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Review Article

Nanostructured Lipid Carrier-Based Thermoresponsive Nasal Gels For Nose-To-Brain Drug Delivery: Current Advances And Future Perspectives

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ABSTRACT

Direct delivery of therapeutics to the central nervous system remains difficult because the blood-brain barrier restricts the entry of many molecules. Intranasal administration has therefore attracted sustained interest as a non-invasive strategy that can support systemic absorption and, for suitable molecules and formulations, transport toward the brain through pathways associated with the olfactory and trigeminal regions. However, short residence time, mucociliary clearance, restricted dose volume, variable deposition and enzymatic or physicochemical instability can limit the fraction of a nasally administered dose that reaches its intended site. Nanostructured lipid carriers (NLCs), composed of a blend of solid and liquid lipids stabilized by surfactants, provide a flexible lipid matrix for drug incorporation and can improve apparent solubility, protect labile compounds and modulate release. Thermoresponsive in situ gels address a different limitation: they can be administered as low-viscosity liquids and undergo gelation after exposure to nasal temperature, thereby increasing local residence time. Combining NLCs with thermoresponsive gels is consequently a rational dual-platform strategy in which the nanocarrier controls drug disposition while the gel controls retention and administration behavior. This review critically examines nasal anatomy relevant to nose-to-brain delivery, NLC structure and manufacture, thermoresponsive polymers, formulation variables, characterization methods, published examples of NLC-loaded nasal gels, and current translational limitations. Particular emphasis is placed on the need to distinguish promising preclinical brain-targeting observations from demonstrated clinical benefit. Future progress will depend on reproducible deposition in the upper nasal cavity, physiologically relevant models, robust safety assessment, scalable manufacturing, device-formulation integration and quality-by-design approaches.

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1. INTRODUCTION

Drug delivery to the brain is constrained by specialized vascular barriers that maintain central nervous system homeostasis but also restrict the penetration of many therapeutic molecules. Intranasal administration has emerged as an attractive alternative because the nasal cavity provides a highly vascular mucosa and anatomical connections with the central nervous system. Evidence from experimental systems supports transport associated with the olfactory and trigeminal pathways, although the relative contribution of direct neuronal/perineural transport, extracellular pathways and systemic absorption varies with the molecule, formulation, dose, deposition site and experimental model.¹

The intranasal route is not intrinsically equivalent to brain targeting. A formulation deposited predominantly in the anterior or respiratory region may be cleared, swallowed or absorbed systemically before a meaningful fraction reaches the upper nasal region. Rapid mucociliary clearance, small administrable volume, mucus turnover, local enzymes, nasal pathology and interspecies anatomical differences complicate interpretation of preclinical results. These constraints have stimulated the development of formulations that improve retention, protect the drug and promote contact with relevant mucosal surfaces.²

Lipid-based nanocarriers are among the most extensively investigated nanosystems for this purpose. Nanostructured lipid carriers represent a second-generation lipid nanoparticle concept in which a solid lipid is deliberately combined with a liquid lipid. The resulting less-ordered matrix can provide greater space for drug accommodation and can reduce drug expulsion associated with highly ordered lipid crystals. NLCs have consequently been explored for controlled release, solubility

enhancement, protection of incorporated compounds and site-oriented delivery.³

A complementary strategy is the use of stimuli-responsive nasal gels. Thermoresponsive systems are designed to remain sufficiently fluid during preparation and administration but to increase in viscosity or form a gel at nasal temperature. Poloxamer 407 is particularly prominent because of its reversible temperature-dependent micellization and gelation. Nevertheless, poloxamer gels may require modification with mucoadhesive polymers because mechanical strength and retention can be insufficient when the formulation is diluted by nasal fluid.⁴

Integrating NLCs with a thermoresponsive in situ gel therefore addresses two formulation problems simultaneously: the lipid nanoparticle provides a microenvironment for the drug, while the gel matrix prolongs mucosal contact and reduces immediate drainage. This review focuses on the scientific basis, formulation design, evaluation and translational status of this combined platform. It also emphasizes a critical point for interpretation: enhanced nasal retention, ex vivo permeation or increased brain exposure in animals is supportive evidence for delivery performance, but it does not by itself establish clinical efficacy in humans.¹

2. NASAL CAVITY AS A GATEWAY FOR BRAIN-ORIENTED DELIVERY

2.1 Anatomical and physiological considerations

The human nasal cavity is divided functionally into vestibular, respiratory and olfactory regions. The respiratory mucosa occupies most of the cavity and is highly vascularized, making it important for systemic absorption. The olfactory mucosa is located mainly in the superior nasal cavity and has direct anatomical relationships with



the olfactory bulb through the cribriform plate. Branches of the trigeminal nerve innervate both respiratory and olfactory regions and provide another anatomical connection between the nasal cavity and the central nervous system.²

For formulation scientists, deposition is as important as permeability. Conventional drops and sprays can deposit substantially in anterior regions, whereas efficient access to the superior-posterior region depends on device geometry, plume characteristics, administration technique and nasal anatomy. Recent reviews therefore stress that a promising formulation cannot be evaluated independently of its delivery device.⁵

The nasal mucus layer provides hydration and protection but also acts as a dynamic diffusional barrier. Ciliary activity transports mucus toward the nasopharynx, producing mucociliary clearance that can rapidly remove deposited material. Increasing viscosity or introducing mucoadhesive interactions can extend residence time, but excessive viscosity can impair spread, reduce sprayability or disturb physiological clearance. The formulation objective is therefore not maximum viscosity; it is a balanced rheological profile compatible with administration, distribution, gelation and mucosal function.⁶

2.2 Proposed routes from nose to brain

Following intranasal administration, a drug may enter the systemic circulation through the vascular respiratory epithelium and subsequently reach the brain if it can cross the blood-brain barrier. In

parallel, experimental evidence supports pathways associated with the olfactory and trigeminal nerves. Transport may involve intracellular processes within neurons for some materials, but extracellular or perineural routes are often considered important because reported delivery can occur faster than classical axonal transport alone would predict.⁷

The olfactory route is commonly associated with movement from the olfactory mucosa toward the olfactory bulb, whereas trigeminal-associated transport may provide access toward brainstem regions. These pathways should not be treated as mutually exclusive. The measured concentration in brain tissue after intranasal dosing may represent a combination of direct nasal-to-brain transport and indirect systemic delivery. Appropriate pharmacokinetic comparisons and indices of brain targeting are therefore useful when mechanistic claims are made.⁷

2.3 Barriers to effective intranasal delivery

Important barriers include limited dosing volume, mucociliary clearance, enzymatic degradation, mucus binding, variable nasal patency, formulation leakage, swallowing, local irritation and difficulty in reproducibly depositing the dose in the olfactory region. Disease state, age and inter-individual anatomy can further alter deposition and absorption. Animal models add another source of uncertainty because the relative area of olfactory epithelium and nasal geometry differ substantially between species.²

Table 1. Major intranasal delivery barriers and formulation-level responses.

Barrier	Potential consequence	Formulation response
Mucociliary clearance	Short contact time and dose loss	Mucoadhesion; temperature-triggered viscosity increase



Restricted nasal volume	Leakage and swallowing at excessive volume	Concentrated formulation; efficient device
Poor aqueous solubility	Low dissolved fraction at mucosa	Lipid nanocarrier or other solubilizing system
Drug instability	Degradation before absorption	Encapsulation and suitable pH/excipients
Mucus/epithelial barrier	Reduced diffusion or permeability	Particle-size/surface optimization; cautious enhancer use
Variable upper-nasal deposition	Inconsistent access to olfactory region	Device-formulation co-development
Local tolerability	Irritation or ciliary dysfunction	Biocompatible excipients; pH/osmolality and safety testing

3. NANOSTRUCTURED LIPID CARRIERS

3.1 Concept and structural rationale

NLCs were developed to address limitations recognized in first-generation solid lipid nanoparticles. In a conventional solid lipid nanoparticle, progressive ordering of the lipid matrix during storage can reduce the space available for incorporated drug and promote expulsion. NLCs deliberately mix solid and liquid lipids to create a less perfectly ordered matrix. The original NLC concept described imperfect, amorphous or structureless, and multiple-type matrices, each representing a different way of creating accommodation space for the drug.³

The imperfect type uses structurally different lipids to introduce lattice defects. The amorphous type is designed to minimize formation of a highly ordered crystalline state, while the multiple type contains small oil compartments within a solid lipid matrix. In practice, the final internal organization depends on lipid identity, ratio, thermal history, surfactant system and

manufacturing process, and simplified structural categories should therefore be interpreted as formulation concepts rather than universal microscopic architectures.³

3.2 Components of NLCs

A typical NLC contains a solid lipid, a liquid lipid, one or more surfactants and an aqueous phase. Candidate solid lipids include glycerides, fatty acids and wax-like materials that are solid at relevant storage and body temperatures. Liquid lipids may include pharmaceutically acceptable oils or medium-chain lipid excipients. Surfactants reduce interfacial tension and stabilize the newly formed particles. Selection should be guided by drug solubility in the lipid phase, miscibility of the solid and liquid lipids, safety for the intended route, achievable particle size, physical stability and the desired release profile.⁸

For nasal formulations, excipient selection requires an additional safety filter. A material that is acceptable orally or topically is not automatically optimal for repeated nasal exposure.



Surfactant concentration should be sufficient for colloidal stability but not unnecessarily high, and the finished formulation should be assessed for pH, osmolality, local compatibility and effects on

relevant epithelial or ciliary models where feasible.⁶

3.3 Preparation methods

Table 2. Common preparation approaches for nanostructured lipid carriers.⁸

Method	Principle and considerations
Hot homogenization and high-shear/probe-sonication approaches	The drug is incorporated into the molten lipid phase when compatible, and a hot aqueous surfactant phase is emulsified with the lipid phase. High shear, high-pressure homogenization or sonication reduces droplet size before cooling solidifies the lipid matrix. The approach is comparatively straightforward but thermal exposure can be unsuitable for heat-sensitive compounds.
Cold homogenization	The drug-containing lipid melt is cooled and milled before dispersion and homogenization. This can reduce thermal exposure and drug partitioning into the aqueous phase, although achieving very small particle sizes may be more difficult.
Microemulsion method	A warm microemulsion containing lipid, surfactant/co-surfactant and water is dispersed into cold water, causing lipid precipitation and nanoparticle formation. Dilution volume and subsequent concentration steps can influence practicality at scale.
Solvent emulsification/evaporation or diffusion	Lipids are dissolved in a suitable organic solvent and emulsified in an aqueous phase; solvent removal or diffusion produces the lipid particles. These methods can be useful for heat-sensitive compounds but require control of residual solvent and scalable solvent handling.
Melt emulsification followed by ultrasonication	A molten lipid mixture is emulsified in heated surfactant solution and the emulsion is reduced by ultrasonication before cooling. It is widely used in laboratory studies because equipment requirements are modest, although sonication energy, probe heating and batch reproducibility require control.

3.4 Critical quality attributes of NLCs

Particle size and size distribution influence colloidal stability, diffusion through mucus,



release behavior and interaction with epithelial surfaces. Dynamic light scattering is widely used to report hydrodynamic diameter and polydispersity index, while electron microscopy provides complementary information on morphology and dry-state or vitrified particle appearance. The values obtained by DLS and microscopy need not be identical because the methods measure different physical properties.⁸

Zeta potential is commonly used as an indicator of surface electrokinetic behavior and can support interpretation of colloidal stability, but a single numerical threshold should not be treated as universally predictive. Steric stabilization by non-ionic surfactants can maintain stability even when the magnitude of zeta potential is modest. Entrapment efficiency and drug loading should be measured with a validated separation and assay procedure that can distinguish untrapped drug from carrier-associated drug.⁸

Thermal analysis and diffraction methods can help determine changes in lipid crystallinity, polymorphism and drug physical state. These measurements are especially relevant to NLCs because the intended advantage of the system is closely linked to a deliberately disordered lipid matrix. Stability testing should follow particle size, distribution, drug content, encapsulation, appearance and evidence of phase separation or crystallization over time.³

4. THERMORESPONSIVE IN SITU NASAL GELS

4.1 Principle of thermally triggered gelation

A thermoresponsive nasal formulation is intended to be sufficiently fluid during handling and administration and to undergo a reversible increase in viscosity or gel formation after exposure to the nasal environment. This behavior can reduce

immediate drainage and may prolong contact with the mucosa. The clinically relevant target is not simply 'gelation at body temperature'; the formulation must remain administrable under realistic storage and handling conditions and must gel within an appropriate temperature window after deposition and dilution by nasal secretions.⁴

4.2 Poloxamer-based systems

Poloxamer 407 is a non-ionic PEO-PPO-PEO triblock copolymer. As temperature and concentration increase, dehydration of the hydrophobic polypropylene oxide blocks favors micellization and, at sufficiently high polymer concentration, packing of micelles produces a gel-like network. Poloxamer 188 is often combined with Poloxamer 407 to modify gelation behavior. Drug, salts, surfactants and additional polymers can shift the transition temperature; consequently, gelation must be measured in the complete formulation rather than inferred from polymer concentration alone.⁹

Poloxamer systems have practical advantages, including reversible gelation and ease of preparation by cold methods. Their limitations include dilution sensitivity and sometimes insufficient mucoadhesion or mechanical strength. Addition of a mucoadhesive polymer can improve retention, but this also changes viscosity, gelation, diffusion and spray characteristics. Formulation optimization must therefore consider interactions among the nanocarrier dispersion, thermogelling polymer and mucoadhesive component.⁹

4.3 Mucoadhesive adjuncts

Chitosan, carbomers, cellulose derivatives and other hydrophilic polymers have been investigated as mucoadhesive adjuncts in nasal gels. Mucoadhesion may arise through hydrogen bonding, electrostatic interactions, polymer



interpenetration and hydration-dependent contact with mucus. Chitosan is particularly interesting because its protonated amino groups can interact with negatively charged mucin under suitable pH conditions. Nevertheless, the magnitude of mucoadhesion measured in vitro depends strongly on the test geometry, tissue or substrate, contact time and applied force, so values from different studies should not be compared without methodological context.¹⁰

5. WHY COMBINE NLCs WITH THERMORESPONSIVE GELS?

An NLC dispersion and a thermoresponsive gel solve different problems. The nanoparticle can improve drug incorporation, protect the drug and influence release, but a low-viscosity dispersion may be cleared rapidly from the nasal cavity. A gel can increase residence time, yet a conventional molecularly dispersed drug may still suffer from low solubility or rapid partitioning away from the application site. Embedding NLCs in a thermogelling matrix can therefore create a hierarchical system in which the drug is associated with the lipid carrier, the carrier is distributed through the aqueous polymer phase, and the polymer network changes rheologically after administration.¹

The combination is frequently described as synergistic, but synergy should be demonstrated rather than assumed. A rigorous study should compare relevant controls, for example free drug solution, drug-containing gel without NLCs, NLC dispersion without gel and NLC-loaded gel. Such comparisons can distinguish whether an observed improvement arises from the nanocarrier, the gel, or their combination.¹

The gel matrix can also alter the behavior of the nanoparticles. Polymer concentration and gel microstructure may slow nanoparticle diffusion

and drug release, while surfactants carried with the NLC dispersion can change the gelation temperature of poloxamers. Conversely, a strongly interacting polymer may affect particle aggregation or surface properties. Compatibility should therefore be confirmed after incorporation rather than assuming that an optimized NLC remains unchanged in the final gel.⁴

6. FORMULATION DEVELOPMENT AND OPTIMIZATION

6.1 Preformulation and excipient screening

Development should begin with drug-lipid solubility or partitioning studies, solid-liquid lipid miscibility, surfactant screening and assessment of drug stability at processing temperatures. For the gel phase, polymer concentration should be screened over a range that provides manageable low-temperature viscosity and an appropriate transition after nasal administration. The influence of NLC dispersion volume on polymer concentration must be accounted for when the final gel is prepared.⁸

6.2 Quality-by-design perspective

A quality-by-design framework is useful because the combined platform contains several interacting variables. A quality target product profile can define route, dosage form, dose uniformity, administration behavior, intended gelation range, particle attributes and stability. Potential critical material attributes include lipid ratio, surfactant type, polymer grade and polymer concentration; critical process parameters can include homogenization energy, sonication conditions, temperature and cooling rate. Responses may include particle size, PDI, entrapment efficiency, gelation temperature, viscosity, mucoadhesion and release or permeation measures.¹



Design-of-experiments methods can identify interactions that one-factor-at-a-time studies may miss. However, statistical optimization does not substitute for pharmaceutical judgment. A mathematically optimal point is useful only if the predicted formulation is experimentally verified

and remains robust to realistic manufacturing and storage variability.¹

7. CHARACTERIZATION OF THE COMBINED NLC-IN SITU GEL

Table 3. Suggested characterization package for an NLC-loaded thermoresponsive nasal gel.

Evaluation	Purpose / interpretation
Appearance, pH and osmolality	Screen for physical acceptability and compatibility with nasal administration; interpret pH together with drug stability and mucosal tolerability.
Particle size/PDI after gel incorporation or recovery	Confirm that incorporation does not cause unacceptable aggregation. Sample preparation and dilution must be described.
Zeta potential	Support interpretation of surface behavior and colloidal stability; do not use as a stand-alone stability criterion.
Entrapment efficiency/drug loading	Quantify carrier-associated drug with an appropriate separation method and validated assay.
Gelation temperature/time	Determine the sol-gel transition of the complete formulation, ideally considering dilution with simulated nasal fluid.
Rheology/viscosity	Characterize flow before and after gelation; shear-dependent behavior is relevant to administration and retention.
Mucoadhesion	Assess retention-related interaction using a defined substrate/tissue, contact time and force protocol.
In vitro release	Characterize drug liberation from the combined matrix; membrane and sink conditions must be justified.
Ex vivo permeation	Estimate transport across excised nasal tissue while controlling tissue integrity, diffusion area, receptor conditions and sampling corrections.
Morphology and solid-state analysis	Use microscopy, DSC/XRD or related methods when needed to understand particle form and lipid/drug physical state.
Safety/compatibility	Histology, ciliary function or relevant epithelial-cell models can identify formulation-associated injury; safety conclusions should remain proportional to the model.

Stability	Follow physical, chemical and performance attributes under justified storage conditions.
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7.1 In vitro release and ex vivo permeation: interpretation cautions

Release and permeation experiments answer different questions. In vitro release primarily examines liberation of drug from the dosage form under the selected experimental conditions. Ex vivo permeation introduces a biological membrane and estimates movement across or retention within tissue. For Franz-type diffusion experiments, receptor volume, exposed area, temperature, stirring, sampling volume and replacement medium must be recorded. Cumulative permeation calculations should correct for drug removed during serial sampling. An irregular absorbance sequence should not be converted into an apparently smooth release curve without investigating dilution, blank correction, analytical range, sampling and calculation errors.

Excised nasal tissue provides greater biological relevance than an inert membrane, but it still lacks blood flow, mucus renewal and intact neural connections. Consequently, ex vivo permeation can support a nasal transport claim but cannot demonstrate actual brain targeting. Brain targeting requires appropriate in vivo pharmacokinetic or other validated translational evidence, while clinical efficacy requires human studies.²

8. PUBLISHED EXAMPLES OF NLC-BASED THERMORESPONSIVE NASAL SYSTEMS

The literature contains several examples demonstrating the feasibility of integrating lipid nanocarriers with nasal in situ gels. These studies are valuable for formulation design, but their endpoints and models differ, so direct numerical comparison should be made cautiously.

Table 4. Selected published examples relevant to NLC-loaded thermoresponsive/in situ nasal systems

Example	Formulation approach	Relevance	Ref.
Carbamazepine NLC thermosensitive gel	Microemulsion followed by probe sonication; NLC incorporated into a poloxamer-based in situ gel; formulation variables were studied using a Box-Behnken design.	Demonstrated a structured optimization approach linking gel composition with gelation and diffusion behavior.	13
Rizatriptan benzoate NLC in situ nasal gel	NLC-based nasal gel developed for brain-oriented delivery of an antimigraine drug.	Provides a disease-relevant example of combining NLCs and nasal gel technology for migraine-oriented delivery.	14
Rivastigmine lipid nanosystem thermosensitive gels	NLC and nanoemulsion formulations incorporated into thermosensitive nasal	Illustrates the value of integrating physicochemical,	15



	gels and evaluated for rheology, texture, release, cell compatibility and deposition in a nasal cast.	biological and deposition assessments rather than relying on particle characterization alone.	
Paroxetine NLC thermosensitive gel	NLCs prepared by a microemulsion approach and incorporated into a poloxamer mixture; in vitro and in vivo evaluations were reported.	Shows continuing application of NLC-gel systems to CNS-active drugs, while also highlighting the predominance of preclinical evidence.	16
Carnosic acid NLC thermosensitive nanogel	Melt emulsification/ultrasonication with QbD/central composite optimization; ex vivo permeation and nasal ciliotoxicity were among reported evaluations.	Recent example emphasizing formulation optimization and local safety-related assessment.	17

9. EVALUATION OF NOSE-TO-BRAIN DRUG DELIVERY PERFORMANCE

Recent systematic and narrative reviews indicate that intranasal lipid nanoparticles frequently produce favorable brain exposure or pharmacodynamic findings in animal models compared with selected controls. Nevertheless, the evidence base is heterogeneous in drug properties, species, dose, devices, analytical methods and comparator formulations. The exact contribution of direct nose-to-brain transport is often difficult to separate from systemic absorption.¹¹

A formulation should therefore be described with language matched to the evidence. Particle size, entrapment efficiency and gelation demonstrate formulation characteristics. Ex vivo permeation demonstrates transport across an excised membrane under defined conditions. Histology can support local compatibility in the tested model. None of these endpoints alone demonstrates therapeutic efficacy or prophylactic activity.

Similarly, increased brain concentration in an animal study supports brain delivery but does not establish clinical superiority.²

This distinction is especially important in review writing because exaggerated conclusions can propagate from one paper to another. The most defensible interpretation is that NLC-loaded thermoresponsive nasal gels are a promising preclinical platform with a mechanistic rationale and a growing experimental literature, but translation requires stronger human-relevant deposition, pharmacokinetic, safety and efficacy evidence.¹

10. SAFETY AND BIOCOMPATIBILITY

Nasal formulations contact a sensitive mucosal surface with an essential clearance function. Safety evaluation should therefore address not only overt tissue damage but also subtler effects on epithelial integrity and ciliary function. Excipients, surfactants, pH, osmolality and exposure duration can influence tolerability.



Repeated-dose use raises additional concerns because a formulation that is well tolerated after a single exposure may not be innocuous with chronic administration.⁶

Histopathological examination of treated nasal mucosa can reveal epithelial disruption, erosion, edema, inflammatory infiltration or other structural changes relative to untreated and control tissues. Cell-based models can complement tissue studies by assessing viability or barrier effects. However, absence of visible damage in one ex vivo experiment should be described as compatibility under the tested conditions rather than proof of long-term clinical safety.

11. MANUFACTURING, STABILITY AND DEVICE CONSIDERATIONS

Translation requires a manufacturing process that can reproducibly control particle size, distribution, drug content and lipid state at a practical scale. Probe sonication is convenient in laboratory development but can introduce local heating, metal contamination risk from probe wear and scale-up challenges. High-pressure homogenization is more readily scalable for some lipid nanoparticle processes, but process intensity and thermal history can alter drug distribution and particle properties. A scale-up strategy should therefore be built around defined critical process parameters rather than simple multiplication of batch quantities.⁸

The gel component adds additional constraints. The product must be fillable and doseable, remain stable during storage, and provide consistent transition behavior after administration. A formulation that gels too early may be difficult to spray or dispense; one that gels too late may drain before a stable gel is formed. Container-closure compatibility and dose uniformity are therefore integral to performance.

For nose-to-brain delivery, device performance deserves particular attention. Droplet size distribution, spray angle, plume geometry, actuation force and administration orientation influence regional deposition. Emerging devices designed to improve upper-nasal deposition may help bridge the gap between promising formulation properties and reproducible delivery to the olfactory region.⁵

12. CURRENT LIMITATIONS AND TRANSLATIONAL GAPS

Human nasal anatomy differs substantially from commonly used laboratory animals, making direct scaling of deposition and brain-targeting data unreliable.

Many studies compare an optimized nanogel with a simple drug solution but do not include enough controls to separate the contributions of NLCs and the gel matrix.

Definitions and methods for gelation temperature, mucoadhesion and ex vivo permeation vary, limiting cross-study comparison.

Upper-nasal deposition is often assumed rather than experimentally demonstrated with a clinically relevant device.

Long-term local safety, ciliary function and repeated-dose tolerability are less frequently studied than short-term physicochemical performance.

Manufacturing scalability, sterilization or microbial-control strategy, container compatibility and shelf-life are often addressed late in development.

Clinical evidence specifically validating NLC-based thermoresponsive nose-to-brain products remains limited; promising preclinical results



should not be presented as established clinical effectiveness.

These gaps are consistent with broader reviews of intranasal lipid nanoparticles and nose-to-brain delivery, which emphasize uncertainty in transport mechanisms, interspecies translation and the need for human-relevant evaluation.¹

13. FUTURE PERSPECTIVES

Future development should move from formulation-centric optimization toward integrated product design. Particle characteristics, gel rheology, nasal deposition and device performance need to be optimized together. Computational fluid dynamics, realistic nasal casts and imaging-based deposition studies can help determine whether the formulation reaches the intended nasal region before biological efficacy is investigated.⁵

Human-relevant epithelial models and standardized ex vivo methods may improve early screening, while physiologically based pharmacokinetic models could help integrate deposition, absorption, systemic exposure and potential direct transport. Such models remain challenging because several physiological parameters governing olfactory and trigeminal transport are incompletely quantified.⁵

Analytical characterization is also becoming more sophisticated. Conventional DLS, microscopy, DSC and X-ray diffraction remain useful, but advanced structural methods can provide deeper insight into lipid organization and nanoparticle behavior. These tools should be used to answer specific development questions rather than to accumulate characterization endpoints without a decision framework.¹²

Finally, successful translation will require clear evidence standards. Claims of 'nose-to-brain targeting' should be supported by appropriately designed pharmacokinetic and mechanistic studies; claims of improved treatment should require pharmacodynamic or clinical evidence. Maintaining this distinction will strengthen the credibility of the field and help prioritize formulations with genuine translational potential.¹¹

13.1 Critical formulation trade-offs

Optimization of an NLC-loaded thermoresponsive nasal gel involves trade-offs rather than a single desirable direction for every variable. Increasing surfactant concentration can facilitate particle-size reduction, but excessive surfactant may increase local tolerability concerns and can modify poloxamer micellization. Increasing polymer concentration usually strengthens temperature-dependent gelation and raises viscosity, yet a highly viscous formulation may be difficult to dispense and may spread poorly over the nasal mucosa. Similarly, strong mucoadhesion can improve retention, but a formulation must still distribute to the intended region before immobilization. These relationships explain why particle optimization and gel optimization should not be performed as completely independent exercises.

The same principle applies to drug release. Very rapid release may negate the reservoir function of the lipid carrier, whereas excessively slow release may reduce the amount of drug available for mucosal transport during the residence period. An appropriate profile depends on the drug, intended dosing interval, permeability and therapeutic objective. Consequently, a formulation should not be described as superior solely because it produces the slowest release. Release data should instead be interpreted together with permeation, retention

and, when available, pharmacokinetic performance.

Particle size also illustrates the danger of universal numerical targets. Smaller particles can offer a larger surface area and may move differently through mucus, but the biological behavior of a nasal nanocarrier depends on surface chemistry, mucus interactions, aggregation state and formulation viscosity in addition to nominal hydrodynamic diameter. A narrow distribution and reproducibility across batches are often more informative for pharmaceutical quality than pursuit of the smallest achievable diameter. Likewise, zeta potential must be interpreted in the context of steric stabilization and the complete excipient system.

Gelation temperature is another response that requires contextual interpretation. A formulation should remain usable during manufacture, filling, storage and administration, then undergo the intended rheological transition after deposition. Nasal surface temperature is not a single invariant value, and the formulation can be diluted by mucus immediately after administration. For this reason, characterization under only one undiluted laboratory condition may overestimate in-use performance. Evaluating the effect of physiologically relevant dilution and temperature variation can provide a more robust picture of gel behavior.

13.2 Recommended reporting framework for future studies

Transparent reporting would improve comparability across studies. For the NLC phase, authors should report the identity and quantity of solid lipid, liquid lipid and surfactant; drug concentration; aqueous-phase composition; batch size; processing temperature; homogenization speed or pressure and duration; sonication

amplitude or energy where applicable; cooling conditions; and storage conditions. Particle-size measurements should specify instrument principle, dilution medium, temperature and number of replicates. Entrapment measurements should describe how free drug was separated and how dilution factors were handled.

For the gel phase, the exact final polymer concentrations after addition of the NLC dispersion should be stated. The preparation temperature and hydration time are important for poloxamer systems. Gelation testing should identify the operational definition used to call the transition point, because visual tube inversion, rheological crossover and other methods do not necessarily produce identical values. Rheological reports should include instrument geometry or spindle, temperature, shear rate or rotational speed, and whether measurements were obtained before or after thermal equilibration.

Permeation studies should identify the animal species and tissue region, collection and transport conditions, membrane orientation, diffusion area, receptor volume and composition, temperature, stirring, donor dose, sampling schedule and replacement procedure. When serial samples are withdrawn, cumulative permeation calculations should correct for previously removed drug. Tissue integrity and appropriate blank or control experiments should be described. These details are essential because apparently small methodological differences can substantially change calculated flux and cumulative permeation.

Finally, brain-targeting studies should report the comparator formulations and routes needed to interpret mechanism. Brain concentrations after intranasal dosing alone cannot establish that transport occurred directly from the nose. Plasma exposure, relevant intravenous or other comparators when scientifically justified, and



appropriate pharmacokinetic analysis can strengthen interpretation. Device type, administration position and delivered volume should also be documented because they influence nasal deposition. Standardized reporting across these domains would make future evidence easier to reproduce, compare and translate.

13.3 Translational priorities for formulation development

Future studies should evaluate the complete dosage form rather than treating nanoparticle optimization and gel optimization as unrelated stages. Changes in lipid concentration, surfactant level or particle surface can alter the rheological environment after incorporation into a polymer solution. Conversely, increasing the concentration of a thermoresponsive polymer can influence diffusion of both the encapsulated drug and the carrier. A rational development programme should therefore reassess particle size, distribution, drug content and physical stability after the optimized NLC dispersion has been incorporated into the final nasal gel.¹

Another priority is to connect laboratory gelation measurements with conditions that occur during administration. A transition measured in an undiluted sample does not fully reproduce contact with nasal secretions, temperature gradients or shear during spraying. Evaluation after controlled dilution and under physiologically relevant temperatures can identify formulations that appear satisfactory in a vial but lose their desired rheological behaviour after administration. This is particularly relevant for poloxamer systems because their micellization and gelation are concentration- and temperature-dependent.⁹

The biological evaluation strategy should also progress in stages. Initial release and ex vivo permeation experiments can identify formulation-

dependent differences, while tissue compatibility studies can screen for overt local injury. These tests are valuable for formulation selection, but their conclusions should remain limited to the experimental model. Demonstration of preferential brain exposure requires appropriately designed pharmacokinetic studies, and demonstration of therapeutic benefit requires pharmacodynamic or clinical evidence matched to the intended indication.¹¹

Finally, reproducibility should be treated as a central quality attribute. Reporting only the best batch can obscure variability arising from homogenization, sonication, cooling or polymer hydration. Replicate batches, defined process parameters and stability testing provide a stronger basis for translation. This approach also makes design-of-experiments results more meaningful because the predicted optimum can be challenged experimentally rather than accepted solely from statistical desirability.⁸

14. CONCLUSION

Nanostructured lipid carriers incorporated into thermoresponsive intranasal in situ gels represent a rational strategy for addressing multiple limitations of nasal drug delivery. NLCs provide a versatile lipid matrix for drug incorporation and release modulation, whereas thermoresponsive gels can improve local retention by undergoing a temperature-dependent increase in viscosity after administration. The combined system is therefore attractive for drugs intended for brain-oriented delivery, particularly when conventional formulations are limited by solubility, instability or rapid nasal clearance.

The promise of the platform should nevertheless be interpreted within the strength of available evidence. Formulation characterization, release, ex vivo permeation and mucosal compatibility are



essential development steps, but they do not independently prove brain targeting or therapeutic efficacy. Future work should prioritize device-formulation integration, reproducible upper-nasal deposition, physiologically relevant models, repeated-dose safety, scalable manufacturing and well-controlled translational studies. With these advances, NLC-loaded thermoresponsive nasal gels may evolve from a predominantly preclinical research platform toward more robust and clinically testable nose-to-brain delivery products.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Nguyen TT, Maeng HJ. Pharmacokinetics and Pharmacodynamics of Intranasal Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Nose-to-Brain Delivery. *Pharmaceutics*. 2022 Mar 5;14(3):572. doi: 10.3390/pharmaceutics14030572. PMID: 35335948; PMCID: PMC8948700.
2. Lochhead JJ, Thorne RG. Intranasal delivery of biologics to the central nervous system. *Adv Drug Deliv Rev*. 2012;64(7):614-628.
3. Müller RH, Radtke M, Wissing SA. Nanostructured lipid matrices for improved microencapsulation of drugs. *Int J Pharm*. 2002;242(1-2):121-128. doi:10.1016/S0378-5173(02)00180-1.
4. Agrawal M, Saraf S, Saraf S, Dubey SK, Puri A, Patel RJ, et al. Stimuli-responsive in situ gelling system for nose-to-brain drug delivery. *J Control Release*. 2020;327:235-265.
5. Erdő F, Bors LA, Farkas D, Bajza Á, Gizurarson S. Evaluation of intranasal delivery route of drug administration for brain targeting. *Brain Res Bull*. 2018;143:155-170.
6. Schipper NGM, Verhoef JC, Merkus FWHM. The nasal mucociliary clearance: relevance to nasal drug delivery. *Pharm Res*. 1991;8(7):807-814. doi:10.1023/A:1015830907632.
7. Selvaraj K, Gowthamarajan K, Karri VVSNR. Nose to brain transport pathways an overview: potential of nanostructured lipid carriers in nose to brain targeting. *Artif Cells Nanomed Biotechnol*. 2018;46(8):2088-2095. doi:10.1080/21691401.2017.1420073.
8. Khosa A, Reddi S, Saha RN. Nanostructured lipid carriers for site-specific drug delivery. *Biomed Pharmacother*. 2018;103:598-613. doi:10.1016/j.biopha.2018.04.055.
9. Russo E, Villa C. Poloxamer hydrogels for biomedical applications. *Pharmaceutics*. 2019;11(12):671.
10. Ugwoke MI, Verbeke N, Kinget R. The biopharmaceutical aspects of nasal mucoadhesive drug delivery. *J Pharm Pharmacol*. 2001;53(1):3-21. doi:10.1211/0022357011775145.
11. Pires PC, Rodrigues M, Alves G, Santos AO. Intranasal delivery of nanostructured lipid carriers, solid lipid nanoparticles and nanoemulsions: a current overview of in vivo studies. *Acta Pharm Sin B*. 2021;11(4):925-940.
12. Alam R, et al. Nanostructured lipid carriers in drug targeting: characterization, patents, and recent innovations. *Curr Pharm Des*. 2026.



- doi:10.2174/0113816128411459260217142345.
13. Patil S, Babbar A, Mathur R, Mishra A, Sawant K. Development of carbamazepine nanostructured lipid carrier loaded thermosensitive gel for intranasal delivery. *Adv Pharm Bull.* 2021;11. doi:10.34172/apb.2021.016.
 14. Mathure D, Ranpise H, Awasthi R, Pawar A. Formulation and characterization of nanostructured lipid carriers of rizatriptan benzoate-loaded in situ nasal gel for brain targeting. *Assay Drug Dev Technol.* 2022;20(5):211-224. doi:10.1089/adt.2022.044.
 15. Cunha S, Amaral MH, Lobo JMS, Silva AC. Thermosensitive in situ hydrogels of rivastigmine-loaded lipid-based nanosystems for nose-to-brain delivery: characterisation, biocompatibility, and drug deposition studies. *Int J Pharm.* 2022. doi:10.1016/j.ijpharm.2022.121624.
 16. Akbar, K., Rehman, M.U., Shah, F.A. et al. Paroxetine Loaded Nanostructured Lipid Carriers Based In-situ Gel for Brain Delivery via Nasal Route for Enhanced Anti-Depressant Effect: In Vitro Prospect and In Vivo Efficacy. *AAPS PharmSciTech* 25, 248 (2024). <https://doi.org/10.1208/s12249-024-02954-z>
 17. Warsi, M.H., Ali, A., Mirza, M.A. et al. Design and evaluation of carnosic acid-loaded thermosensitive lipidic nanogels for nasal delivery: ex vivo permeation, nasal ciliotoxicity, and antioxidant assessment. *3 Biotech* 15, 193 (2025). <https://doi.org/10.1007/s13205-025-04367-6>.

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