calorimetry thermogram of pure viloxazine hydrochloride showing a sharp melting endotherm with onset at 186.92 °C and peak at 188.38 °C. (b) Fourier-transform infrared spectrum of the pure drug over 400–4000 cm⁻¹ used as the reference for compatibility assessment.

3.2 Viloxazine–chitosan system (VXCN)

Table 2. Box–Behnken design matrix and observed responses for viloxazine-loaded chitosan nanoparticles (VXCN 1–17).

Run	Chitosan (% w/w)	TPP (% w/w)	Stirring speed (rpm)	Particle size (nm)	Entrapment efficiency (%)	PDI
VXCN1	0.3	2.5	500	157.5	88.0	0.213
VXCN2	0.3	2.0	450	162.7	77.3	0.264
VXCN3	0.2	2.0	500	156.6	80.0	0.269
VXCN4	0.3	2.0	450	162.9	79.6	0.265
VXCN5	0.4	0.1	450	160.0	91.0	0.199
VXCN6	0.4	2.0	400	165.6	87.0	0.198
VXCN7	0.3	0.1	400	157.0	77.0	0.315
VXCN8	0.4	2.5	450	164.6	89.0	0.187
VXCN9	0.3	2.0	450	162.8	81.0	0.265
VXCN10	0.4	2.0	500	161.9	83.0	0.185
VXCN11	0.2	2.0	400	159.9	73.0	0.314
VXCN12	0.3	2.0	450	161.5	77.0	0.249
VXCN13	0.3	2.5	400	165.1	80.5	0.258
VXCN14	0.2	2.5	450	155.0	88.0	0.261
VXCN15	0.3	0.1	500	159.3	73.0	0.263
VXCN16	0.3	2.0	450	162.7	76.0	0.262
VXCN17	0.2	0.1	450	157.1	67.0	0.314

Values are means of three determinations.

Across the seventeen VXCN runs, particle size varied only between 155.0 and 165.6 nm, entrapment efficiency between 67.0 and 91.0%, and polydispersity index between 0.185 and 0.315 (Table 2). The narrowness of the size range is itself informative: ionic gelation under these conditions produces particles whose dimensions are relatively insensitive to the factors examined, whereas payload varies over a twenty-four point range. The dominant influence on both size and entrapment was chitosan concentration, which contributed the largest single sum of squares to each model.

The quadratic model for particle size was significant ($F = 15.41$, $p = 0.0008$) with non-significant lack of fit ($p = 0.1483$), and took the form

$$Y_1 = 162.52 + 3.33X_1 + 15.15X_2 + 3.19X_3 - 8.42X_1X_2 - 1.25X_1X_3 + 4.38X_2X_3 - 0.7333X_1^2 - 13.36X_2^2 + 6.82X_3^2$$

The positive linear coefficients for all three factors indicate that increases in chitosan, tripolyphosphate or stirring speed each enlarge the particle, but the magnitudes are unequal and the interaction terms are substantial. Tripolyphosphate exerts the strongest linear effect, which follows from its role as the crosslinking agent: additional phosphate increases the number of ionic bridges and the mass of polymer recruited into each particle.

The negative X_1X_2 interaction shows that this enlarging effect is progressively offset as chitosan concentration rises, because at high polymer concentration the crosslinker becomes limiting and further addition consolidates rather than extends the network. The pronounced negative quadratic term in tripolyphosphate confirms that the relationship reverses beyond an intermediate concentration.

Entrapment efficiency was likewise well modelled ($F = 20.32$, $p = 0.0003$; lack of fit $p = 0.6049$), with chitosan and tripolyphosphate both contributing significantly and a strong negative interaction between them. Polydispersity index gave the most robust model of the three ($F = 32.73$, $p < 0.0001$), chitosan concentration alone accounting for more than half the total sum of squares. Response surfaces are presented in Figure 3, and the distribution of entrapment efficiency and zeta potential across the design in Figure 4. All batches carried a positive surface charge in the region of +15 to +22 mV, consistent with the cationic character of protonated chitosan and, importantly, with the electrostatic mucoadhesion on which the intranasal strategy depends.

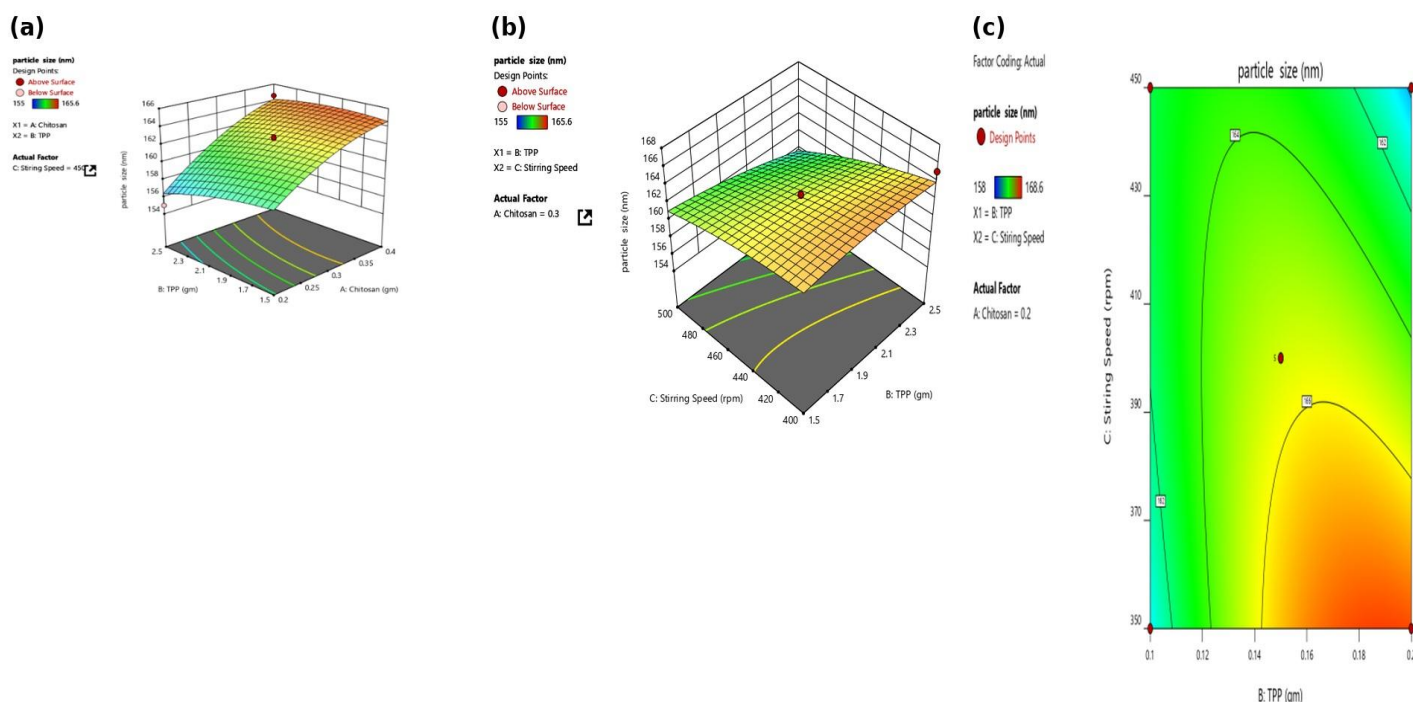


Figure 3. Response-surface and contour representations for the VXCN system. (a) Three-dimensional surface showing the joint effect of chitosan and tripolyphosphate concentration on particle size. (b) Three-dimensional surface for entrapment efficiency. (c) Contour plot of particle size as a function of tripolyphosphate concentration and stirring speed. The curvature evident in each surface reflects the significant quadratic terms retained in the fitted models.

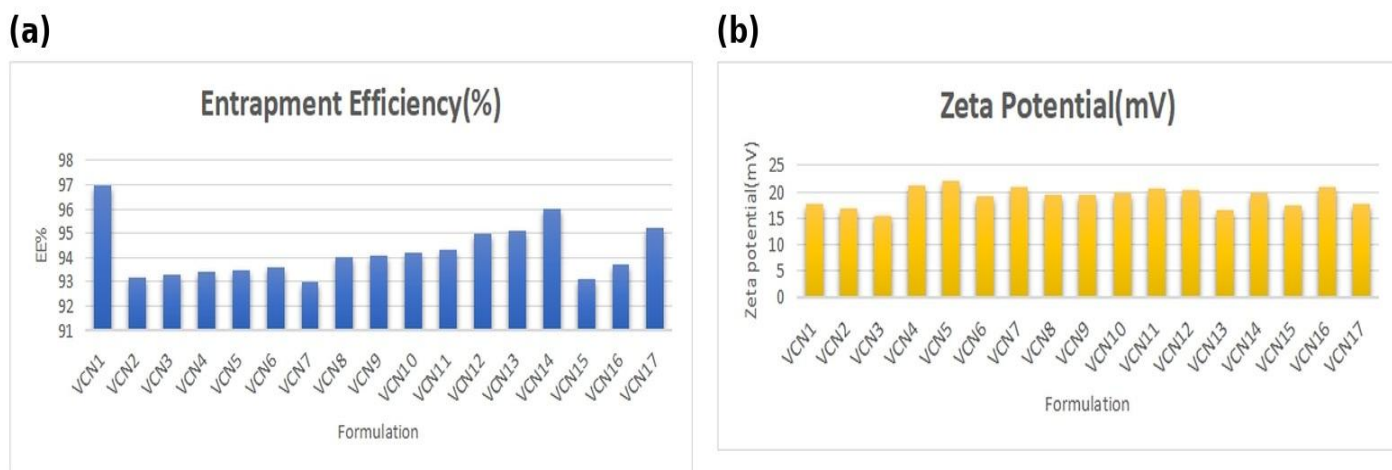


Figure 4. Distribution of responses across the VXCN design. (a) Entrapment efficiency of the seventeen design runs. (b) Corresponding zeta potential values, all positive and in the region of +15 to +22 mV, consistent with the cationic character of protonated chitosan and favourable for electrostatic interaction with anionic nasal mucin.

3.3 Viloxazine–polycaprolactone system (VPNS)

Table 3. Box–Behnken design matrix for viloxazine-loaded polycaprolactone nanoparticles (VPNS 1–17).

Run	PCL (% w/v)	Tween 20 (% w/v)	Sonication time (min)
VPNS1	2.0	2.0	4
VPNS2	5.0	2.0	4
VPNS3	2.0	7.0	4
VPNS4	5.0	7.0	4
VPNS5	2.0	4.5	3
VPNS6	5.0	4.5	3
VPNS7	2.0	4.5	5
VPNS8	5.0	4.5	5
VPNS9	3.5	2.0	4
VPNS10	3.5	7.0	4
VPNS11	3.5	2.0	5
VPNS12	3.5	7.0	5
VPNS13	3.5	4.5	4
VPNS14	3.5	4.5	4
VPNS15	3.5	4.5	4
VPNS16	3.5	4.5	4
VPNS17	3.5	4.5	4

Observed response ranges across the design: particle size 272.34–480.65 nm; entrapment efficiency 61.43–86.21%.

The polycaprolactone system behaved very differently. Particle size across the design ranged from 272.34 to 480.65 nm and entrapment efficiency from 61.43 to 86.21%, both ranges far wider than those of the chitosan system and centred at a considerably larger size. The particle-size model was highly significant ($F = 164.86$, $p < 0.0001$) and was governed principally by polymer concentration and surfactant concentration:

$$Y_1 = 393.20 + 60.61X_1 - 44.57X_2 - 16.10X_3 + 2.50X_1X_2 + 9.50X_1X_3 + 0.25X_2X_3 - 14.98X_1^2 + 1.77X_2^2 - 2.72X_3^2$$

The signs are mechanistically coherent. Increasing polycaprolactone concentration raises the viscosity of the dispersed organic phase, resisting droplet breakup during emulsification and yielding larger particles; the coefficient of +60.61 makes this by far the dominant term. Tween 20 acts in opposition, lowering interfacial tension and stabilising newly formed droplets against coalescence, hence the negative coefficient of –44.57. Extended sonication contributes additional shear energy and reduces size further, though its influence is modest by comparison.

Entrapment efficiency followed a parallel logic ($F = 98.38$, $p < 0.0001$):

$$Y_2 = 81.96 + 7.89X_1 - 7.42X_2 - 2.08X_3 + 2.08X_1X_2 + 2.14X_1X_3 - 0.56X_2X_3 - 0.43X_1^2 + 0.36X_2^2 - 2.15X_3^2$$

Higher polymer concentration increases entrapment by providing more matrix into which drug may partition and by accelerating polymer precipitation, which shortens the interval during which drug can escape into the aqueous phase. Surfactant has the opposite effect: by improving the wetting of the organic–aqueous interface it facilitates partitioning of drug out of the forming particle. The tension between these two terms is the central formulation trade-off of the polycaprolactone system, since the conditions that minimise size are precisely those that reduce payload.

3.4 Venlafaxine–chitosan system (VFCN)

Table 4. Box–Behnken design matrix and observed responses for venlafaxine-loaded chitosan nanoparticles (VFCN 1–17).

Run	Chitosan (% w/w)	TPP (% w/w)	Stirring speed (rpm)	Particle size (nm)	Entrapment efficiency (%)	PDI
VFCN1	0.2	0.15	400	165.7	76.3	0.364
VFCN2	0.1	0.15	350	162.9	72.0	0.414
VFCN3	0.1	0.10	400	158.0	87.0	0.361
VFCN4	0.1	0.15	400	158.0	78.6	0.361
VFCN5	0.2	0.15	350	165.9	76.0	0.415
VFCN6	0.2	0.20	400	165.7	75.0	0.362
VFCN7	0.2	0.15	350	165.8	80.0	0.365
VFCN8	0.2	0.15	400	160.5	87.0	0.313
VFCN9	0.2	0.15	350	164.9	82.0	0.285
VFCN10	0.2	0.10	400	160.1	66.0	0.414
VFCN11	0.2	0.15	350	162.3	72.0	0.363
VFCN12	0.2	0.15	350	167.6	88.0	0.287
VFCN13	0.2	0.20	400	168.1	79.5	0.358
VFCN14	0.2	0.15	350	159.6	79.0	0.369
VFCN15	0.3	0.15	350	171.3	86.0	0.298
VFCN16	0.3	0.10	400	163.5	90.0	0.299
VFCN17	0.2	0.15	400	164.5	76.0	0.349

Values are means of three determinations.

The venlafaxine–chitosan system reproduced the qualitative behaviour of its viloxazine counterpart while operating over a compressed factor range. Particle size across the design lay between 158.0 and 171.3 nm, entrapment efficiency between 66.0 and 90.0%, and polydispersity index between 0.285 and 0.415 (Table 4). The particle-size model was significant ($F = 33.66$, $p < 0.0001$; lack of fit $p = 0.2027$):

$$Y_1 = 165.52 + 2.94X_1 + 1.10X_2 - 1.54X_3 + 1.68X_1X_2 - 0.100X_1X_3 - 2.48X_2X_3 - 1.03X_1^2 - 2.31X_2^2 - 0.485X_3^2$$

Entrapment efficiency was described by a model of comparable adequacy ($F = 20.87$, $p = 0.0003$):

$$Y_2 = 77.18 + 5.25X_1 + 4.69X_2 + 0.8125X_3 - 5.75X_1X_2 - 2.75X_1X_3 + 2.88X_2X_3 + 3.35X_1^2 + 2.22X_2^2 - 0.7775X_3^2$$

and the polydispersity index by

$$Y_3 = 0.3610 - 0.0486X_1 - 0.0215X_2 - 0.0194X_3 + 0.0102X_1X_2 + 0.0080X_1X_3 + 0.0018X_2X_3 - 0.0208X_1^2 + 0.0013X_3^2$$

The negative coefficient on chitosan concentration in the polydispersity model deserves comment, since it indicates that raising polymer concentration narrows rather than broadens the size distribution. This runs counter to the intuition that more polymer produces more heterogeneous assemblies, and is best explained by the crosslinking stoichiometry: at higher chitosan concentration the tripolyphosphate is comprehensively consumed and particle formation proceeds through a single dominant mechanism, whereas at low polymer concentration excess crosslinker permits competing modes of aggregation. The stronger model for this response than for the corresponding viloxazine system ($F = 35.76$ against 32.73) supports the interpretation.

3.5 Venlafaxine–PLGA system (VPLNP)

Table 5. Box–Behnken design matrix for venlafaxine-loaded PLGA nanoparticles (VPLNP 1–17).

Run	PLGA (mg)	PVA (mg)	Sonication time (min)
VPLNP1	200	3	10
VPLNP2	100	2	7.5
VPLNP3	150	3	7.5
VPLNP4	150	3	7.5
VPLNP5	150	3	7.5
VPLNP6	200	2	7.5
VPLNP7	100	3	5
VPLNP8	200	4	7.5
VPLNP9	100	3	10
VPLNP10	150	3	7.5
VPLNP11	150	4	5
VPLNP12	150	4	10
VPLNP13	150	2	10
VPLNP14	200	3	5
VPLNP15	150	3	7.5
VPLNP16	150	2	5
VPLNP17	100	4	7.5

Responses evaluated: particle size, entrapment efficiency and zeta potential.

The PLGA system yielded the most efficient encapsulation of the four. Both models were highly significant — particle size $F = 57.24$ and entrapment efficiency $F = 67.25$, each with $p < 0.0001$ — and in both cases PLGA mass overwhelmingly dominated the variance, contributing 642.61 of 725.64 total sum of squares for size and 352.45 of 364.84 for entrapment. Poly(vinyl alcohol) mass and sonication time were, by contrast, statistically marginal for both responses.

This concentration of variance in a single factor is itself a useful finding. It implies that the PLGA system possesses a wide operating window with respect to stabiliser concentration and emulsification energy, and that manufacturing control need be exercised principally over polymer charge. From a scale-up perspective this is an advantage over the chitosan systems, in which three factors and several interactions contributed materially and the design space is correspondingly more constrained.

3.6 Model adequacy and validation of the four design spaces

Table 6. Consolidated analysis of variance for the fitted quadratic models across all four nanoparticulate systems.

System	Response	Sum of squares	Mean square	Model F	p-value	Lack of fit (p)	Inference
VXCN	Particle size (Y_1)	159.15	17.68	15.41	0.0008	0.1483	Significant
VXCN	Entrapment efficiency (Y_2)	668.87	74.32	20.32	0.0003	0.6049	Significant
VXCN	Polydispersity index (Y_3)	0.0281	0.0031	32.73	< 0.0001	0.1315	Significant
VPNS	Particle size (Y_1)	48607.63	5400.85	164.86	< 0.0001	0.1130	Significant
VPNS	Entrapment efficiency (Y_2)	887.78	98.64	98.38	< 0.0001	0.1247	Significant
VFCN	Particle size (Y_1)	163.41	18.16	33.66	< 0.0001	0.2027	Significant
VFCN	Entrapment efficiency (Y_2)	669.53	74.39	20.87	0.0003	0.6298	Significant
VFCN	Polydispersity index (Y_3)	0.0281	0.0031	35.76	< 0.0001	0.1546	Significant
VPLNP	Particle size (Y_1)	725.64	80.63	57.24	< 0.0001	n.s.	Significant
VPLNP	Entrapment efficiency (Y_2)	364.84	40.54	67.25	< 0.0001	n.s.	Significant

Values are taken from the Design-Expert analysis-of-variance output for each response. Model terms were retained at $p < 0.05$. Non-significant lack of fit indicates that the quadratic model describes the data without systematic deviation. n.s. = not significant.

Optima located by the desirability function are shown in Figure 5 for the two chitosan systems, each returning a desirability of 1.000. Confirmation batches were manufactured at the predicted settings of all four systems and characterised under identical conditions (Table 7).

Agreement between prediction and observation was close throughout. The largest deviation across the twelve validated responses was 4.76%, recorded for the polydispersity index of VXCN, and nine of the twelve responses agreed to within 2%. Percentage bias of this magnitude across four independently constructed models, three polymers and two drugs constitutes strong evidence that the quadratic response surfaces describe the underlying physics rather than fitting noise, and that the design spaces are genuinely predictive within the ranges examined.

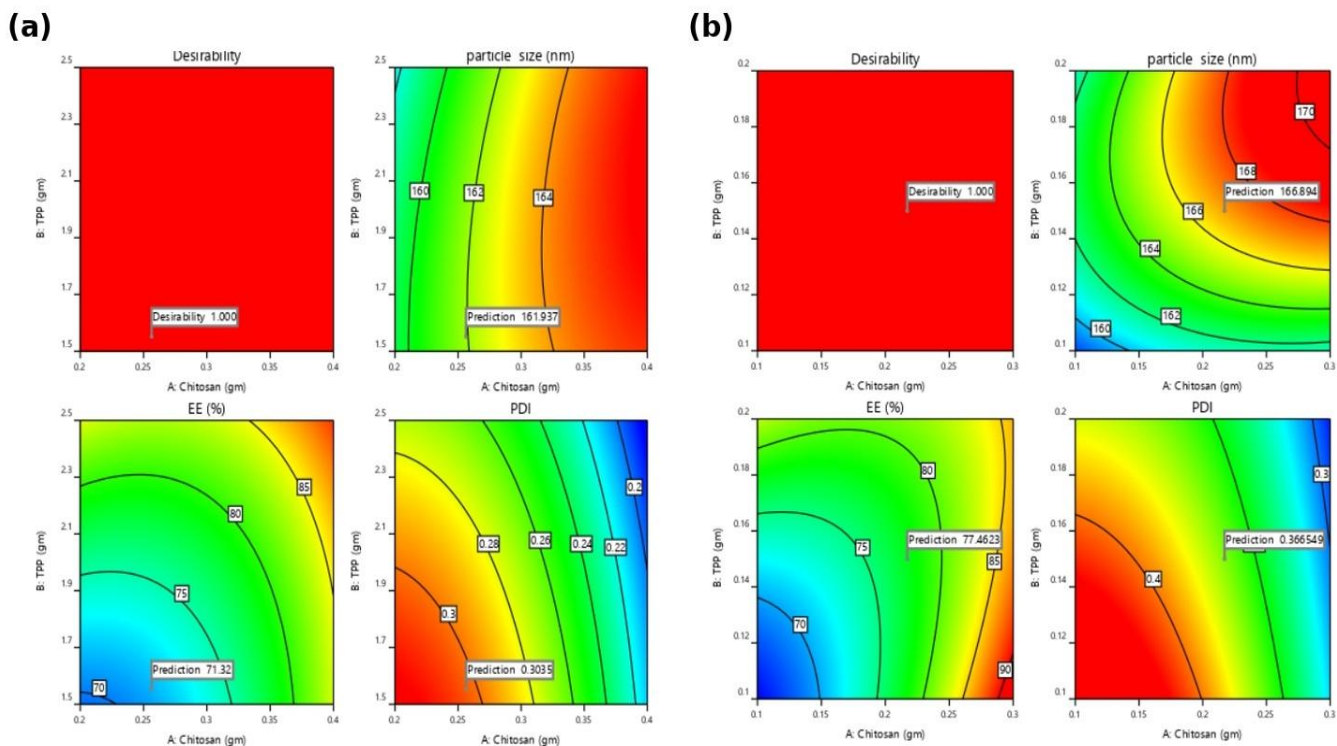


Figure 5. Desirability overlays generated by the optimisation routine. (a) VXCN system, showing the desirability surface together with the superimposed contours for particle size, entrapment efficiency and polydispersity index; the located optimum returned a desirability of 1.000 at 0.25% chitosan, 1.5% tripolyphosphate and 426.34 rpm. (b) Corresponding overlay for the VFCN system, with an optimum at 0.2% chitosan, 0.15% tripolyphosphate and 350 rpm.

Table 7. Point-prediction validation of the four optimised formulations.

System	Response variable	Predicted	Observed	Bias (%)
VXCN	Particle size (nm)	161.93	160.0	1.19
	Entrapment efficiency (%)	71.32	70.1	1.71
	Polydispersity index	0.42	0.40	4.76
VPNS	Particle size (nm)	324.10	323.7	0.12
	Entrapment efficiency (%)	79.07	78.12	1.20
	Polydispersity index	0.40	0.39	2.50
VFCN	Particle size (nm)	169.00	170.7	1.01
	Entrapment efficiency (%)	77.18	78.2	1.32
	Polydispersity index	0.349	0.351	0.57
VPLNP	Particle size (nm)	173.00	172.0	0.58
	Entrapment efficiency (%)	84.00	83.61	0.46
	Zeta potential (mV)	-25.8	-24.9	3.49

Bias was calculated as the absolute difference between predicted and observed values expressed as a percentage of the predicted value. Confirmation batches were prepared and characterised independently of the design runs.

3.7. Morphology, size distribution and surface charge of the optimised carriers

Optimised particles from all four systems were spherical, discrete and free of substantial aggregation on electron microscopy (Figure 7), and their apparent dimensions corroborated the hydrodynamic diameters obtained by light scattering (Figure 6). The absence of clumping is significant for the intranasal route because aggregates exceeding a few hundred nanometres would be cleared mechanically rather than taken up across the epithelium.

Surface charge separated the carriers cleanly by polymer class. The chitosan systems carried a cationic charge in the viloxazine case and -15.5 mV in the venlafaxine case, whereas PLGA gave -24.9 mV. Interpretation requires care. The conventional threshold for electrostatic colloidal stability is approximately ± 30 mV, and none of the present systems attains it; a lower threshold near ± 20 mV applies where stabilisation is steric rather than electrostatic [23]. The chitosan systems fall below even the steric threshold on charge alone, and their physical stability must therefore be attributed to the crosslinked network and, in the gel formulations, to immobilisation within the Carbopol matrix. The PLGA system, at -24.9 mV, sits within the range conventionally described as moderately stable. Reporting these values against the accepted criteria rather than describing them uniformly as favourable is, in the authors' view, the more defensible course, and the three-month stability data provide the empirical test that the electrokinetic measurement alone cannot.

Polydispersity indices ranged from 0.351 to 0.40 in the optimised carriers. Values below 0.2 are generally regarded as indicating a narrow distribution, and the range 0.2–0.4 as acceptable for polymeric nanoparticles [24]. The present systems therefore occupy the upper portion of the acceptable band rather than the monodisperse region, and are described accordingly.

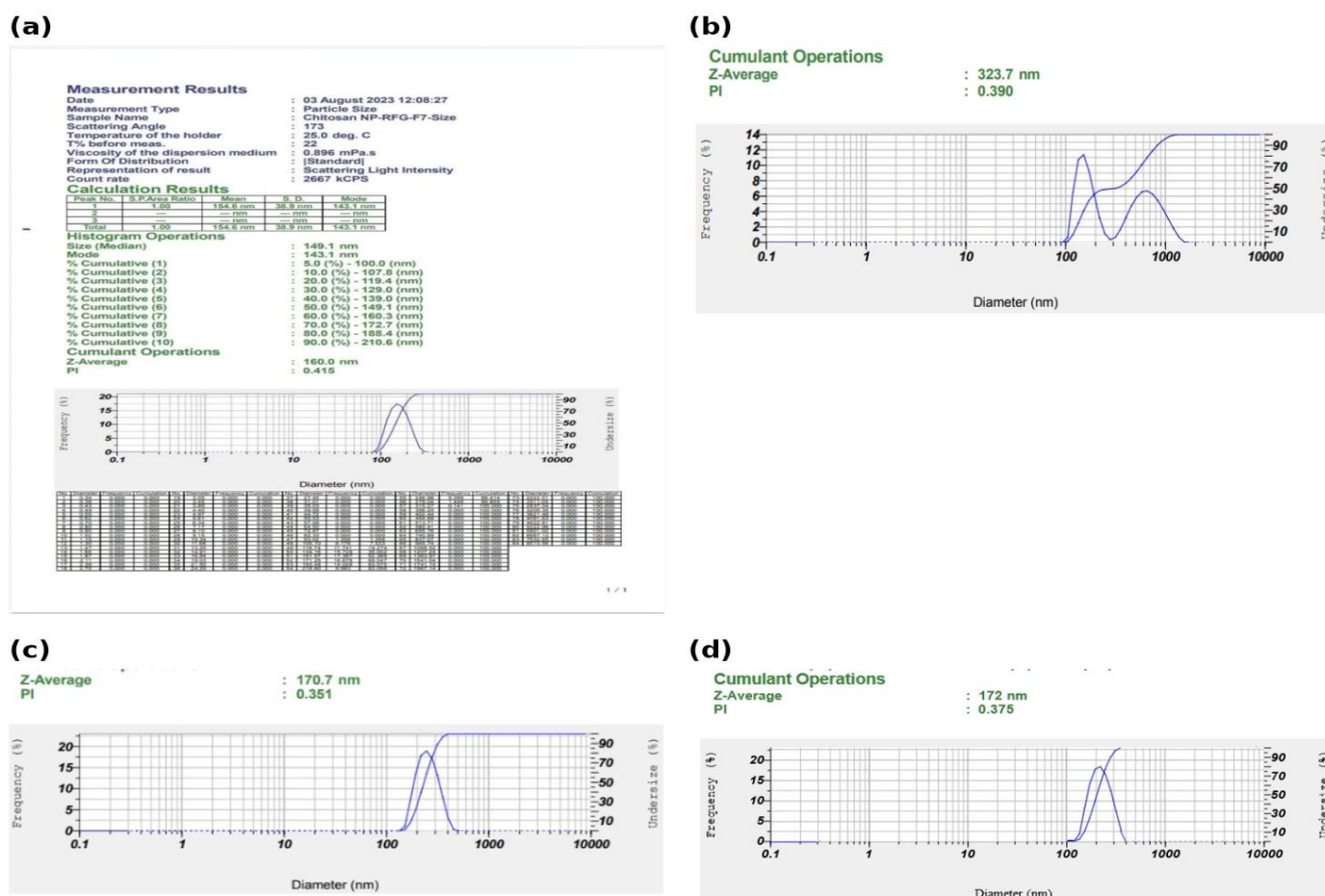


Figure 6. Particle size and zeta potential distributions of the optimised formulations obtained by dynamic light scattering and electrophoretic mobility. (a) Opt-VXCN-NPs, Z-average 160.0 nm. (b) Opt-VPNS, Z-average 323.7 nm. (c) Opt-VFCN-NPs, Z-average 170.7 nm with polydispersity index 0.351. (d) Opt-VPLNPs, Z-average 172.0 nm with polydispersity index 0.375.

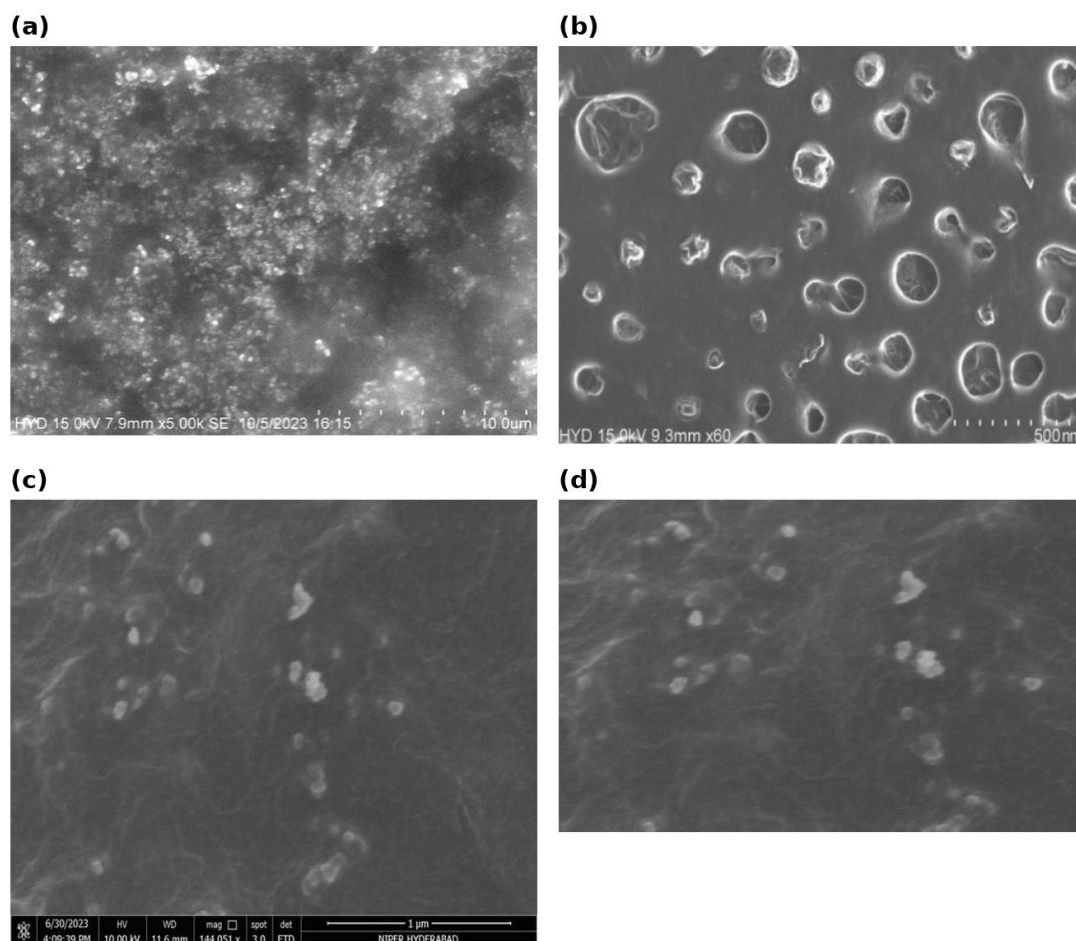


Figure 7. Scanning electron micrographs of the four optimised nanoparticulate systems. (a) Opt-VXCN-NPs. (b) Opt-VPNS. (c) Opt-VFCN-NPs. (d) Opt-VPLNPs. All systems present discrete, approximately spherical particles without substantial aggregation, and apparent dimensions correspond to the hydrodynamic diameters determined by light scattering.

3.8. In-situ gel formulation and characterisation

Both chitosan nanoparticle dispersions were successfully converted into in-situ gelling vehicles, and all ten batches remained clear with no visible particulate matter that might irritate the nasal mucosa or impede administration (Table 8). Measured pH lay between 5.28 and 5.73 across the series, comfortably within the physiological range of the nasal cavity and therefore unlikely to provoke irritation or impair ciliary function. Gelling temperature is the critical attribute of such a system, since the formulation must remain a low-viscosity liquid in the container and at the moment of instillation yet convert to a gel on contact with the mucosa. Values between 25 and 37 °C satisfy this requirement; a lower transition would cause premature gelation at room temperature and a higher one would leave the formulation liquid in the nose. Batches VXCN-NPG4 and VFCN-G5 gelled at 31.4 and 29.8 °C respectively, placing both securely inside the window. Viscosity rose in parallel with Carbopol content, from 33.4 to 65.4 cps in the viloxazine series and 40.3 to 64.8 cps in the venlafaxine series, and gel strength followed the same trend.

Drug content ranged from 80.14 to 94.75% and from 80.26 to 97.14% respectively. On the combination of nasal-compatible pH, appropriate sol–gel transition, highest drug content and greatest gel strength within their series, VXCN-NPG4 and VFCN-G5 were selected for permeation and histopathological study. The gelling temperature of batch VXCN-NPG1 was not determined and is reported as such.

Table 8. Physicochemical characterisation of the in-situ gel batches prepared from the optimised chitosan nanoparticle dispersions.

Batch	Clarity	pH	Gelling temperature (°C)	Viscosity (cps)	Drug content (%)	Gel strength (s)
VXCN-NPG1	Clear	5.68	n.d.	33.4	80.14	65.31
VXCN-NPG2	Clear	5.73	40.6	43.6	80.26	69.61
VXCN-NPG3	Clear	5.71	33.2	51.3	92.64	37.28
VXCN-NPG4	Clear	5.58	31.4	65.4	94.75	74.90
VXCN-NPG5	Clear	5.39	29.8	59.8	87.14	45.30
VFCN-G1	Clear	5.68	34.6	40.3	89.32	40.25
VFCN-G2	Clear	5.73	40.6	43.6	80.26	41.32
VFCN-G3	Clear	5.72	33.2	51.3	92.64	37.28
VFCN-G4	Clear	5.28	31.4	58.4	94.75	40.90
VFCN-G5	Clear	5.71	29.8	64.8	97.14	55.30

Batches VXCN-NPG4 and VFCN-G5 (highlighted) were selected for permeation and histopathological evaluation. n.d. = not determined.

3.9 Ex-vivo permeation across goat nasal mucosa

Permeation profiles across excised goat nasal mucosa are shown in Figure 8 and the corresponding data in Table 9. Every optimised carrier substantially exceeded the permeation achieved by its plain drug dispersion at every sampling point. Cumulative permeation from the plain dispersions reached 60% at 24 h, whereas the optimised polycaprolactone and PLGA nanosuspensions each attained 96%, and the viloxazine in-situ gel delivered 82% within 8 h.

The shape of the profiles is as informative as their endpoint. All nanoparticulate systems rose steeply over the first four hours and then entered a sustained phase, whereas the plain dispersions ascended more gradually throughout. This biphasic pattern — an initial rapid phase attributable to drug associated with or near the particle surface, followed by matrix-controlled release — is characteristic of polymeric nanocarriers and is precisely the profile required of a nasal product, which must establish therapeutic concentrations quickly before mucociliary clearance intervenes and then maintain them.

The absolute values compare favourably with published work on the same route. Venlafaxine permeation across sheep nasal mucosa has been reported at 66.5% over 7 h for an unformulated preparation [25], and an escitalopram chitosan nanoparticle in-situ gel achieved 80.72% across goat mucosa over 8 h [26]; the 82% recorded here at 8 h for VXCN-NPG4 is consistent with the latter. It should nonetheless be acknowledged that excised mucosa is an imperfect surrogate. Tissue thickness varies between and within animals, and the reliability of integrity markers in excised nasal preparations has been questioned [27]; comparisons between laboratories should therefore be treated as indicative rather than quantitative.

Table 9. Cumulative percentage permeation across excised goat nasal mucosa

Time (h)	Plain drug dispersion (%)	Opt-VPNS nanosuspension (%)	Opt-VPLNP nanosuspension (%)
0	0	0	0
2	20	36	31
4	32	55	59
8	46	78	78
12	53	88	84
24	60	96	96

Values are means of three determinations. The viloxazine in-situ gel VXCN-NPG4 reached 82% cumulative permeation at 8 h under the same experimental conditions.

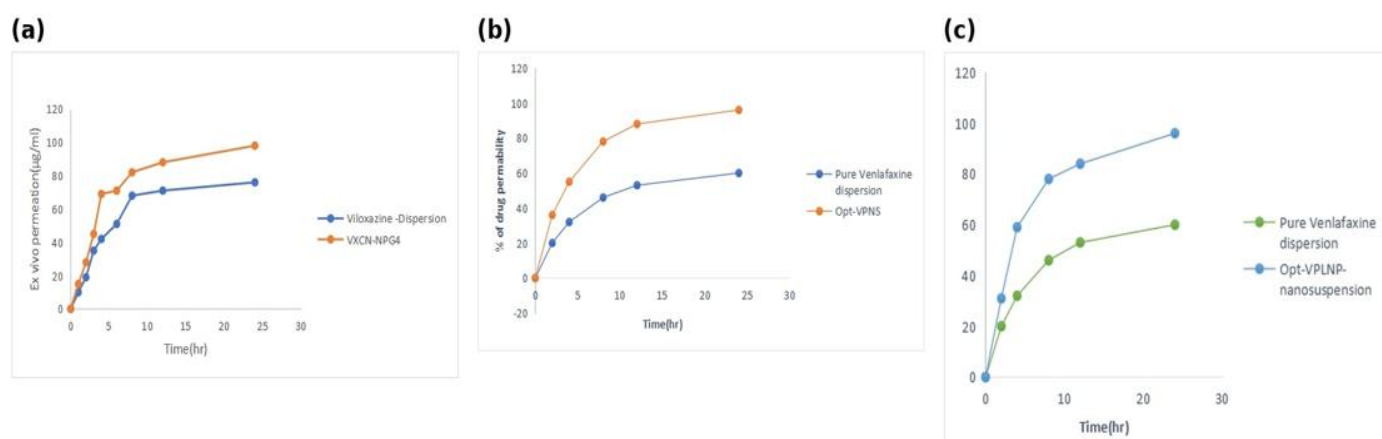


Figure 8. Ex-vivo permeation profiles across excised goat nasal mucosa mounted in Franz diffusion cells. (a) Viloxazine in-situ gel VXCN-NPG4 compared with plain viloxazine dispersion. (b) Opt-VPNS nanosuspension compared with plain drug dispersion. (c) Opt-VPLNP nanosuspension compared with plain drug dispersion. All nanoparticulate systems exhibit a biphasic profile with a rapid initial phase followed by sustained permeation.

3.10. Histopathological assessment of mucosal integrity

Histopathological sections are presented in Figure 9. Tissue exposed to the optimised formulations retained continuous epithelium with an intact ciliated border, preserved submucosal architecture and no necrosis, and was essentially indistinguishable from untreated control tissue in the case of the viloxazine formulations and the PLGA nanosuspension. Sections exposed to the venlafaxine chitosan gel showed minor epithelial change without disruption of the underlying structure. That chitosan produces some epithelial effect is expected rather than anomalous, since its permeation-enhancing action operates precisely through transient modification of tight junctions; the finding that this modification was slight and unaccompanied by inflammatory infiltrate or loss of continuity supports the tolerability of the formulation while indicating that repeat-dose tolerance deserves specific study.

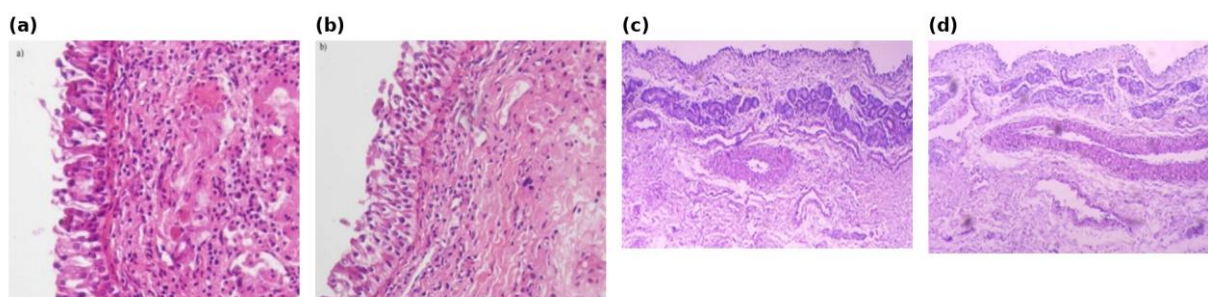


Figure 9. Haematoxylin and eosin stained sections of goat nasal mucosa examined by light microscopy following permeation. (a) Untreated control tissue equilibrated in buffer alone. (b) Tissue exposed to the viloxazine in-situ gel VXCN-NPG4. (c) Untreated control for the venlafaxine series. (d) Tissue exposed to the venlafaxine in-situ gel VFCN-G5. Epithelial continuity and submucosal architecture are preserved throughout; no necrosis or inflammatory infiltrate was observed.

3.11. Stability of the optimised formulations

Over three months of ambient storage no formulation showed visible change in appearance, and instrumental parameters drifted only marginally (Table 10). The polycaprolactone nanosuspension was the most invariant, its particle size moving by 0.3 nm and its entrapment efficiency by 0.11 percentage points across the period. The chitosan systems drifted somewhat more, VXCN-NPG4 losing 3.1 percentage points of entrapment and VFCN-G5 1.3 points, with small increases in particle size. The direction and magnitude of these changes are consistent with slow relaxation of the ionically crosslinked network and modest drug redistribution, and remain within limits that would not compromise performance. Notably, the systems with the weakest electrokinetic stabilisation did not prove the least stable, reinforcing the argument that stabilisation in crosslinked and gel-embedded carriers is not principally electrostatic.

Table 10. Stability of the optimised formulations over three months of ambient storage.

Formulation	Parameter	0 month	1 month	2 months	3 months
VXCN-NPG4	Particle size (nm)	160.0	160.1	161.9	162.0
	Entrapment efficiency (%)	70.1	70.0	68.0	67.0
	Polydispersity index	0.40	0.40	0.30	0.30
Opt-VPNS	Particle size (nm)	323.7	323.9	324.0	324.0
	Entrapment efficiency (%)	78.12	78.11	78.09	78.01
	Polydispersity index	0.39	0.39	0.40	0.40
VFCN-G5	Particle size (nm)	170.7	170.9	171.0	171.9
	Entrapment efficiency (%)	78.2	77.9	77.1	76.9
	Polydispersity index	0.35	0.35	0.36	0.37

Storage was conducted in sealed amber vials under ambient conditions in accordance with International Council for Harmonisation guidance.

3.12. Comparative analysis: polymer class as the determinant of carrier performance

Table 11. Consolidated comparison of the four optimised nanoparticulate systems.

Attribute	VXCN	VPNS	VFCN	VPLNP
Drug	Viloxazine	Viloxazine	Venlafaxine	Venlafaxine
Polymer	Chitosan (natural)	PCL (synthetic)	Chitosan (natural)	PLGA (synthetic)
Method	Ionic gelation	Emulsification–solvent evaporation	Ionic gelation	Single-emulsion solvent evaporation
Optimised composition	0.25% chitosan, 1.5% TPP, 426 rpm	3.5% PCL, 4.5% Tween 20, 4 min	0.2% chitosan, 0.15% TPP, 350 rpm	159.89 mg PLGA, 3.5 mg PVA, 6.7 min
Particle size (nm)	160.0	323.7	170.7	172.0
Entrapment efficiency (%)	70.1	78.12	78.2	83.61
Polydispersity index	0.40	0.39	0.351	0.375
Zeta potential (mV)	Positive (cationic)	Not determined	−15.5	−24.9
Delivery form	In-situ gel (VXCN-NPG4)	Nanosuspension	In-situ gel (VFCN-G5)	Nanosuspension
Ex-vivo permeation	82% at 8 h	96% at 24 h	96% at 24 h	96% at 24 h
Mucosal integrity	Preserved	Preserved	Minor epithelial change	Preserved

Zeta potential was not determined for the VPNS system.

Taken together, the four design spaces support the study hypothesis. Grouping the optimised carriers by drug produces no coherent pattern: the two viloxazine systems differ from one another in particle size by a factor of two and in entrapment by eight percentage points. Grouping them by polymer class produces an orderly one. The two chitosan carriers converge on 160.0 and 170.7 nm with entrapment of 70.1 and 78.2%; the two polyesters achieve higher payloads of 78.12 and 83.61%. Polymer identity, not drug identity, organises the data.

The mechanistic basis of this separation lies in how each polymer forms a particle. Ionic gelation assembles chitosan through electrostatic crosslinking in a wholly aqueous environment, and the resulting network is hydrated, comparatively loose and formed under mild shear. Such a network confers small dimensions and a cationic or weakly anionic surface well suited to mucoadhesion, but it offers a relatively polar interior with limited capacity to retain drug against a concentration gradient into the surrounding aqueous phase. Emulsion-based methods operate on an entirely different principle: drug is partitioned into an organic phase and then physically imprisoned as the polymer precipitates during solvent removal. The matrix so formed is denser and more hydrophobic, which explains the systematically higher entrapment observed for both polyesters and, in the polycaprolactone case, the larger dimensions that follow from viscous resistance to droplet breakup.

This reasoning also accounts for the position of PLGA as the strongest overall performer. It combines the high entrapment characteristic of an emulsion-formed polyester with a particle size equivalent to that of the chitosan systems, because its lower intrinsic viscosity in dichloromethane permits finer emulsification than polycaprolactone in acetone at comparable polymer loading. It additionally provides the most negative zeta potential of the series. The relevant comparison here is with the mechanistic literature on intact-particle transport: evidence that the trigeminal pathway predominates for intact polymeric nanoparticles [9] implies that carriers must survive as entities within the mucosa, which favours the denser polyester matrices, whereas the mucoadhesive and tight-junction-modulating properties of chitosan [12,13] favour retention and paracellular passage. These are different mechanisms of advantage, and the present data indicate that they are not simultaneously maximisable in a single carrier.

That conclusion carries a practical consequence. The polycaprolactone system illustrates the cost of ignoring it: at 323.7 nm it lies outside the range generally considered favourable for transmucosal uptake, notwithstanding its respectable 78.12% entrapment, and its optimisation revealed that the conditions minimising size are the same conditions that reduce payload. A formulator confronting this trade-off must decide which attribute governs performance for the specific application rather than pursuing both. Where residence time and paracellular transport are limiting, chitosan with in-situ gelation is indicated; where payload and particle integrity are limiting, PLGA is the stronger candidate.

The present findings are consistent with, and extend, the small comparative literature. Studies contrasting chitosan-coated with uncoated PLGA have reported enhanced permeation attributable to the polysaccharide [19,20], while a critical reappraisal has questioned whether chitosan decoration reliably improves transport into the brain [21]. The evidence here suggests that both positions may be correct in their own terms, because the benefit conferred by chitosan is one of mucosal residence and junctional modulation rather than of intrinsic carrier capacity, and will therefore appear or disappear depending on which step limits delivery in a given model. Framing the question as polymer-versus-polymer without specifying the rate-limiting step is unlikely to yield a stable answer.

Three limitations of interpretation should be stated. First, viloxazine was paired with polycaprolactone and venlafaxine with PLGA rather than each drug with all three polymers, so the polyester comparison is not fully crossed and drug and polymer effects cannot be entirely separated within that class. Second, zeta potential was not determined for the polycaprolactone system, leaving the surface-charge comparison incomplete. Third,

in-vitro and ex-vivo permeation, however carefully executed, cannot establish that material reaching the receptor compartment would reach the brain in vivo.

4. Industrial Significance and Practical Applications

For pharmaceutical development, the principal value of this work is the reduction of polymer selection from a matter of precedent to a matter of specification. A formulator can now enter the design phase with quantitative expectations: ionic gelation of chitosan will deliver particles of 160–171 nm with entrapment near 70–78% and a mucoadhesive surface; emulsion-based polyester processing will deliver 78–84% entrapment, with PLGA achieving this at comparable size and polycaprolactone at roughly twice the size. Development cycles can be shortened accordingly.

The manufacturing implications differ appreciably between the systems. The PLGA design space concentrated almost all response variance in a single factor, polymer mass, with stabiliser concentration and sonication time statistically marginal. A process of this character is robust to routine variation in two of its three inputs and is correspondingly straightforward to transfer and to control at scale. The chitosan systems, in which three factors and several interactions contributed materially, demand tighter control of a more constrained design space. Where robustness is the dominant commercial consideration, this asymmetry may outweigh the mucoadhesive advantage of the polysaccharide.

Both preparation routes use established pharmaceutical excipients and unit operations available at manufacturing scale. Ionic gelation is particularly attractive on environmental and safety grounds, requiring neither organic solvent nor elevated temperature, whereas the emulsion routes require solvent removal and its associated residual-solvent control. The in-situ gelling vehicle offers a further practical benefit in that it is filled and administered as a liquid, permitting conventional metered nasal devices while gelling in place to resist clearance.

Beyond the two antidepressants studied, the framework is applicable wherever a CNS-active molecule must reach the brain without the systemic exposure that oral dosing entails. The comparative data are directly transferable to other small-molecule neuropsychiatric agents with unfavourable oral pharmacokinetics, and the unified design approach provides a template for evaluating additional polymers on equal terms. The in-situ gelling nasal platform developed here may be adapted to agents requiring prolonged mucosal residence, and the demonstration that mucosal architecture is preserved supports further development toward repeat-dose evaluation.

5. Limitations of the Study

1. The study is confined to in-vitro and ex-vivo evidence. It establishes that the formulations are manufacturable, statistically optimised, reproducible, physically stable, capable of enhanced transmucosal permeation and tolerated by nasal tissue, but it does not establish delivery to the brain in a living animal, and no such claim is advanced.
2. The polyester comparison is not fully crossed, viloxazine having been paired with polycaprolactone and venlafaxine with PLGA. A complete factorial pairing of both drugs with all three polymers would allow drug and polymer contributions within the polyester class to be resolved unambiguously.
3. Zeta potential was determined for the venlafaxine systems but not for the polycaprolactone carrier, leaving the electrokinetic comparison incomplete.
4. Per-run response data were tabulated in full for the two chitosan systems; for the polycaprolactone and PLGA systems the individual run responses are represented through their fitted models and observed ranges rather than as complete matrices.
5. Excised goat nasal mucosa, while widely used and readily available, differs from human nasal tissue in thickness and enzymatic complement, and the reliability of integrity markers in such preparations

has been questioned [27]. Absolute permeation values should therefore be regarded as comparative rather than predictive of human performance.

6. Histopathological assessment followed a single exposure. Repeat-dose mucosal tolerance, which is the clinically relevant question for a chronic indication such as depression, remains to be established.

6. Future Scope

1. The immediate priority is in-vivo evaluation: pharmacokinetic determination of brain and plasma exposure with calculation of drug targeting efficiency and direct transport percentage, accompanied by pharmacodynamic assessment in a validated model of depression, under appropriate institutional animal ethics approval.
2. A fully crossed design pairing both drugs with all three polymers would complete the comparison and permit formal statistical partitioning of drug and polymer effects.
3. Extension of the framework to additional biodegradable polymers, including polymer blends and surface-functionalised variants, would broaden the selection map. Chitosan-coated polyester carriers are of particular interest, since they may capture the mucoadhesive advantage of the polysaccharide alongside the payload advantage of the polyester.
4. Repeat-dose mucosal tolerance and ciliotoxicity studies are required before clinical translation, together with evaluation of the formulations in a metered nasal device to establish spray pattern, droplet size and deposition.
5. Scale-up feasibility should be examined, with attention to the robustness asymmetry identified between the PLGA and chitosan design spaces, and long-term stability extended under accelerated conditions.

7. Conclusion

Four antidepressant-loaded biodegradable nanocarriers were developed and optimised within a single Box–Behnken framework, permitting a direct comparison of chitosan, polycaprolactone and poly(lactide-co-glycolide) that is not confounded by methodological difference. All four quadratic models proved statistically significant with non-significant lack of fit, and confirmation batches agreed with prediction to within 4.8% for every response, establishing that the design spaces are genuinely predictive.

The central finding is that polymer class, rather than the identity of the encapsulated drug, governs the critical quality attributes of these carriers. Chitosan minimised particle size and delivered a surface suited to mucoadhesion but the lowest payload; the polyesters delivered higher payloads, with PLGA uniquely combining high entrapment, small size and the strongest electrokinetic stabilisation. The trade-off between mucoadhesive potential and encapsulation capacity proved systematic and mechanistically interpretable in terms of how each polymer forms a particle.

All optimised carriers raised transmucosal permeation from 60% to 96% at 24 h relative to plain drug dispersion while preserving nasal mucosal architecture, and remained physically stable over three months. The in-situ gelling chitosan formulations combined nasal-compatible pH with sol–gel transition inside the physiological window.

These results supply a rational and statistically grounded basis for polymer selection in intranasal CNS formulation development, and identify the viloxazine–polycaprolactone system as a novel carrier whose dimensional characteristics illustrate the cost of optimising payload without regard to size. Confirmation of brain delivery in vivo is the necessary next step.

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Ethical Statement

No live-animal experiments were performed in this study. Nasal mucosa used for ex-vivo permeation and histopathological evaluation was obtained post-mortem from a local abattoir as a by-product of routine commercial slaughter, and its use did not require institutional animal ethics committee approval.

Conflict Of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions (Credit)

Anshuman Mohanty: Conceptualisation, Methodology, Investigation, Formal analysis, Data curation, Visualisation, Writing – original draft. Abhinandan Danodia: Conceptualisation, Methodology, Supervision, Validation, Writing – review and editing, Project administration. Dibya Lochan Mohanty: Methodology, Resources, Supervision, Validation, Writing – review and editing.

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