International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Intranasal and Pulmonary Lipid Nanoparticles for Gene Delivery: Turning Challenges into Opportunities

Yaman Tayyar[1–3], Adi Idris[2,4,*], Hadi Yassine[1,*]

[1]Biomedical Research Centre, QU Health, Qatar University, Doha, Qatar; [2]Institute for Biomedicine and Glycomics, Griffith University, Brisbane, QLD, Australia; [3]Prorenata Biotech, Doha, Qatar; [4]Centre for Immunology and Infection Control, School of Biomedical Sciences, Queensland University of Technology, Brisbane, QLD, Australia

*These authors contributed equally to this work

Correspondence: Hadi Yassine, Biomedical Research Center, Qatar University, Doha, Qatar, Tel +974 4403 6819, Email hyassine@qu.edu.qa

Abstract: Delivery of nano-therapeutics through the nasal route offers a promising approach for several applications, including intranasal conditions, pulmonary delivery, brain targeting, and vaccination. Despite its potential, this method faces significant challenges, including overcoming the mucosal barrier, ensuring consistent absorption, controlling the deposition area, and managing immunogenic responses. This review provides a comprehensive overview of the current state of nasally delivered lipid nanoparticles (LNPs) for gene medicine, focusing on the specific barriers encountered in this delivery route and strategies to overcome them. We examine how formulation composition affects stability during aerosolization, analyze the impact of particle characteristics on mucociliary clearance, and evaluate interactions with the lung surfactant layer. The review also compares delivery devices including metered-dose inhalers, dry powder inhalers, and nebulizers, highlighting how device selection influences LNP integrity and deposition patterns. Furthermore, we explore potential safety considerations with intranasal LNPs and propose approaches to mitigate adverse effects. By addressing these challenges with evidence-based strategies, this review aims to advance the development and clinical application of intranasal and pulmonary LNP delivery systems for gene-based therapeutics and vaccines.

Keywords: lipid nanoparticles, LNPs, gene medicine, intranasal delivery

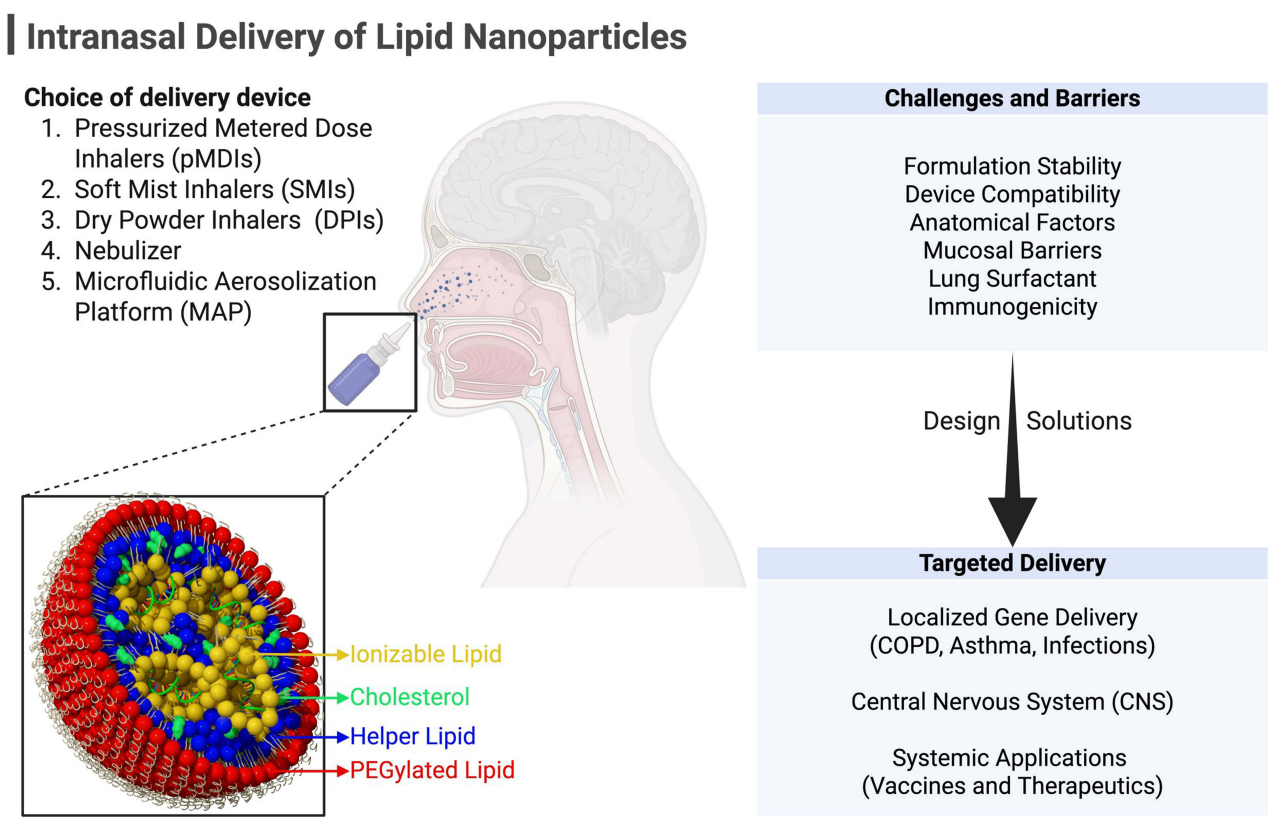
Introduction

Lipid nanoparticles (LNPs) and other lipid-based delivery systems have emerged as a groundbreaking modality for administering gene-based therapeutics and vaccines. These delivery systems are on a trajectory to become more dominant than the traditionally used viral vectors for delivering gene medicines owing to several advantages related to their safety profile, flexibility in formulation, and reduced immunogenicity, which collectively enhance their potential for widespread clinical application.[1–3] LNPs exhibit distinct physicochemical characteristics that facilitate the encapsulation of a wide range of genetic materials, including messenger RNA (mRNA) and deoxyribonucleic acid (DNA), while concurrently providing a protective barrier against enzymatic degradation. This attribute is particularly vital within the context of gene medicine, where the protection of delivery and the bioavailability of therapeutic agents are paramount for achieving optimal therapeutic results.[1–3]

As the landscape of gene-based therapeutics continues to evolve, integrating LNPs into nasal delivery systems presents a promising avenue for enhancing therapeutic efficacy and patient compliance.[4] Recent advancements in this field demonstrates the ability for LNPs to be fine-tuned, not only for optimal encapsulation but also targeted delivery to specific tissues such as the lungs. In this regard, this capability could revolutionize treatments for respiratory diseases by allowing localized action with minimal systemic exposure, thus reducing potential side effects associated with a broader distribution all the way through the fine bronchiolar labyrinth structure.[4–6]

Received: 14 January 2025
Accepted: 15 April 2025
Published: 23 June 2025

Graphical Abstract



Intranasal (IN) delivery is a non-invasive and patient-centric approach that markedly enhances upper and lower respiratory tract bioavailability and potentially allows direct targeting of the central nervous system (CNS).[7–9] For the purposes of our review, we will use the term "intranasal delivery" to encompass nasal administration via the nasal route to include the upper and lower respiratory tract, and CNS targets accessed. Other applications for delivering genes through the nasal route include the treatment of lower respiratory pulmonary conditions, such as chronic obstructive pulmonary disease (COPD) and asthma,[10–12] respiratory infections,[13–15] and vaccination.[16–20] Although intranasal administration is characterized by clear, accessible anatomy, relative immune privilege, and low enzyme activity, a number of significant challenges remain to be addressed.[21–25]

One of the primary challenges in optimizing LNPs for intranasal delivery is achieving precise control over its physicochemical properties to avoid administration-related degradation, reduce mucociliary clearance and control its tissue deposition site. Other considerations related to cellular barriers include low cellular uptake and endosomal escape rates. Nevertheless, innovations in formulation techniques, including the use of ionizable lipids and helper lipids with specific chain lengths, can potentially modulate transfection efficiencies and therapeutic outcomes.[21–25] Moreover, exploring additional formulation strategies, such as utilizing mucoadhesive agents that prolong retention time, may further improve the efficacy of LNP-mediated therapies by facilitating the sustained release of therapeutic cargo and enhancing local concentrations at the site of action.[26–28] As development in these areas improve, these advancements not only promise to refine existing applications but also pave the way for novel interventions targeting a broader spectrum of diseases through more sophisticated delivery mechanisms.

The primary aim of this review is to conduct a thorough examination of the contemporary landscape in intranasal applications of LNP technology. In short, we seek to elucidate not only the significant challenges that researchers encounter in the intranasal delivery space but also the innovative strategies being utilized to overcome these obstacles.

Lipid Nanoparticles; an Introduction

The journey in LNP development for nucleic acid delivery began over six decades ago. Early studies on liposomes, small vesicles made up of one or more lipid bilayers that can encapsulate and transport drugs and other molecules to specific sites in the body, led to the regulatory approval of several lipid-based drug formulations, including the antifungal agent, Abelcet[29] and chemotherapeutic agents Myocet,[30] and Marqibo.[31] These formulations paved the way for more advanced LNP systems, particularly in the context of gene delivery. Indeed, the first US Food Drug Administration (FDA) approved for LNP product was granted in 2018 for Onpattro (patisiran), an LNP encapsulated small interfering RNA (siRNA) therapeutic for treating a genetic liver disease called transthyretin-induced amyloidosis.[32] LNPs gained further traction in the field of mRNA vaccines, exemplified by the rapid development and deployment of COVID-19 vaccines, which showcased its potential for delivering genetic material effectively and safely.[33]

A typical formulation for LNPs consists of a carefully curated blend of four essential lipid components; ionizable cationic lipids, phospholipids, cholesterol, and polyethylene glycol (PEG)-lipids.[34,35] The ionizable cationic lipids are the primary functional components that facilitate electrostatic interactions with negatively charged nucleic acids, enabling efficient encapsulation. At physiological pH, these lipids maintain a near-neutral charge, minimizing toxicity and undesired interactions while becoming positively charged in the acidic environment of endosomes to promote endosomal escape.[36] Phospholipids, such as distearoylphosphatidylcholine (DSPC) or dioleoylphosphatidylethanolamine (DOPE), act as structural lipids that stabilize the LNP architecture and influence membrane fusion properties. Cholesterol enhances the rigidity and stability of the lipid bilayer, reduces permeability, and helps maintain the structural integrity of LNPs during storage and administration. PEG-lipids serve multiple functions: they stabilize LNPs during formation by preventing aggregation, extend circulation time by creating a hydrophilic shield that reduces recognition by the immune system, and influence cellular uptake and biodistribution patterns.[37–40]

The optimal composition of LNPs remains a topic of ongoing debate. Notably, formulations that include an ionizable lipid at a molar ratio of 33% have demonstrated remarkable mRNA transfection efficiency, both in vitro and in vivo.[41] The intricate interplay between the types and ratios of these lipids plays a crucial role in determining LNP performance. Modifications to the lipid composition, whether through altering the types of lipids used, adjusting their proportions, introducing or omitting specific components, can significantly impact nanoparticle physicochemical properties. For instance, LNP size and surface charge can be tailored to optimize its interaction with cellular membranes, thereby altering cellular uptake efficiency. Furthermore, these adjustments directly influence the release kinetics of the encapsulated therapeutic agents, as well as the overall stability of the nanoparticles.[34,35,41] The efficacy of the LNPs in delivering its payload is intricately linked to these factors, as is its safety profile in therapeutic applications. Understanding the nuanced dynamics of lipid interactions and its effects on LNP behavior is essential for the development of effective and safe delivery systems for gene medicines.

The clinical utility of LNPs for gene delivery has been demonstrated through several successful applications that have either received regulatory approval or are in advanced clinical trials. The first FDA-approved LNP-based therapeutic, Onpattro (patisiran), marked a significant milestone in 2018 for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR) by delivering siRNA to silence the production of transthyretin protein in the liver.[32,42] This success was followed by the unprecedented rapid development and deployment of mRNA-LNP COVID-19 vaccines (BNT162b2 by Pfizer/BioNTech and mRNA-1273 by Moderna), which demonstrated remarkable efficacy and safety profiles, further validating the clinical potential of LNP delivery systems.[43]

Beyond these approved therapies, numerous LNP-based gene delivery systems are advancing through clinical trials for various indications. For instance, Moderna's mRNA-1944, an LNP-formulated mRNA encoding an anti-Chikungunya virus antibody, has shown promising results in Phase 1 trials with successful antibody expression in humans.[44,45] Additionally, Intellia Therapeutics' NTLA-2001, a CRISPR-Cas9-based therapy delivered using LNPs, has entered clinical trials for transthyretin amyloidosis (Clinical Trials NCT05697861, NCT04601051, and NCT06128629). This

represents an important advancement as one of the first in vivo CRISPR genome editing therapies to reach clinical testing.

For respiratory applications specifically, several LNP-based gene therapies are under clinical investigation. Translate Bio's MRT5005, an inhaled mRNA therapy encoding cystic fibrosis transmembrane conductance regulator (CFTR) protein, entered clinical trials for cystic fibrosis treatment (Clinical Trial NCT03375047). Similarly, Arcturus Therapeutics has developed ARCT-032, another inhaled mRNA therapy for cystic fibrosis that has advanced to clinical evaluation (Clinical Trial NCT05712538). These respiratory-focused therapies are particularly relevant to intranasal delivery approaches, as they utilize similar administration routes and face comparable physiological barriers.

Beyond respiratory conditions, LNP-mRNA therapeutics are being evaluated for metabolic disorders, including Moderna's mRNA-3704 for methylmalonic acidemia (Clinical Trial NCT03810690) and mRNA-3927 (Clinical Trial NCT04159103) for propionic acidemia.[46] Arcturus Therapeutics' ARCT-810, which delivers ornithine transcarbamylase (OTC) mRNA for OTC deficiency, has also entered clinical development (Clinical Trial NCT05526066). These examples highlight the versatility of LNP delivery systems across various therapeutic applications and administration routes.

In this review, we focus on inhalable LNPs due to its many advantages and unique features. For instance, inhalable LNPs reduce systemic toxicity and can achieve higher localized drug cargo concentrations in the lungs[47] while also having the potential to modify the LNP surface with specific ligands that target particular cell types within the respiratory tract.[48] Indeed, these LNPs have been shown to protect its therapeutic cargo from enzymatic degradation[46,49] and improve its cellular uptake.[50] Lastly, these inhalable LNPs can be tailored to provide a therapeutic effect distal to the lungs, with the potential to extend its therapeutic effects in the brain for the treatment of neurological disorders.[7–9,51,52]

Challenges and Opportunities for Intranasal LNP Delivery

Delivering LNPs intranasally provides opportunities such as direct access to the lungs, avoiding first-pass metabolism by minimizing systemic exposure and the potential for brain delivery. However, the process of administering nanoparticles intranasally, in addition to the complex pulmonary environment, poses many challenges for LNPs to effectively deliver its cargo. Understanding the challenges and barriers is essential for designing an effective and safe intranasal formulation. Here, we will categorize these challenges into pre-cellular and cellular barriers.

Formulation Stability and Integrity

The administration of pharmacological agents through the pulmonary pathway (eg, via aerosolization) necessitates that these substances endure the mechanical stresses applied to these agents during the procedure. This includes factors such as shear forces, turbulence, and the potential for aggregation.[53,54] This is of special concern in the case of LNPs due to its high surface energy, especially in suspension form, which could promote its aggregation by Ostwald ripening and recrystallization.[55] LNP instability during aerosolization poses a significant barrier to achieving successful pulmonary delivery. Several strategies could be explored to overcome these issues, including optimization of particle size, surface charge, and the choice of lipid composition.[56] For instance, the inclusion of PEG-lipids was shown to be essential in preventing LNP aggregation. However, fine tuning the ratio of its composition is essential to improve the colloidal stability whilst not impacting its cellular uptake.[57] Other strategies to improve the colloidal stability include charge-assisted stabilization (CAS) by utilizing a peptide-lipid conjugates,[58] employing stabilizing excipients such as trehalose, dextran, and leucine,[57] and the use of advanced atomization techniques, such as residual free atomizer.[59] To further study and improve the stability of LNPs, techniques such as single particle automated Raman trapping analysis (SPARTA) and small-angle X-ray and neutron scattering (SAXS/SANS) have been utilized to link LNP composition to its internal structure.[60] Aside from PEG, the role of the helper lipids was found to be critical in modulating its transfection efficiency in airway epithelial cells using unsaturated lipids, such as those derived from oleyl groups, as opposed to their saturated counterparts.[61]

Anatomical and Administration Considerations

The optimal size range for the effective deposition of intranasally delivered particles in the pulmonary regions of the lungs is between 1–5μm in diameter.[62] While larger particles tend to be predominantly retained within the oropharyngeal

region of the upper respiratory tract,[63] nano-sized particles are often easily expelled from the respiratory system upon inhalation due to the effects of Brownian motion, which facilitates its suspension and movement within the respiratory pathways.[62] One potential strategy for alleviating this concern is to encapsulate these nanoparticles within microparticles that are designed to release its nanoparticle contents upon contact with the mucus or fluid present in the lung environment, thereby enhancing its deposition and therapeutic efficacy.[64] The strategy of the nano-embedded microparticles (NEM) holds promise and has been successfully used to improve the intranasal delivery of LNPs.[65–70] Further, to ensure the effective and uniform delivery to the intended site within the pulmonary route, the selection of an appropriate delivery device is critical.[61,71–73] Various applicator devices have been utilized for the intranasal administration of LNPs, each offering unique advantages and limitations. These devices include inhalers, nebulizers, and other applicators.

Inhalers

Inhalers are widely used as an effective method for delivering therapeutic agents directly to the pulmonary tract. Its popularity stems from their ease of use, portability, and ability to deliver precise doses of medication. In the context of LNP delivery, inhalers have been explored for their potential to provide targeted treatment for various respiratory conditions. The three main types of inhalers include pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), and soft mist inhalers (SMIs).

Pressurized Metered Dose Inhalers (pMDIs)

Pressurized Metered Dose Inhalers (pMDIs) are one of the most common inhaler types used for delivering medications to the lungs. These devices utilize a propellant to disperse a specific dose of the medication in aerosol form, which patients inhale through a mouthpiece. The primary advantage of pMDIs is its ability to deliver a consistent and precise dose of medication, making it highly reliable for patients requiring regular dosing. The aerosolization process in pMDIs involves the rapid expansion and atomization of a formulation through a nozzle, which can potentially impact the stability of LNPs. However, studies have shown that with careful formulation design, the structural integrity and functionality of LNPs can be preserved. This typically involves optimizing the propellant, surfactants, and other excipients to ensure that LNPs are not destabilized during aerosolization. For instance, the use of hydrofluoroalkane (HFA) propellants, which are less likely to disrupt lipid structures, has been found to be beneficial in maintaining the integrity of LNPs.[19,47,74–76] Furthermore, the actuator nozzle and surrounding conditions significantly impact the atomization process, which in turn affects the droplet size distribution and deposition of the drug in the respiratory tract. Computational fluid dynamics (CFD) simulations have shown that different nozzle designs can influence drug deposition, with twin nozzles increasing deposition in the mouth-throat region, potentially affecting the delivery of LNPs.[62,77,78]

Soft Mist Inhalers (SMIs)

SMIs represent a newer category of inhalers that provide a unique method of delivering medication to the lungs. SMIs do not use a propellant; instead, they generate a slow-moving mist using a mechanical action. This mist is finer and slower compared to aerosols produced by pMDIs, resulting in a longer duration of mist of the inhaler airstream, which allows more time for the patient to inhale the medication.

SMIs offer several advantages over pMDIs, particularly in terms of inhalation technique and deposition efficiency. Notably, they were found to be one of the most effective applicators for inhalable mRNA-LNPs, that when coupled with a trehalose buffer system, can withstand the shear forces of aerosolization and effectively protect and deliver their cargo.[56] However, they have higher cost compared with other inhalers, and limited availability of medications in soft mist formulation.[79]

Dry Powder Inhalers (DPIs)

DPIs offer an alternative to pMDIs, particularly for patients who find it difficult to coordinate inhalation with actuation. DPIs deliver medication in a dry powder form that is aerosolized by the patient's inhalation effort rather than a propellant.[12] This design eliminates the need for synchronization, making DPIs more user-friendly for individuals

with limited dexterity or lung capacity. In addition, dry form may be more suitable for delivering LNPs due to their superior physical stability.[80,81] Administering LNPs using this approach primarily targets the nasal cavity but may also result in some deposition in the lungs if particles are too fine.[82] It is important to note here that the DPI approach has been effectively used to overcome the blood-brain barrier.[83] However, the drying process can potentially affect the stability and integrity of LNPs.[80,84]

Nebulizers

Nebulizers are devices that convert liquid formulations into fine mists, making them particularly suitable for delivering LNPs to the lungs.[85] These devices are advantageous for patients who have difficulty using inhalers, such as children or the elderly. Nebulizers have shown promise in delivering significantly more mRNA packaged in LNPs to the lungs compared to conventional LNP formulations optimized for systemic delivery. Despite their advantages, nebulizers can be cumbersome, requiring longer administration times and regular maintenance.[86,87] Most importantly, without extensive optimization, LNPs tend to break up during nebulization, impacting its delivery efficiency. LNPs aerosolized using a nebulizer results in an increase in particle size and decreased encapsulation, which is attributed to shear forces impacting the particle.[3,4,88,89] More recently, Kim, Jozićet al developed a microfluidic aerosolization platform (MAP) specifically for LNPs, offering advantages such as preserving the structural and physicochemical integrity of lipid nanoparticles, avoiding aggregation, and improving cell transfection.[90]

Other Intranasal Delivery Devices and Formulations

A variety of other intranasal applicators have been developed to improve deposition patterns in the nasal cavity. Traditional liquid nasal spray pumps are simple and convenient but tend to deposit a large portion of the dose in the anterior, non-ciliated region, with relatively little reaching the upper/posterior nasal cavity.[91,92] This limits drug access to deeper regions (eg the olfactory cleft or nasopharynx). Liquid droppers can achieve slightly deeper delivery beyond the nasal valve, but are less patient-friendly and often yield inconsistent dosing [93,94] Dry powder nasal insufflators (solid dose devices) avoid the need for preservatives and can improve stability, but the powder must be well dispersed to coat the mucosa uniformly. Recent innovations like bi-directional nasal delivery systems (eg Exhalation Delivery Systems) use the patient's exhaled breath to propel formulations into the nasal passages.[95–97] These systems create a closed soft palate and a positive pressure airflow, resulting in significantly greater deposition in the superior and posterior regions (including the olfactory area) compared to conventional sprays. Notably, bi-directional devices can deliver drug broadly across the nasal cavity while minimizing lung deposition, which is advantageous for both sinus therapies and nose-to-brain applications.

Mucociliary Clearance

Mucociliary clearance (MCC) is an important physiological procedure that aids the expulsion of inhaled molecules and pathogens from the respiratory tract. This process has a significant impact on the retention and efficiency of LNPs when inhaled.[98,99] Many factors, such as nanoparticle size, surface composition, and the physical properties of the mucus and the respiratory tract, play a role in determining the interactions between the mucus and LNPs. The mucus layer acts as a shield that stops particles from reaching the epithelial surface. This shield mainly consists of a semi-liquid substance composed of water and glycoproteins, which have a direct influence on the penetration and retention of nanoparticles.[98,99] Although some studies claim that the mucociliary clearance of nanoparticles does not depend on its size, shape, or charge,[100,101] a considerable body of evidence suggests otherwise.[102–108] For instance, particles larger than 500 nm were found to be rapidly trapped and immobilized in mucus, while ones under 300nm had significantly better diffusion rates.[102,109] The surface charge of nanoparticles also plays a critical role in determining its fate in the respiratory tract. Mucus is rich in negatively charged groups, which readily interact with positive nanoparticles, resulting in its adhesion. This could be beneficial to some extent to increase nanoparticle retention time.[106] However, slightly negatively charged particles tend to have better mucus penetration properties.[105,110,111] In summary, neutral net charge was found to perform the best in terms of overall efficacy.[112] Hence, LNPs based on ionizable lipids may provide an opportunity for improving the therapeutic potential of these delivery systems in the pulmonary tract.

Various other strategies to improve mucus penetration have also been tested. For instance, PEGylation, the process of attaching PEG chains to nanoparticles, was found to play a crucial role in enhancing nanoparticle mucus penetrating ability.[113,114] PEG layers shield the particles from electrostatic and hydrogen bonding interactions with mucin, a major component in mucus, and, as a result, act as a steric barrier preventing adhesion to the mucin network.[103,113,115] It is also notable that denser PEG coatings achieve higher efficiency in penetration.[103,116] Other modifications, such as incorporating rhamnolipids,[117] pulmonary surfactant lipids, such as DPPC,[118–121] modifying with cell-penetrating peptides,[122,123] and using mucoadhesive agents,[124–126] were also found to improve the mucus penetrating properties of nanoparticles.

As mentioned earlier, the physicochemical properties of mucus greatly influence the ability of nanoparticles to reach their cellular targets. Hence, it is safe to assume that modulating the mucus layer may be a viable option to facilitate the cellular uptake of LNPs in the pulmonary tract. One such strategy is the use of mucolytic agents, such as N-acetylcysteine (NAC), to reduce the viscosity of the mucus, allowing deeper penetration of the particles.[127] Pre-adjustment of the mucus pH levels in the pulmonary tract may also facilitate the cellular uptake of some particles.[113] Finally, variations in parameters related to mucus rheological characteristics as well as ciliary movements may affect the speed of mucus transport and, as a result, the time nanoparticles spend within the respiratory tract.[109,128]

The Lung Surfactant Problem

The pulmonary surfactant is a critical component of the respiratory system, which is produced by type II alveolar epithelial cells.[129–131] It is a complex mixture composed predominantly of lipids (about 90%) and proteins (approximately 10%), with phosphatidylcholines—particularly dipalmitoylphosphatidylcholine (DPPC)—being the main lipid constituents. The surfactant also contains specific proteins, namely surfactant protein A (SP-A), SP-B, SP-C, and SP-D, which play vital roles in its function.[129,132] This surfactant layer, with a thickness of about 0.2–0.5 μm, lines the alveolar surface and is essential for normal respiratory mechanics.[133–135]

The primary function of the lung surfactant is to reduce surface tension at the air-liquid interface within the alveoli, thereby preventing alveolar collapse during exhalation and facilitating lung expansion during inhalation.[135–138] By lowering and regulating the surface tension, the surfactant improves lung compliance and enhances oxygenation, which is crucial for efficient gas exchange.[135,137,139] Additionally, surfactant proteins (SP), particularly SP-A and SP-D, contribute to the innate immune defense by recognizing and binding to pathogens and toxins, thus playing a role in host defense mechanisms.[140–142] The surfactant also acts as a biological barrier that influences the retention time of inhaled particles and determines pulmonary drug bioavailability. Its presence can significantly impact the deposition, absorption, and clearance of inhaled therapeutics, including nanoparticles.[129] For instance, surfactant proteins and lipids can adsorb onto the surface of nanoparticles (especially those >100 nm), forming a “corona” that alters their physicochemical properties and biological fate. This corona can affect the nanoparticles’ mucoadhesive properties, mucus permeability, cellular uptake, retention in bronchoalveolar lavage fluid, lung tissue absorption, systemic exposure, and extrapulmonary distribution.[138,143,144] Moreover, these interactions can impact the physicochemical properties of the surfactant itself, potentially affecting surfactant metabolism, particle clearance, and its biophysical functions.[132,139] This could lead to disruptions in surfactant activity, affecting lung function and potentially leading to adverse effects.

To overcome the detrimental effect of the lung surfactant on the successful delivery of nanoparticles, it is important to consider the charge, shape, and composition of nanoparticles. For instance, neutral-to-negative surface charged nanoparticles with moderate surface polarity were all found to be important factors to facilitate nanoparticle transit across the lung surfactant barrier.[82] Additionally, molecular dynamics simulations have shown that the shape of the nanoparticles significantly affects their ability to penetrate the pulmonary surfactant layer. While spherical nanoparticles have been the primary focus in past studies, recent research highlights that non-spherical nanoparticles exhibit different translocation behaviors. Hydrophilic nanoparticles smaller than 5nm can penetrate the surfactant layer regardless of shape, while larger particles show shape-dependent translocation, with certain geometries like tetrahedral and cylindrical NPs causing less disruption compared to cubic and spherical shapes.[85,145]

Recent studies have shown promising results with engineered LNPs that include β-sitosterol, to enhance transfection potency and substantial expression in the airway and alveolar epithelium,[85] and conditioning the surface properties with grafting polymers.[146] Understanding the role of the lung surfactant as a barrier has also led to innovative strategies to

enhance nanoparticle delivery, such as the development of nanoparticles that mimic the composition and properties of the lung surfactant. Pre-coating nanoparticles with pulmonary surfactant components, such as commercial surfactant preparations like Curosurf®, was found to improve nanoparticle stability and promote intracellular delivery of therapeutic agents like small interfering RNAs (siRNA) in the lung, both in vitro and in vivo.[147–149] The incorporation of surfactant proteins, particularly SP-B, can facilitate efficient cytosolic delivery of encapsulated nucleic acids into target cells, enhancing therapeutic efficacy.[135,150]

Safety of Administering LNPs Intranasally

LNPs are relatively immunologically inert, hence why it is acceptably safe in humans. However, several considerations should be considered when designing a formulation for intranasal use. Taking mRNA-based vaccines as an example, the type and dose of the mRNA itself, the produced antigen, and the delivering LNPs, could result in adverse events.[20]

It is evident that the safety of IN delivery of LNPs has not yet been examined extensively, and only a few studies focused on assessing the composition of the LNPs. For instance, Polyethylenimine (PEI) was shown to elevate the levels of the proinflammatory cytokine, interleukin (IL)-6, and result in weight loss in animals.[151,152] In another study by Andries, De Filette,[153] LNPs containing GL67, DOPE, and DMPE-PEG5000 led to an increase in pro-inflammatory cytokines (eg, tumour necrosis factor (TNF) α and IL-6), suggesting the need to avoid these charged and surface-active molecules when designing IN LNPs.[153]

One of the most debated components of any LNP formulation is PEG. Anti-PEG IgE and IgM antibodies generated in patients administered with LNP formulated COVID-19 vaccines were shown to be responsible for serious side effects related to LNPs, such as acute organ toxicity, allergies, and the accelerated blood clearance (ABC) phenomenon mediated by IgM.[154] Approaches to limit these adverse events include shortening the length of the PEG lipid to allow easy separation from the LNP surface[155,156] and using a reduced PEG molecular weight to reduce circulation times.[157–159] Lastly, substituting PEG with other molecules, such as cleavable PEG-cholesterol derivatives or polysarcosine (PSar) is also being researched.[160–162]

Conclusions

LNP-based systems have emerged as a leading delivery platform for gene medicine that was shown to be effective, safe, and versatile. IN administration of these LNPs holds several advantages: it is patient-friendly, non-invasive, and has the potential to provide targeted delivery to the respiratory tract and even to the central nervous system (CNS). Although progress in this field is evident, several critical challenges, knowledge gaps, and regulatory hurdles must be addressed before IN LNP formulations can reach their full clinical potential.

One of the most significant challenges for this route is the biological barriers within the nasal and pulmonary environments. While recent advances have led to improved LNP compositions, including the use of ionizable lipids and PEGylation strategies, the precise mechanisms by which nanoparticles interact with and traverse the nasal epithelium remain incompletely understood. Studies employing pharmacological inhibitors and advanced imaging techniques have started exploring the endocytic pathways involved in LNP uptake.[163] Such insights can guide the rational design of nanoparticles to exploit specific cellular entry routes, thereby enhancing transfection efficiencies and therapeutic outcomes.

The difficulty in translating preclinical findings to humans is hindered by anatomical and physiological differences between animal models and human nasal passages.[124,164] To bridge this translational gap, more research has to be done to develop physiological and disease models that better correlate with human nasal anatomy and conditions. These approaches can improve the predictability of deposition patterns, absorption kinetics, and eventual clinical performance of IN formulations.

Formulation stability during aerosolization is another critical concern. LNPs must withstand shear forces, turbulence, and potential aggregation as they transition from a liquid formulation to an inhalable aerosol. The use of hybrid nanoparticles—blending lipids for biocompatibility and polymers for enhanced binding affinity—can improve stability under these mechanical stresses, ensuring the LNPs maintain integrity, avoid premature release of their genetic cargo, and achieve efficient gene expression at the target site.[89] Strategies such as employing nano-embedded microparticles (NEM)

and carefully selecting excipients also help achieve optimal aerodynamic properties and sustained release profiles.[19,57,69,70]

Device selection is integral to successful IN delivery. Pressurized metered-dose inhalers, soft mist inhalers, dry powder inhalers, and nebulizers each offer unique advantages and challenges in terms of droplet size distribution, particle stability, and deposition efficiency.[71,80,84,165] Computational modelling, high-throughput screening, and structure-function analyses are increasingly employed to match LNP formulations with the most suitable delivery devices. Moreover, applying Quality by Design (QbD) principles can help streamline product development, ensuring that each step—from lipid selection to device engineering—is optimized to meet regulatory standards and maximize patient acceptance.[166,167]

Beyond formulation and device parameters, overcoming innate lung defenses is critical. Mucociliary clearance, mucus viscosity, and lung surfactant layers all influence nanoparticle fate.[82,98,105,168] While smaller or neutral-to-slightly negative particles and PEGylated formulations show improved mucus penetration, these design features must be balanced against the need for robust cellular uptake and sufficient residence time. Further modulation of mucus properties through mucolytics and adjusting pH can also improve nanoparticle transport to underlying epithelial cells.[109,113,114]

Safety and immunogenicity remain areas that require closer scrutiny. Although LNP-based products have demonstrated acceptable safety profiles, potential inflammatory responses resulted from certain lipid components or PEG-related adverse effects highlights the need for thorough toxicological assessments. Designing LNPs that minimize inflammatory cytokine release and exploring alternatives to PEG can alleviate safety concerns. Such considerations become even more critical when developing intranasal gene therapies that may require repeated dosing.[154–156]

It is important to acknowledge that while this review comprehensively addresses the challenges and opportunities of LNP delivery systems via the intranasal route, there remains a significant knowledge gap regarding the specific effects of these challenges on gene delivery efficiency and effectiveness. The field currently lacks sufficient research directly correlating LNP formulation parameters and delivery barriers with quantitative gene expression outcomes in intranasal applications. This knowledge gap presents an important opportunity for future studies to establish clearer connections between the physicochemical properties of LNPs, their interactions with biological barriers in the nasal cavity and respiratory tract, and the resulting gene expression levels in target tissues.

Despite promising advances, relatively few nanoparticle-based intranasal products have reached the market, and an integrated approach is needed to improve the outcomes. In looking ahead, addressing knowledge gaps in nanoparticle uptake, refining hybrid nanoparticle platforms, and developing human-relevant in vitro models will be critical. Advances in computational modelling and high-resolution imaging can expedite our understanding of nanoparticle transport across respiratory barriers. Additionally, leveraging new biomaterials, novel ligands, and surfactant-mimicking coatings may further improve nanoparticle targeting, reduce clearance, and increase the therapeutic index. These efforts, coupled with ongoing innovations in formulation science, device engineering, and regulatory science, are set to reshape the landscape of intranasal LNP-based gene delivery.

Funding

This research was funded by the Qatar Research Development and Innovation Council (QRDI) under the Academic Research Grant (ARG) program, grant number ARG01-0522-230279.

Disclosure

Adi Idris and Hadi Yassine are joint senior authors for this study. Dr Yaman Tayyar is the founder of Prorenata Biotech, a private institute developing novel Lipid Nanoparticle formulations and manufacturing devices. In addition, Dr Yaman Tayyar has a patent for Geno, a portable device to manufacture LNPs pending to Prorenata Biotech. The authors declare no other competing interests in this work.

References

1. Cullis PR, Felgner PL. The 60-year evolution of lipid nanoparticles for nucleic acid delivery. *Nat Rev Drug Discov*. 2024;23(9):709–722. doi:10.1038/s41573-024-00977-6
2. Kon E, Ad-El N, Hazan-Halevy I, Stotsky-Oterin L, Peer D. Targeting cancer with mRNA–lipid nanoparticles: key considerations and future prospects. *Nat Rev Clin Oncol*. 2023;20(11):739–754. doi:10.1038/s41571-023-00811-9
3. Jeong M, Lee Y, Park J, Jung H, Lee H. Lipid nanoparticles (LNPs) for in vivo RNA delivery and their breakthrough technology for future applications. *Adv Drug Delivery Rev*. 2023;200:114990. doi:10.1016/j.addr.2023.114990
4. Qiu M, Tang Y, Chen J, et al. Lung-selective mRNA delivery of synthetic lipid nanoparticles for the treatment of pulmonary lymphangioleiomyomatosis. *Proc Natl Acad Sci*. 2022;119(8):e2116271119. doi:10.1073/pnas.2116271119
5. Dilliard SA, Cheng Q, Siegwart DJ. On the mechanism of tissue-specific mRNA delivery by selective organ targeting nanoparticles. *Proc Natl Acad Sci*. 2021;118(52):e2109256118. doi:10.1073/pnas.2109256118
6. Liu S, Cheng Q, Wei T, et al. Membrane-destabilizing ionizable phospholipids for organ-selective mRNA delivery and CRISPR–Cas gene editing. *Nature Mater*. 2021;20(5):701–710. doi:10.1038/s41563-020-00886-0
7. Xu K, Duan S, Wang W, et al. Nose-to-brain delivery of nanotherapeutics: transport mechanisms and applications. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2024;16(2):e1956. doi:10.1002/wnan.1956
8. Koo J, Lim C, Oh KT. Recent advances in intranasal administration for brain-targeting delivery: a comprehensive review of lipid-based nanoparticles and stimuli-responsive gel formulations. *Int J Nanomed*. 2024;19:1767–1807. doi:10.2147/IJN.S439181
9. Gandhi S, Shastri DH, Shah J, Nair AB, Jacob S. Nasal delivery to the brain: harnessing nanoparticles for effective drug transport. *Pharmaceutics*. 2024;16(4):481. doi:10.3390/pharmaceutics16040481
10. Jessamine V, Mehndiratta S, De Rubis G, et al. The application of nanoparticles as advanced drug delivery systems in attenuating COPD. *Heliyon*. 2024;10(3):e25393. doi:10.1016/j.heliyon.2024.e25393
11. Feng X, Shi Y, Zhang Y, Lei F, Ren R, Tang X. Opportunities and challenges for inhalable nanomedicine formulations in respiratory diseases: a review. *Int J Nanomed*. 2024;19:1509–1538. doi:10.2147/IJN.S446919
12. Zhang M, Lu H, Xie L, Liu X, Cun D, Yang M. Inhaled RNA drugs to treat lung diseases: disease-related cells and nano-bio interactions. *Adv Drug Deliv Rev*. 2023;203:115144. doi:10.1016/j.addr.2023.115144
13. Ramachandran S, Prakash P, Mohtar N, Kumar KS, Parumasivam T. Review of inhalable nanoparticles for the pulmonary delivery of anti-tuberculosis drugs. *Pharm Dev Technol*. 2023;28(10):978–991. doi:10.1080/10837450.2023.2279691
14. Zhang Y, Almazi JG, Ong HX, et al. Nanoparticle delivery platforms for RNAi therapeutics targeting COVID-19 disease in the respiratory tract. *Int J Mol Sci*. 2022;23(5).
15. Huang Z, Kłodzińska SN, Wan F, Nielsen HM. Nanoparticle-mediated pulmonary drug delivery: state of the art towards efficient treatment of recalcitrant respiratory tract bacterial infections. *Drug Deliv Transl Res*. 2021;11(4):1634–1654. doi:10.1007/s13346-021-00954-1
16. Hussain W, Chaman S, Koser HN, et al. Nanoparticle-mediated mucosal vaccination: harnessing nucleic acids for immune enhancement. *Curr Microbiol*. 2024;81(9):279. doi:10.1007/s00284-024-03803-9
17. Kehagia E, Papakyriakopoulou P, Valsami G. Advances in intranasal vaccine delivery: a promising non-invasive route of immunization. *Vaccine*. 2023;41(24):3589–3603. doi:10.1016/j.vaccine.2023.05.011
18. Tang J, Cai L, Xu C, et al. Nanotechnologies in delivery of DNA and mRNA vaccines to the nasal and pulmonary mucosa. *Nanomaterials*. 2022;12(2).
19. Mossadeq S, Shah R, Shah V, Bagul M. Formulation, device, and clinical factors influencing the targeted delivery of COVID-19 vaccines to the lungs. *AAPS Pharm Sci Tech*. 2022;24(1):2. doi:10.1208/s12249-022-02455-x
20. Jansen EM, Frijlink HW, Hinrichs WL, Ruigrok MJ. Are inhaled mRNA vaccines safe and effective? A review of preclinical studies. *Expert Opin Drug Deliv*. 2022;19(11):1471–1485. doi:10.1080/17425247.2022.2131767
21. Kandil R, Merkel OM. Pulmonary delivery of siRNA as a novel treatment for lung diseases. *Therapeutic Delivery*. 2019;10(4):203–206. doi:10.4155/tde-2019-0009
22. Wang H, Qin L, Zhang X, Guan J, Mao S. Mechanisms and challenges of nanocarriers as non-viral vectors of therapeutic genes for enhanced pulmonary delivery. *J Control Release*. 2022;352:970–993. doi:10.1016/j.jconrel.2022.10.061
23. Agnihotri V, Agrawal Y, Goyal S, Sharma C, Ojha S. An update on advancements and challenges in Inhalational drug delivery for pulmonary arterial hypertension. *Molecules*. 2022;27(11):3490. doi:10.3390/molecules27113490
24. Arora D, Bhatt S, Kumar M, et al. Intranasal lipid particulate drug delivery systems: an update on clinical challenges and biodistribution studies of cerebroactive drugs in alzheimer's disease. *Curr Pharm Des*. 2020;26(27):3281–3299. doi:10.2174/1381612826666200331085854
25. Thanki K, Blum KG, Thakur A, Rose F, Foged C. Formulation of RNA interference-based drugs for pulmonary delivery: challenges and opportunities. *Ther Deliv*. 2018;9(10):731–749. doi:10.4155/tde-2018-0029
26. Altay Benetti A, Tan EYZ, Chang ZW, et al. Design and characterization of a new formulation for the delivery of COVID-19-mRNA vaccine to the nasal mucosa. *Vaccines*. 2024;12(4):409. doi:10.3390/vaccines12040409
27. Wan H, Deng K, Huang Z, et al. Pathogen-mimicking nanoparticles based on rigid nanomaterials as an efficient subunit vaccine delivery system for intranasal immunization. *Adv Healthc Mater*;2024. e2401120. doi:10.1002/adhm.202401120
28. Gao X, Xiong Y, Chen H, et al. Mucus adhesion vs. mucus penetration? Screening nanomaterials for nasal inhalation by MD simulation. *J Control Release*. 2023;353:366–379. doi:10.1016/j.jconrel.2022.11.051
29. Adedoyin A, Bernardo JF, Swenson CE, et al. Pharmacokinetic profile of ABELCET (amphotericin B lipid complex injection): combined experience from phase I and phase II studies. *Antimicrob Agents Chemother*. 1997;41(10):2201–2208. doi:10.1128/AAC.41.10.2201
30. Batist G, Barton J, Chaikin P, Swenson C, Welles L. Myocet (liposome-encapsulated doxorubicin citrate): a new approach in breast cancer therapy. *Expert Opin Pharmacother*. 2002;3(12):1739–1751. doi:10.1517/14656566.3.12.1739
31. Silverman JA, Deitcher SR. Marqibo® (vincristine sulfate liposome injection) improves the pharmacokinetics and pharmacodynamics of vincristine. *Cancer Chemother Pharmacol*. 2013;71(3):555–564. doi:10.1007/s00280-012-2042-4
32. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379(1):11–21. doi:10.1056/NEJMoa1716153

33. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603–2615. doi:10.1056/NEJMoa2034577
34. Witzigmann D, Kulkarni JA, Leung J, Chen S, Cullis PR, van der Meel R. Lipid nanoparticle technology for therapeutic gene regulation in the liver. *Adv Drug Deliv Rev*. 2020;159:344–363. doi:10.1016/j.addr.2020.06.026
35. Cullis PR, Hope MJ. Lipid nanoparticle systems for enabling gene therapies. *Mol Ther*. 2017;25(7):1467–1475. doi:10.1016/j.ymthe.2017.03.013
36. Han X, Zhang H, Butowska K, et al. An ionizable lipid toolbox for RNA delivery. *Nat Commun*. 2021;12(1):7233. doi:10.1038/s41467-021-27493-0
37. Hald Albertsen C, Kulkarni JA, Witzigmann D, Lind M, Petersson K, Simonsen JB. The role of lipid components in lipid nanoparticles for vaccines and gene therapy. *Adv Drug Delivery Rev*. 2022;188:114416. doi:10.1016/j.addr.2022.114416
38. Eygeris Y, Gupta M, Kim J, Sahay G. Chemistry of lipid nanoparticles for RNA delivery. *Acc Chem Res*. 2022;55(1):2–12. doi:10.1021/acs.accounts.1c00544
39. Chen SP, Blakney AK. Immune response to the components of lipid nanoparticles for ribonucleic acid therapeutics. *Curr Opin Biotechnol*. 2024;85:103049. doi:10.1016/j.copbio.2023.103049
40. Wu S, Lin L, Shi L, Liu S. An overview of lipid constituents in lipid nanoparticle mRNA delivery systems. *WIREs Nanomed Nanobiotechnol*. 2024;16(4):e1978. doi:10.1002/wnan.1978
41. Chander N, Basha G, Yan Cheng MH, Witzigmann D, Cullis PR. Lipid nanoparticle mRNA systems containing high levels of sphingomyelin engender higher protein expression in hepatic and extra-hepatic tissues. *Mol Ther Meth Clin Develop*. 2023;30:235–245. doi:10.1016/j.omtm.2023.06.005
42. Akinc A, Maier MA, Manoharan M, et al. The onpattro story and the clinical translation of nanomedicines containing nucleic acid-based drugs. *Nature Nanotechnol*. 2019;14(12):1084–1087. doi:10.1038/s41565-019-0591-y
43. Verbeke R, Lentacker I, De Smedt SC, Dewitte H. The dawn of mRNA vaccines: the COVID-19 case. *J Control Release*. 2021;333:511–520. doi:10.1016/j.jconrel.2021.03.043
44. Deng YQ, Zhang NN, Zhang YF, et al. Lipid nanoparticle-encapsulated mRNA antibody provides long-term protection against SARS-CoV-2 in mice and hamsters. *Cell Res*. 2022;32(4):375–382. doi:10.1038/s41422-022-00630-0
45. August A, Attarwala HZ, Himansu S, et al. A phase 1 trial of lipid-encapsulated mRNA encoding a monoclonal antibody with neutralizing activity against Chikungunya virus. *Nat Med*. 2021;27(12):2224–2233. doi:10.1038/s41591-021-01573-6
46. Dandekar P, Venkataraman C, Mehra A. Pulmonary targeting of nanoparticle drug matrices. *J Aerosol Med Pulm Drug Deliv*. 2010;23(6):343–353. doi:10.1089/jamp.2009.0784
47. Leong EWX, Ge R. Lipid nanoparticles as delivery vehicles for inhaled therapeutics. *Biomedicines*. 2022;10(9):2179. doi:10.3390/biomedicines10092179
48. Mangal S, Gao W, Li T, Zhou QT. Pulmonary delivery of nanoparticle chemotherapy for the treatment of lung cancers: challenges and opportunities. *Acta Pharmacol Sin*. 2017;38(6):782–797. doi:10.1038/aps.2017.34
49. Osman N, Kaneko K, Carini V, Saleem I. Carriers for the targeted delivery of aerosolized macromolecules for pulmonary pathologies. *Expert Opin Drug Deliv*. 2018;15(8):821–834. doi:10.1080/17425247.2018.1502267
50. Donahue ND, Acar H, Wilhelm S. Concepts of nanoparticle cellular uptake, intracellular trafficking, and kinetics in nanomedicine. *Adv Drug Deliv Rev*. 2019;143:68–96. doi:10.1016/j.addr.2019.04.008
51. Agosti E, Zeppieri M, Antonietti S, et al. Navigating the nose-to-brain route: a systematic review on lipid-based nanocarriers for central nervous system disorders. *Pharmaceutics*. 2024;16(3):329. doi:10.3390/pharmaceutics16030329
52. Nemmar A, Hoet PH, Vanquickenborne B, et al. Passage of inhaled particles into the blood circulation in humans. *Circulation*. 2002;105(4):411–414. doi:10.1161/hc0402.104118
53. Matthews AA, Ee PLR, Ge R. Developing inhaled protein therapeutics for lung diseases. *Mol Biomed*. 2020;1(1):11. doi:10.1186/s43556-020-00014-z
54. Fröhlich E, Salar-Behzadi S. Oral inhalation for delivery of proteins and peptides to the lungs. *Eur J Pharm Biopharm*. 2021;163:198–211. doi:10.1016/j.ejpb.2021.04.003
55. D'Addio SM, Prud'homme RK. Controlling drug nanoparticle formation by rapid precipitation. *Adv Drug Delivery Rev*. 2011;63(6):417–426. doi:10.1016/j.addr.2011.04.005
56. Miao H, Huang K, Li Y, et al. Optimization of formulation and atomization of lipid nanoparticles for the inhalation of mRNA. *Int J Pharm*. 2023;640:123050. doi:10.1016/j.ijpharm.2023.123050
57. Xu Y, Turan ET, Shi Z, Franzyk H, Thakur A, Foged C. Inhalable composite microparticles containing siRNA-loaded lipid-polymer hybrid nanoparticles: saccharides and leucine preserve aerosol performance and long-term physical stability. *Front Drug Delivery*. 2022;2.
58. Liu S, Shan X, Ma X, et al. Charge-assisted stabilization of lipid nanoparticles enables inhaled mRNA delivery for mucosal vaccination. *Nat Commun*. 2023. 15(1):9471.
59. Ichihara F, Lee K, Sakamoto M, Higashi H, Seto T. Aerosolization of colloidal nanoparticles by a residual-free atomizer. *Aerosol Sci Technol*. 2020;54(10):1223–1230. doi:10.1080/02786826.2020.1770197
60. Barriga HMG, Pence IJ, Holme MN, et al. Coupling lipid nanoparticle structure and automated single-particle composition analysis to design phospholipase-responsive nanocarriers. *Adv Mater*. 2022;34(26):2200839. doi:10.1002/adma.202200839
61. Tam A, Kulkarni J, An K, et al. Lipid nanoparticle formulations for optimal RNA-based topical delivery to murine airways. *Eur J Pharm Sci*. 2022;176:106234. doi:10.1016/j.ejps.2022.106234
62. Ibrahim M, Verma R, Garcia-Contreras L. Inhalation drug delivery devices: technology update. *Med Devices*. 2015;8:131–139.
63. Zhu C, Chen J, Yu S, et al. Inhalable nanocomposite microparticles with enhanced dissolution and superior aerosol performance. *Mol Pharm*. 2020;17(9):3270–3280. doi:10.1021/acs.molpharmaceut.0c00390
64. Keil TWM, Baldassi D, Merkel OM. T-cell targeted pulmonary siRNA delivery for the treatment of asthma. *Wiley Interdiscip Rev Nanomed Nanobiotechnol*. 2020;12(5):e1634. doi:10.1002/wnan.1634
65. Keil TWM, Feldmann DP, Costabile G, Zhong Q, da Rocha S, Merkel OM. Characterization of spray dried powders with nucleic acid-containing PEI nanoparticles. *Eur J Pharm Biopharm*. 2019;143:61–69. doi:10.1016/j.ejpb.2019.08.012

66. Keil TW, Zimmermann C, Baldassi D, et al. Impact of crystalline and amorphous matrices on successful spray drying of siRNA polyplexes for inhalation of nano-in-microparticles. *Adv Ther*. 2021;4(6).
67. Xu Y, Harinck L, Lokras AG, et al. Leucine improves the aerosol performance of dry powder inhaler formulations of siRNA-loaded nanoparticles. *Int J Pharm*. 2022;621:121758. doi:10.1016/j.ijpharm.2022.121758
68. Xu Y, Thakur A, Zhang Y, Foged C. Inhaled RNA therapeutics for obstructive airway diseases: recent advances and future prospects. *Pharmaceutics*. 2021;13(2):177. doi:10.3390/pharmaceutics13020177
69. Party P, Klement ML, Szabó-Révész P, Ambrus R. Preparation and characterization of ibuprofen containing nano-embedded-microparticles for pulmonary delivery. *Pharmaceutics*. 2023;15(2):545. doi:10.3390/pharmaceutics15020545
70. Costabile G, Mitidieri E, Visaggio D, et al. Boosting lung accumulation of gallium with inhalable nano-embedded microparticles for the treatment of bacterial pneumonia. *Int J Pharm*. 2022;629:122400. doi:10.1016/j.ijpharm.2022.122400
71. Carneiro SP, Greco A, Chiesa E, Genta I, Merkel OM. Shaping the future from the small scale: dry powder inhalation of CRISPR-Cas9 lipid nanoparticles for the treatment of lung diseases. *Expert Opin Drug Deliv*. 2023;20(4):471–487. doi:10.1080/17425247.2023.2185220
72. Kammona O, Alexopoulos AH, Karakosta P, Kotti K, Karageorgiou V, Kiparissides C. Nanocarrier aided nasal vaccination: an experimental and computational approach. *Ind Eng Chem Res*. 2011;50(2):590–601. doi:10.1021/ie100307t
73. Bhattamisra SK, Shak AT, Xi LW, et al. Nose to brain delivery of rotigotine loaded chitosan nanoparticles in human SH-SY5Y neuroblastoma cells and animal model of Parkinson's disease. *Int J Pharm*. 2020;579:119148. doi:10.1016/j.ijpharm.2020.119148
74. Sarode A, Patel P, Vargas-Montoya N, et al. Inhalable dry powder product (DPP) of mRNA lipid nanoparticles (LNPs) for pulmonary delivery. *Drug Deliv Transl Res*. 2024;14(2):360–372. doi:10.1007/s13346-023-01402-y
75. Das SC, Khadka P, Shah R, McGill S, Smyth HDC. Chapter 14 - Nanomedicine in pulmonary delivery. In: Kesharwani P, Taurin S, Greish K, editors. *Theory and Applications of Nonparenteral Nanomedicines*. Academic Press; 2021:319–354.
76. Sellers WFS. Asthma pressurised metered dose inhaler performance: propellant effect studies in delivery systems. *Allergy Asthma Clin Immunol*. 2017;13(1):30. doi:10.1186/s13223-017-0202-0
77. Al-Halifa S, Gauthier L, Arpin D, Bourgault S, Archambault D. Nanoparticle-based vaccines against respiratory viruses. *Front Immunol*. 2019;10:22. doi:10.3389/fimmu.2019.00022
78. Jahed M, Kozinski J, Pakzad L. The impact of actuator nozzle and surroundings condition on drug delivery using pressurized-metered dose inhalers. *Biomech Model Mechanobiol*. 2023;22(6):2117–2133. doi:10.1007/s10237-023-01754-x
79. Wang J, Wang P, Shao Y, He D. Advancing treatment strategies: a comprehensive review of drug delivery innovations for chronic inflammatory respiratory diseases. *Pharmaceutics*. 2023;15(8):2151. doi:10.3390/pharmaceutics15082151
80. Chan HW, Chow S, Zhang X, Zhao Y, Tong HHY, Chow SF. Inhalable nanoparticle-based dry powder formulations for respiratory diseases: challenges and strategies for translational research. *AAPS Pharm Sci Tech*. 2023;24(4):98. doi:10.1208/s12249-023-02559-y
81. Liang W, Pan HW, Vllasaliu D, Lam JKW. Pulmonary delivery of biological drugs. *Pharmaceutics*. 2020;12(11):1025. doi:10.3390/pharmaceutics12111025
82. Kassab G, Doran K, Mo Y, Zheng G. Inhalable gene therapy and the lung surfactant problem. *Nano Lett*. 2023;23(22):10099–10102. doi:10.1021/acs.nanolett.3c03547
83. Xinchen Y, Jing T, Jiaoqiong G. Lipid-based nanoparticles via nose-to-brain delivery: a mini review. *Front Cell Dev Biol*. 2023;11:1214450. doi:10.3389/fcell.2023.1214450
84. Abu Elella MH, Al Khatib AO, Al-Obaidi H. Spray-dried nanolipid powders for pulmonary drug delivery: a comprehensive mini review. *Pharmaceutics*. 2024;16(5):680. doi:10.3390/pharmaceutics16050680
85. Kim J, Jozic A, Lin Y, et al. Engineering lipid nanoparticles for enhanced intracellular delivery of mRNA through inhalation. *ACS Nano*. 2022;16(9):14792–14806. doi:10.1021/acsnano.2c05647
86. Neary MT, Mulder LM, Kowalski PS, MacLoughlin R, Crean AM, Ryan KB. Nebulised delivery of RNA formulations to the lungs: from aerosol to cytosol. *J Control Release*. 2024;366:812–833. doi:10.1016/j.jconrel.2023.12.012
87. Munir M, Setiawan H, Awaludin R, Kett VL. Aerosolised micro and nanoparticle: formulation and delivery method for lung imaging. *Clin Transl Imaging*. 2023;11(1):33–50. doi:10.1007/s40336-022-00527-3
88. Jia Y, Wang X, Li L, Li F, Zhang J, Liang XJ. Lipid nanoparticles optimized for targeting and release of nucleic acid. *Adv Mater*. 2024;36(4):e2305300. doi:10.1002/adma.202305300
89. Zoulikha M, Xiao Q, Boafo GF, Sallam MA, Chen Z, He W. Pulmonary delivery of siRNA against acute lung injury/acute respiratory distress syndrome. *Acta Pharm Sin B*. 2022;12(2):600–620. doi:10.1016/j.apsb.2021.08.009
90. Kim J, Jozić A, Bloom E, et al. Microfluidic platform enables shearless aerosolization of lipid nanoparticles for mRNA inhalation. *ACS Nano*. 2024;18(17):11335–11348. doi:10.1021/acsnano.4c00768
91. Aggarwal R, Cardozo A, Homer J. The assessment of topical nasal drug distribution. *Clin Otolaryngol All Sci*. 2004;29(3):201–205. doi:10.1111/j.1365-2273.2004.00797.x
92. Gizurarson S. Anatomical and histological factors affecting intranasal drug and vaccine delivery. *Current Drug Delivery*. 2012;9(6):566–582. doi:10.2174/156720112803529828
93. Suman JD, Laube BL, Dalby R. Comparison of nasal deposition and clearance of aerosol generated by a nebulizer and an aqueous spray pump. *Pharm Res*. 1999;16(10):1648. doi:10.1023/A:1011933410898
94. Djupesland PG, Skretting A, Winderen M, Holand T. Bi-directional nasal delivery of aerosols can prevent lung deposition. *J Aerosol Med*. 2004;17(3):249–259. doi:10.1089/jam.2004.17.249
95. Liu Y, Wu D. Bi-directional nasal drug delivery systems: a scoping review of nasal particle deposition patterns and clinical application. *Laryngoscope Investig Otolaryngol*. 2023;8(6):1484–1499. doi:10.1002/lio2.1190
96. Djupesland PG, Skretting A, Winderen M, Holand T. Breath actuated device improves delivery to target sites beyond the nasal valve. *Laryngoscope*. 2006;116(3):466–472. doi:10.1097/01.MLG.0000199741.08517.99
97. Farnoud A, Tofighian H, Baumann I, et al. Pulsatile bi-directional aerosol flow affects aerosol delivery to the intranasal olfactory region: a patient-specific computational study. *Front Pharmacol*. 2021;12:746420. doi:10.3389/fphar.2021.746420
98. Yan X, Sha X. Nanoparticle-mediated strategies for enhanced drug penetration and retention in the airway mucosa. *Pharmaceutics*. 2023;15(10):2457. doi:10.3390/pharmaceutics15102457

99. Bhat PG, Flanagan DR, Donovan MD. The limiting role of mucus in drug absorption: drug permeation through mucus solution. *Int J Pharm*. 1995;126(1):179–187. doi:10.1016/0378-5173(95)04120-6
100. Kirch J, Guenther M, Doshi N, et al. Mucociliary clearance of micro- and nanoparticles is independent of size, shape and charge--an ex vivo and in silico approach. *J Control Release*. 2012;159(1):128–134. doi:10.1016/j.jconrel.2011.12.015
101. Kirch J. *The Role of Fluid Dynamics, Microstructure and Mucociliary Clearance in the Micro- and Macroscopic Barrier Properties of Pulmonary Mucus*. Saarland University; 2012.
102. Schneider CS, Xu Q, Boylan NJ, et al. Nanoparticles that do not adhere to mucus provide uniform and long-lasting drug delivery to airways following inhalation. *Sci Adv*. 2017;3(4):e1601556. doi:10.1126/sciadv.1601556
103. Huckaby JT, Lai SK. PEGylation for enhancing nanoparticle diffusion in mucus. *Adv Drug Delivery Rev*. 2018;124:125–139. doi:10.1016/j.addr.2017.08.010
104. Schuster BS, Suk JS, Woodworth GF, Hanes J. Nanoparticle diffusion in respiratory mucus from humans without lung disease. *Biomaterials*. 2013;34(13):3439–3446. doi:10.1016/j.biomaterials.2013.01.064
105. García-Díaz M, Birch D, Wan F, Nielsen HM. The role of mucus as an invisible cloak to transepithelial drug delivery by nanoparticles. *Adv Drug Delivery Rev*. 2018;124:107–124. doi:10.1016/j.addr.2017.11.002
106. Yamamoto H, Kuno Y, Sugimoto S, Takeuchi H, Kawashima Y. Surface-modified PLGA nanosphere with chitosan improved pulmonary delivery of calcitonin by mucoadhesion and opening of the intercellular tight junctions. *J Control Release*. 2005;102(2):373–381. doi:10.1016/j.jconrel.2004.10.010
107. Khutoryanskiy VV. Beyond PEGylation: alternative surface-modification of nanoparticles with mucus-inert biomaterials. *Adv Drug Delivery Rev*. 2018;124:140–149. doi:10.1016/j.addr.2017.07.015
108. Shan W, Zhu X, Tao W, et al. Enhanced oral delivery of protein drugs using zwitterion-functionalized nanoparticles to overcome both the diffusion and absorption barriers. *ACS Appl Mater Interfaces*. 2016;8(38):25444–25453. doi:10.1021/acsami.6b08183
109. Sedaghat MH, Behnia M, Abouali O. Nanoparticle diffusion in respiratory mucus influenced by mucociliary clearance: a review of mathematical modeling. *J Aerosol Med Pulm Drug Deliv*. 2023;36(3):127–143. doi:10.1089/jamp.2022.0049
110. Murgia X, Loretz B, Hartwig O, Hittinger M, Lehr CM. The role of mucus on drug transport and its potential to affect therapeutic outcomes. *Adv Drug Deliv Rev*. 2018;124:82–97. doi:10.1016/j.addr.2017.10.009
111. Aljayyoussi G, Abdulkarim M, Griffiths P, Gumbleton M. Pharmaceutical nanoparticles and the mucin biopolymer barrier. *Bioimpacts*. 2012;2(4):173–174. doi:10.5681/bi.2012.029
112. Dawson M, Wirtz D, Hanes J. Enhanced viscoelasticity of human cystic fibrotic sputum correlates with increasing microheterogeneity in particle transport. *J Biol Chem*. 2003;278(50):50393–50401. doi:10.1074/jbc.M309026200
113. Guo Y, Ma Y, Chen X, et al. Mucus penetration of surface-engineered nanoparticles in various pH microenvironments. *ACS Nano*. 2023;17(3):2813–2828. doi:10.1021/acsnano.2c11147
114. Tafech B, Rokhforouz MR, Leung J, et al. Exploring mechanisms of lipid nanoparticle-mucus interactions in healthy and cystic fibrosis conditions. *Adv Healthc Mater*. 2024;13(18):e2304525. doi:10.1002/adhm.202304525
115. Kaler L, Joyner K, Duncan GA. Machine learning-informed predictions of nanoparticle mobility and fate in the mucus barrier. *APL Bioeng*. 2022;6(2):026103. doi:10.1063/5.0091025
116. Zou H, Boboltz A, Cheema Y, Song D, Cahn D, Duncan GA. Synthetic mucus barrier arrays as a nanoparticle formulation screening platform. *RSC Pharm*. 2024;1(2):218–226. doi:10.1039/D3PM00057E
117. Li P, Chen X, Shen Y, et al. Mucus penetration enhanced lipid polymer nanoparticles improve the eradication rate of Helicobacter pylori biofilm. *J Control Release*. 2019;300:52–63. doi:10.1016/j.jconrel.2019.02.039
118. Wang W, Huang Z, Huang Y, et al. Pulmonary delivery nanomedicines towards circumventing physiological barriers: strategies and characterization approaches. *Adv Drug Deliv Rev*. 2022;185:114309. doi:10.1016/j.addr.2022.114309
119. Hidalgo A, Cruz A, Pérez-Gil J. Pulmonary surfactant and nanocarriers: toxicity versus combined nanomedical applications. *Biochim Biophys Acta Biomembr*. 2017;1859(9 Pt B):1740–1748. doi:10.1016/j.bbamem.2017.04.019
120. Huck BC, Murgia X, Frisch S, et al. Models using native tracheobronchial mucus in the context of pulmonary drug delivery research: composition, structure and barrier properties. *Adv Drug Delivery Rev*. 2022;183:114141. doi:10.1016/j.addr.2022.114141
121. Wang Y, Zhang J, Liu Y, et al. Realveolarization with inhalable mucus-penetrating lipid nanoparticles for the treatment of pulmonary fibrosis in mice. *Sci Adv*. 2024;10(24):eado4791. doi:10.1126/sciadv.ado4791
122. Osman G, Rodriguez J, Chan SY, et al. PEGylated enhanced cell penetrating peptide nanoparticles for lung gene therapy. *J Control Release*. 2018;285:35–45. doi:10.1016/j.jconrel.2018.07.001
123. Leal J, Dong T, Taylor A, et al. Mucus-penetrating phage-displayed peptides for improved transport across a mucus-like model. *Int J Pharm*. 2018;553(1):57–64. doi:10.1016/j.ijpharm.2018.09.055
124. Costa CP, Moreira JN, Sousa Lobo JM, Silva AC. 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. doi:10.1016/j.apsb.2021.02.012
125. Gao H. Progress and perspectives on targeting nanoparticles for brain drug delivery. *Acta Pharmaceutica Sinica B*. 2016;6(4):268–286. doi:10.1016/j.apsb.2016.05.013
126. Youssef NAHA, Kassem AA, Farid RM, Ismail FA, El-Massik MAE, Boraie NA. A novel nasal almotriptan loaded solid lipid nanoparticles in mucoadhesive in situ gel formulation for brain targeting: preparation, characterization and in vivo evaluation. *Int J Pharm*. 2018;548(1):609–624. doi:10.1016/j.ijpharm.2018.07.014
127. Meziu E, Shehu K, Koch M, Schneider M, Kraegeloh A. Impact of mucus modulation by N-acetylcysteine on nanoparticle toxicity. *Int J Pharm X*. 2023;6:100212. doi:10.1016/j.ijpx.2023.100212
128. Bartlett BA, Feng Y, Fromen CA, Ford Versypt AN. Computational fluid dynamics modeling of aerosol particle transport through lung airway mucosa. *Comput Chem Eng*. 2023;179.
129. Xu Y, Parra-Ortiz E, Wan F, et al. Insights into the mechanisms of interaction between inhalable lipid-polymer hybrid nanoparticles and pulmonary surfactant. *J Colloid Interface Sci*. 2023;633:511–525. doi:10.1016/j.jcis.2022.11.059
130. Yue T, Lv R, Xu D, et al. Competitive and/or cooperative interactions of graphene-family materials and benzo[a]pyrene with pulmonary surfactant: a computational and experimental study. *Part Fibre Toxicol*. 2021;18(1):46. doi:10.1186/s12989-021-00436-9

131. Merckx P, De Backer L, Van Hoecke L, et al. Surfactant protein B (SP-B) enhances the cellular siRNA delivery of proteolipid coated nanogels for inhalation therapy. *Acta Biomater*. 2018;78:236–246. doi:10.1016/j.actbio.2018.08.012
132. Schüer JJ, Wölk C, Bakowsky U, Pinnapireddy SR. Comparison of Tanaka lipid mixture with natural surfactant alveofact to study nanoparticle interactions on Langmuir film balance. *Colloids Surf B Biointerfaces*. 2020;188:110750. doi:10.1016/j.colsurfb.2019.110750
133. Bastacky J, Lee CY, Goerke J, et al. Alveolar lining layer is thin and continuous: low-temperature scanning electron microscopy of rat lung. *J Appl Physiol*. 1995;79(5):1615–1628. doi:10.1152/jappl.1995.79.5.1615
134. Radiom M, Sarkis M, Brookes O, Oikonomou EK, Baeza-Squiban A, Berret JF. Pulmonary surfactant inhibition of nanoparticle uptake by alveolar epithelial cells. *Sci Rep*. 2020;10(1):19436. doi:10.1038/s41598-020-76332-7
135. Wang J, Li P, Yu Y, et al. Pulmonary surfactant-biomimetic nanoparticles potentiate heterosubtypic influenza immunity. *Science*. 2020;367 (6480). doi:10.1126/science.aau0810
136. Griese M. Pulmonary surfactant in health and human lung diseases: state of the art. *Eur Respir J*. 1999;13(6):1455–1476. doi:10.1183/09031936.99.13614779
137. Wu Y, Li X, Gan Y, Zhao C. Nanoparticle-mediated surfactant therapy in patients with severe COVID-19: a perspective. *J Mater Chem B*. 2021;9(35):6988–6993. doi:10.1039/D1TB00730K
138. Thai LP, Mousseau F, Oikonomou E, Radiom M, Berret JF. Effect of nanoparticles on the bulk shear viscosity of a lung surfactant fluid. *ACS Nano*. 2020;14(1):466–475. doi:10.1021/acsnano.9b06293
139. Parra E, Pérez-Gil J. Composition, structure and mechanical properties define performance of pulmonary surfactant membranes and films. *Chem. Phys. Lipids*. 2015;185:153–175. doi:10.1016/j.chemphyslip.2014.09.002
140. Wright JR. Immunoregulatory functions of surfactant proteins. *Nat Rev Immunol*. 2005;5(1):58–68. doi:10.1038/nri1528
141. Olmeda B, Martínez-Calle M, Pérez-Gil J. Pulmonary surfactant metabolism in the alveolar airspace: biogenesis, extracellular conversions, recycling. *Ann Anat*. 2017;209:78–92. doi:10.1016/j.aanat.2016.09.008
142. Rogachev AV, Novikova NN, Kovalchuk MV, et al. Permeation of nanoparticles into pulmonary surfactant monolayer: in situ X-ray standing wave studies. *Langmuir*. 2022;38(12):3630–3640. doi:10.1021/acs.langmuir.1c02179
143. Mousseau F, Oikonomou EK, Vacher A, Airiau M, Mornet S, Berret JF. Revealing the pulmonary surfactant Corona on silica nanoparticles by cryo-transmission electron microscopy. *Nanoscale Adv*. 2020;2(2):642–647. doi:10.1039/C9NA00779B
144. Ruge CA, Hillaireau H, Grabowski N, et al. Pulmonary surfactant protein a-mediated enrichment of surface-decorated polymeric nanoparticles in alveolar macrophages. *Mol Pharmaceut*. 2016;13(12):4168–4178. doi:10.1021/acs.molpharmaceut.6b00773
145. Luo Z, Li S, Xu Y, Yan Z, Huang F, Yue T. The role of nanoparticle shape in translocation across the pulmonary surfactant layer revealed by molecular dynamics simulations. *Environ Sci Nano*. 2018;5(8):1921–1932.
146. Bai X, Li M, Hu G. Nanoparticle translocation across the lung surfactant film regulated by grafting polymers. *Nanoscale*. 2020;12 (6):3931–3940. doi:10.1039/C9NR09251J
147. De Backer L, Braeckmans K, Stuart MC, Demeester J, De Smedt SC, Raemdonck K. Bio-inspired pulmonary surfactant-modified nanogels: a promising siRNA delivery system. *J Control Release*. 2015;206:177–186. doi:10.1016/j.jconrel.2015.03.015
148. De Backer L, Naessens T, De Koker S, et al. Hybrid pulmonary surfactant-coated nanogels mediate efficient in vivo delivery of siRNA to murine alveolar macrophages. *J Control Release*. 2015;217:53–63. doi:10.1016/j.jconrel.2015.08.030
149. Merckx P, Lammens J, Nuytten G, et al. Lyophilization and nebulization of pulmonary surfactant-coated nanogels for siRNA inhalation therapy. *Eur J Pharm Biopharm*. 2020;157:191–199. doi:10.1016/j.ejpb.2020.09.011
150. Liu Q, Xue J, Zhang X, et al. The influence of a biomimetic pulmonary surfactant modification on the in vivo fate of nanoparticles in the lung. *Acta Biomater*. 2022;147:391–402. doi:10.1016/j.actbio.2022.05.038
151. Patel AK, Kaczmarek JC, Bose S, et al. Inhaled nanoformulated mRNA polyplexes for protein production in lung epithelium. *Adv Mater*. 2019;31(8):e1805116. doi:10.1002/adma.201805116
152. Tiwari PM, Vanover D, Lindsay KE, et al. Engineered mRNA-expressed antibodies prevent respiratory syncytial virus infection. *Nat Commun*. 2018;9(1):3999. doi:10.1038/s41467-018-06508-3
153. Andries O, De Filette M, De Smedt SC, et al. Innate immune response and programmed cell death following carrier-mediated delivery of unmodified mRNA to respiratory cells. *J Control Release*. 2013;167(2):157–166. doi:10.1016/j.jconrel.2013.01.033
154. Kent SJ, Li S, Amarasena TH, et al. Blood distribution of SARS-CoV-2 lipid nanoparticle mRNA vaccine in humans. *ACS Nano*. 2024;18 (39):27077–27089. doi:10.1021/acsnano.4c11652
155. Wilson SC, Baryza JL, Reynolds AJ, et al. Real time measurement of PEG shedding from lipid nanoparticles in serum via NMR spectroscopy. *Mol Pharmaceut*. 2015;12(2):386–392. doi:10.1021/mp500400k
156. Suzuki T, Suzuki Y, Hihara T, et al. PEG shedding-rate-dependent blood clearance of PEGylated lipid nanoparticles in mice: faster PEG shedding attenuates anti-PEG IgM production. *Int J Pharm*. 2020;588:119792. doi:10.1016/j.ijpharm.2020.119792
157. Miteva M, Kirkbride KC, Kilchrist KV, et al. Tuning PEGylation of mixed micelles to overcome intracellular and systemic siRNA delivery barriers. *Biomaterials*. 2015;38:97–107. doi:10.1016/j.biomaterials.2014.10.036
158. Mehvar R. Modulation of the pharmacokinetics and pharmacodynamics of proteins by polyethylene glycol conjugation. 2000.
159. Jiao J, Jiao X, Wang C, et al. The contribution of PEG molecular weights in PEGylated emulsions to the various phases in the Accelerated Blood Clearance (ABC) phenomenon in rats. *AAPS Pharm Sci Tech*. 2020;21(8):300. doi:10.1208/s12249-020-01838-2
160. Xu H, Wang KQ, Deng YH, Chen DW. Effects of cleavable PEG-cholesterol derivatives on the accelerated blood clearance of PEGylated liposomes. *Biomaterials*. 2010;31(17):4757–4763. doi:10.1016/j.biomaterials.2010.02.049
161. Son K, Ueda M, Taguchi K, Maruyama T, Takeoka S, Ito Y. Evasion of the accelerated blood clearance phenomenon by polysarcosine coating of liposomes. *J Control Release*. 2020;322:209–216. doi:10.1016/j.jconrel.2020.03.022
162. Hu Y, Hou Y, Wang H, Lu H. Polysarcosine as an alternative to PEG for therapeutic protein conjugation. *Bioconjugate Chem*. 2018;29 (7):2232–2238. doi:10.1021/acs.bioconjchem.8b00237
163. Al Khafaji AS, Donovan MD. Endocytic uptake of solid lipid nanoparticles by the nasal mucosa. *Pharmaceutics*. 2021;13(5):761. doi:10.3390/pharmaceutics13050761
164. Costa CP, Barreiro S, Moreira JN, et al. In vitro studies on nasal formulations of Nanostructured Lipid Carriers (NLC) and Solid Lipid Nanoparticles (SLN). *Pharmaceuticals*. 2021;14(8):711. doi:10.3390/ph14080711

165. Dhege CT, Kumar P, Choonara YE. Pulmonary drug delivery devices and nanosystems as potential treatment strategies for acute respiratory distress syndrome (ARDS). *Int J Pharm*. 2024;657:124182. doi:10.1016/j.ijpharm.2024.124182
166. Akel H, Ismail R, Csóka I. Progress and perspectives of brain-targeting lipid-based nanosystems via the nasal route in Alzheimer's disease. *Eur J Pharm Biopharm*. 2020;148:38–53. doi:10.1016/j.ejpb.2019.12.014
167. Areen A, Rita A, Csóka II. Intranasal nanoparticulate systems as alternative route of drug delivery. *Curr Med Chem*. 2019;26(35):6459–6492. doi:10.2174/0929867326666190827151741
168. Liu Q, Guan J, Song R, Zhang X, Mao S. Physicochemical properties of nanoparticles affecting their fate and the physiological function of pulmonary surfactants. *Acta Biomater*. 2022;140:76–87. doi:10.1016/j.actbio.2021.11.034