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Review Article

Inhalable liposomes: a formulation decision framework linking design variables to pulmonary barriers, aerosol platforms, and critical quality attributes

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Abstract

A structured narrative review examined how vesicle composition, size, charge, surface modification, and aerosolization affect pulmonary delivery and used the findings to construct an operational formulation decision framework. PubMed was searched for English-language publications from 2021 to September 2026, with targeted searches of publisher and regulatory sources. Selection was non-systematic and relevance-based, without a formal risk-of-bias assessment; 62 sources were graded according to a four-level hierarchy. Several framework elements—aerosol stability, PEG-lipid effects, and nucleic acid delivery—rely partly on non-liposomal comparators, requiring confirmation in conventional liposomes. The framework is an eight-step decision matrix linking therapeutic objective, deposition region, dominant barrier, formulation variables, aerosol platform, and verification readouts, applied to four disease contexts. Smaller or PEGylated vesicles may improve mucus transport, but PEGylation can reduce cellular uptake and alter surfactant interactions; nebulization and drying may compromise vesicle integrity. Amikacin liposome inhalation suspension remains the principal clinical precedent. The approach supports hypothesis-driven selection but requires prospective validation.

Keywords

alveolar macrophage, mucus penetration, nebulization, PEGylation, vesicle size

Introduction

Pulmonary delivery targets respiratory tissues directly, bypasses hepatic first-pass metabolism for the absorbed fraction, and may limit systemic exposure during local therapy. It nevertheless requires more than a respirable aerosol: the formulation must withstand aerosolization and device passage, and deposited droplets or particles must overcome oropharyngeal deposition, mucus, pulmonary surfactant, epithelial surfaces, and alveolar macrophage clearance. In nanosystems, the aerosol particle governing regional deposition is distinct from the nanoscale carrier that then interacts with pulmonary fluids, cells, and immune clearance.

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PENSOFT

Liposomes are phospholipid-bilayer vesicles that encapsulate hydrophilic compounds in their aqueous core and lipophilic compounds within the bilayer. Their suitability for pulmonary delivery reflects biocompatible phospholipid composition, controllable size and surface characteristics, flexible loading, and controlled release.

Pulmonary liposome development has progressed from experimental carriers to clinical use of amikacin liposome inhalation suspension (ALIS) in treatment-refractory *Mycobacterium avium* complex lung disease and has expanded toward pulmonary fibrosis, inflammatory lung disease, lung cancer, and nucleic acid delivery, although most candidate systems remain preclinical. Despite a growing literature (Zhang et al. 2025b), evidence is organized by indication, carrier class, or delivery platform rather than integrated for formulation decision-making, and no recent review has combined design variables, pulmonary-barrier interactions, aerosol platforms, and verification-relevant quality attributes in one structured framework.

Accordingly, this review was structured around four key questions. First, which liposomal design variables most strongly influence pulmonary-barrier interactions? Second, how do these variables affect aerosol-platform selection? Third, which critical quality attributes (CQAs) are required to verify formulation and aerosol performance? Finally, which translational and regulatory gaps continue to limit clinical development?

The proposed framework links each formulation variable to its physicochemical consequences, the pulmonary barriers it may influence, compatible aerosolization strategies, and the attributes needed to confirm performance, applying International Council for Harmonisation (ICH) Q8(R2), Q9(R1), and Q10 principles rather than proposing a new quality paradigm.

Selected studies involving lipid nanoparticles (LNPs), lipoplexes, nanoemulsions, cubosomes, and hybrid lipid-based systems were included only where they provided transferable insight into variables relevant to inhalable liposomes and were treated as supportive mechanistic comparisons rather than equivalent evidence (see Transferability of evidence from non-liposomal lipid-based systems).

Materials and methods

A structured narrative literature search was conducted to identify English-language articles published between 2021 and 17 September 2026. Searches were performed primarily in PubMed, complemented by hand-searching of publisher platforms; the databases and platforms searched, the full Boolean strategies for the core search and the two focused term sets, and the yield of each component are reported verbatim in Table 1. Because publisher interfaces do not provide Boolean syntax comparable to that of PubMed, that component is reported as hand-searching.

Titles and abstracts were screened for relevance by a single reviewer, with full-text assessment performed where necessary.

Table 1. Summary of literature search and evidence selection.

Search component	Search details	Result/contribution
Database and period	PubMed; English-language publications from 1 January 2021 to 17 September 2026 (PubMed Central used to access full-text articles where available)	Core source of literature
Core PubMed search	(liposome[tiab] OR liposomes[tiab] OR liposomal[tiab] OR proliposome*[tiab]) AND ("pulmonary drug delivery"[tiab] OR "pulmonary delivery"[tiab] OR nebulization[tiab] OR nebulization[tiab] OR "dry powder inhaler"[tiab] OR inhalable[tiab] OR inhalation[tiab]) AND english[lang]; limited to 1 January 2021–17 September 2026	344 records identified
Disease-specific focused search	Core search AND ("pulmonary fibrosis"[tiab] OR "lung cancer"[tiab] OR "amikacin liposome inhalation suspension"[tiab])	134 records identified
Formulation-specific focused search	Core search AND (mRNA[tiab] OR siRNA[tiab] OR "lipid nanoparticle"[tiab] OR PEGylation[tiab] OR "surface charge"[tiab] OR "mucus penetration"[tiab])	44 records identified
Publisher-platform hand-searching	Springer Nature, ScienceDirect, Wiley, and ACS Publications	Supplemented the PubMed search
Intermediate screening stages	Duplicates removed; title/abstract screening; full-text assessment; exclusions	Exact stage-specific counts were not prospectively recorded and were not retrospectively imputed
Structured-search sources cited in the review	Relevant sources selected after title/abstract screening and, where necessary, full-text assessment	43 sources
Additional sources outside the main search	One landmark pre-2021 publication, 17 regulatory or institutional documents, and one methodological reference	19 sources
Total cited sources	43 structured-search sources + 19 additional targeted sources	62 cited sources
Suppl. material 1 selection	Purposive selection using formulation variables, aerosol or delivery characteristics, and evidence level	18 illustrative experimental studies

Note: Disease- and formulation-specific searches were derived from the core PubMed strategy and may contain overlapping records; therefore, their yields should not be summed. Table 1 summarizes search yields and evidence provenance rather than a formal PRISMA screening process. In the formulation-specific term set, mRNA denotes messenger RNA, and siRNA denotes small interfering RNA.

Because this was designed as a narrative review, records were not prospectively logged at each individual stage of a formal systematic-review screening process. Exact counts of duplicates removed, records excluded during title/abstract screening, full texts assessed, and full-text exclusions therefore cannot be reconstructed reliably and were not retrospectively imputed.

Overall, 62 cited sources were included in the review: 43 identified through the structured search and 19 obtained from targeted regulatory, institutional, methodological, or landmark sources. The search yield and the provenance of the cited evidence are summarized in Table 1.

Eligible sources included peer-reviewed primary research and review articles addressing formulation composition, aerosol performance, pulmonary-barrier interactions, disease models, and clinical or regulatory aspects of inhalable liposomal drug delivery. The period was restricted to 2021–2026, although landmark earlier publications were retained where necessary, particularly Griffith et al. (2018), the pivotal trial of amikacin liposome inhalation suspension. Conference abstracts, editorials, letters, patents, and non-English publications were excluded.

Studies of related lipid-based or non-liposomal pulmonary delivery systems were included only where they provided transferable mechanistic or methodological insight and were treated as contextual rather than equivalent evidence (see Transferability of evidence from non-liposomal lipid-based systems).

Suppl. material 1 summarizes 18 representative experimental studies, a purposive illustrative subset rather than the total number of sources included, selected according to four predefined criteria covering quantitative formulation variables, aerosol or delivery characteristics, platform coverage, and evidence level; these criteria are stated in full in the footnote to Suppl. material 1. Where several studies met the same combination of criteria, the most completely reported was retained.

No formal risk-of-bias or methodological-quality assessment was performed, consistent with the narrative-review design. Evidence level was recorded for each study in Suppl. material 1 using the four-level translational hierarchy defined in the Results and discussion. Reporting was guided by the Scale for the Assessment of Narrative Review Articles (SANRA) recommendations (Baethge et al. 2019).

Results and discussion

Evidence was synthesized qualitatively because studies differed in carrier composition, cargo, disease model, and evidence level.

Practical application of the decision framework

The framework is applied as a sequential, hypothesis-generating decision process rather than as an algorithm that predicts an optimal formulation. The sequence is: therapeutic objective and payload → intended deposition site → dominant pulmonary barrier → candidate formulation variables → compatible aerosol platform → critical quality attributes and biological endpoints → experimental confirmation or reformulation. Each candidate strategy is confirmed experimentally and revised if the expected performance is not observed. The decision steps, criteria, and required confirmations are set out in Table 2.

Because the aerodynamic diameter of the emitted droplet or particle, and not the hydrodynamic diameter of the liposome, governs regional deposition, the intended site of action must be translated explicitly into a target aerodynamic size distribution before the formulation variables are fixed (Table 2, step 1a). That translation is approximate rather than deterministic, and the aerosol size of the only approved inhaled liposomal product lies above the range most frequently quoted in the preclinical literature (see Respiratory infections and Evaluation and critical quality attributes), so the target range is a development specification requiring confirmation under disease-relevant conditions, not a fixed optimum.

Disease context determines whether a pulmonary interaction is beneficial or detrimental. For intracellular infection or macrophage-directed therapy, macrophage uptake may be desirable; for extracellular targets or prolonged tissue residence, the same uptake may accelerate clearance or sequestration. Vesicle size, surface charge, PEGylation, and lipid composition are therefore disease- and objective-specific variables rather than universally beneficial characteristics.

Fig. 1 is a structuring aid for the formulation-variable layer of the framework rather than a predictive selection algorithm (Fig. 1A–D).

Disease-specific application of the decision framework

For mucus-rich airway disease, the dominant decision point is whether mucus limits access to an epithelial or extracellular target; any improvement in mucus transport must be confirmed against epithelial delivery and mucociliary clearance in disease-relevant or patient-derived mucus where feasible (Table 2, steps 3–5).

For intracellular pulmonary infection, macrophage uptake may be part of the therapeutic objective rather than an unwanted clearance mechanism, so formulations that reduce cellular recognition, including strongly shielding PEGylation strategies, should not automatically be preferred, and the aerosol platform must preserve the characteristics required for cellular entry (Table 2, steps 4–5).

For pulmonary fibrosis, the framework prioritizes sustained local exposure together with delivery to disease-relevant epithelial or stromal cells; mucus penetration and prolonged retention should not be optimized in isolation because increased extracellular stability can coexist with reduced cellular uptake or inadequate target-site exposure (Table 2, steps 3 and 6).

For lung cancer, priorities depend on whether the intended local action is cytotoxic, immunomodulatory, gene-directed, or a combination; variables should balance regional deposition, tumor penetration, cellular uptake,

Table 2. Decision matrix for inhalable liposomal formulation development.

Development step	Development question	Decision criterion	Candidate strategy to test	Required confirmation
1. Therapeutic objective	Where must the payload act?	Conducting airways, alveolar region, extracellular compartment, or intracellular target	Define the required regional deposition and post-deposition carrier behavior	Confirm aerosol deposition, pulmonary distribution, and biological relevance in a disease model; for tumor targets, include tumor accumulation, biological activity, and systemic exposure
1a. Intended deposition region	Which airway region must receive the dose?	Central or conducting airways, peripheral airways, or alveolar region, according to the target defined in step 1	Set a target aerodynamic size distribution for the intended region, recognizing that healthy-lung deposition estimates may not apply to obstructed or fibrotic lungs	Confirm aerodynamic particle-size distribution (Ph. Eur. 2.9.18 or USP <601>), emitted or delivered dose, and, where justified, regional deposition under disease-relevant conditions
2. Payload requirements	What limits delivery of the payload?	Poor solubility or stability, rapid release, intracellular delivery needs, or systemic toxicity	Optimize lipid composition, loading method, and release profile for the payload	Confirm encapsulation or loading, leakage, release, stability, and biological activity
3. Dominant pulmonary barrier	Which barrier is most likely to limit access to the target?	Mucus, surfactant, epithelial transport, macrophage clearance, or intracellular trafficking—mucus in mucus-rich airway disease, macrophage clearance in intracellular infection, and epithelial or stromal access in fibrosis and lung cancer	Test vesicle size, surface charge, PEGylation, and lipid composition	Confirm using barrier-specific assays with disease-relevant mucus, surfactant, cells, or advanced pulmonary models
4. Macrophage interaction	Is macrophage uptake desirable or undesirable?	Intracellular infection or macrophage-targeted therapy vs. prolonged extracellular or tissue residence	Adjust surface properties to promote or limit macrophage uptake according to the therapeutic objective	Confirm macrophage uptake, intracellular delivery where relevant, pulmonary clearance, inflammatory response, safety, and antimicrobial activity where the target is an intracellular pathogen
5. Aerosol platform	Which platform can deliver the formulation without unacceptable loss of integrity?	Liquid or solid formulation, required dose, inspiratory-flow dependence, and processing sensitivity	Evaluate nebulization, DPI, or another justified inhalation platform	Confirm emitted or delivered dose, aerodynamic particle-size distribution, and liposome integrity before and after actuation
6. Product quality	Which attributes must be controlled in the formulation–device combination?	Attributes affecting identity, stability, release, and aerosol performance	Define product-specific CQAs and acceptance criteria	Confirm with validated or appropriately qualified analytical methods and stability-indicating tests
7. Biological validation	Does the candidate perform as predicted after aerosol delivery?	Agreement between predicted barrier interactions and experimental performance	Retain, refine, or reject the candidate strategy	Confirm in disease-relevant *in vitro* or advanced models, followed by *in vivo* validation where justified

Abbreviations: CQA, critical quality attribute; DPI, dry powder inhaler.

and pulmonary tolerability, recognizing that extensive shielding or prolonged residence can reduce tumor-cell interaction and that local therapy may not address extrapulmonary disease (Table 2, steps 1–2 and 6).

The corresponding figure panels are Fig. 1B–D for mucus-rich airway disease, Fig. 1A, C for intracellular infection, where strongly shielding PEGylation strategies (Fig. 1D) should not be applied by default, and Fig. 1B, D for pulmonary fibrosis. For lung cancer, the principal variables map to Fig. 1B–D, while pH-responsive and targeted strategies are considered in the therapeutic-application sections below. These examples are illustrative rather than universal, and the relevant variables, barriers, aerosol platform, and CQAs must be confirmed experimentally for each formulation; the corresponding evidence levels, limitations, confidence assessments, and confirmatory requirements are collated in Table 5.

Transferability of evidence from non-liposomal lipid-based systems

Evidence from non-liposomal lipid-based systems, including lipid nanoparticles, lipoplexes, nanoemulsions, cubosomes, and hybrid lipid-based carriers, was used only

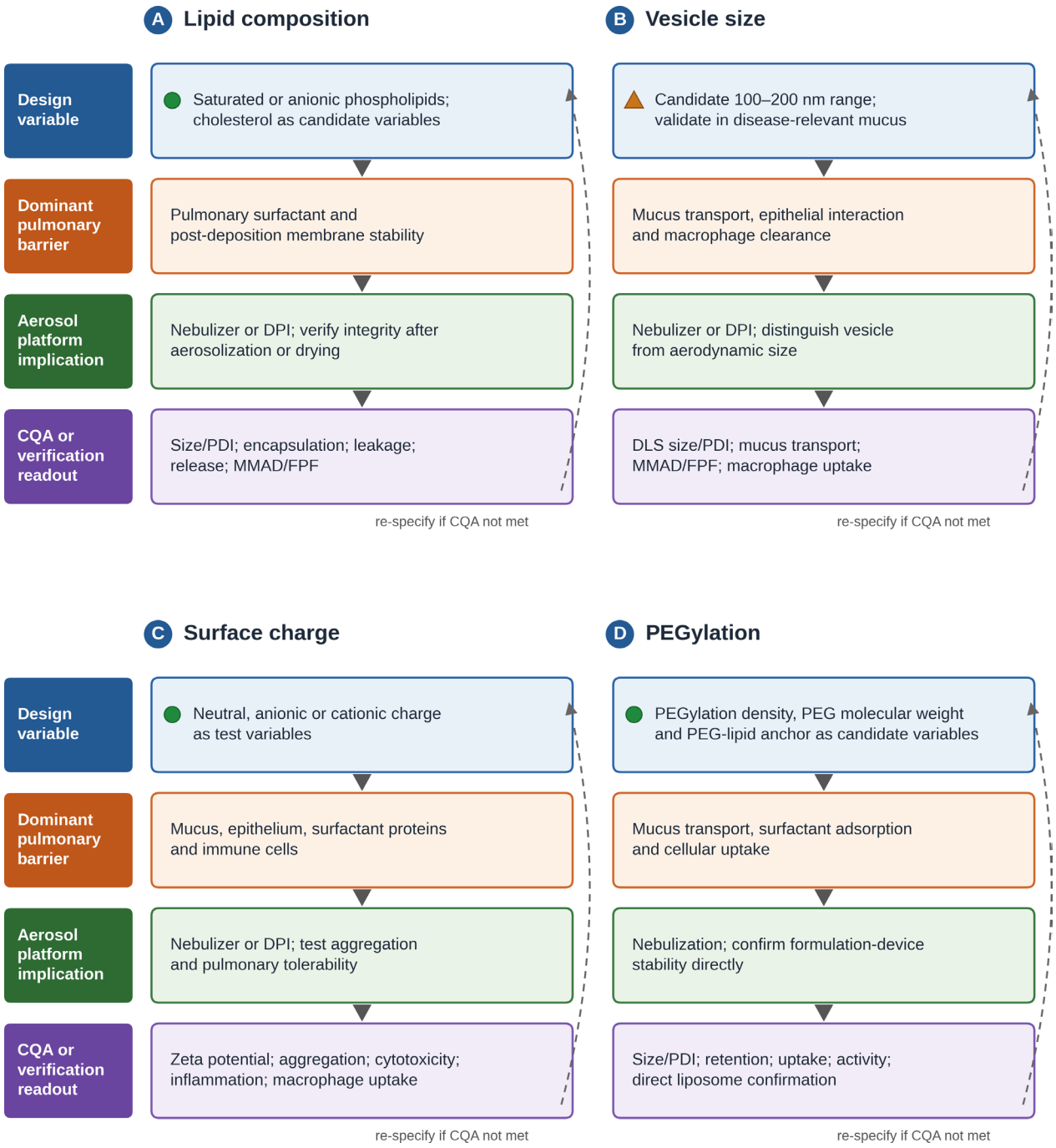

Figure 1. Operational decision framework for inhalable liposome development. **A.** Lipid composition; **B.** Vesicle size; **C.** Surface charge; **D.** PEGylation. Each panel is read from top to bottom: a candidate design variable is linked to the dominant pulmonary barrier, aerosol-platform implication, and CQA or verification readout. Dashed arrows indicate re-specification when the expected readout is not achieved. Markers on the design-variable row indicate the type of the highest-level directly applicable evidence for that variable class, not confidence. Filled green circles denote direct conventional-liposome evidence at Level 1 or 2; amber triangles denote direct conventional-liposome evidence at Level 3 or 4 only. Evidence levels are defined in the Evidence hierarchy and interpretation of findings. Confidence, limitations, and confirmatory testing are reported separately in Table 5. The 100–200 nm range is a model-derived candidate requiring confirmation in disease-relevant or patient-derived mucus. All strategies require formulation-specific validation. Abbreviations: CQA, critical quality attribute; DLS, dynamic light scattering; DPI, dry powder inhaler; FPF, fine particle fraction; MMAD, mass median aerodynamic diameter; PDI, polydispersity index; PEG, polyethylene glycol.

where a specific physicochemical principle was considered potentially transferable to conventional liposomes. Findings on aerosol generation, lipid-airway interactions, mucus-barrier properties, and general effects of surface chemistry may identify mechanisms or variables for testing across lipid-based carriers. By contrast, intracellular delivery, endosomal escape, ionizable-lipid chemistry, and nucleic acid encapsulation efficiency cannot be extrapolated directly because lipid nanoparticles commonly rely on ionizable components and internal architectures

that differ from phospholipid-bilayer liposomes. Observations derived exclusively from non-liposomal carriers were therefore not used to define liposome-specific target values, establish clinical efficacy, or identify preferred liposomal compositions but were retained only as indirect mechanistic evidence requiring direct confirmation in the intended conventional liposomal system.

Evidence hierarchy and interpretation of findings

Evidence was classified according to translational proximity rather than formal methodological quality: Level 1, clinical evidence; Level 2, *in vivo* animal evidence; Level 3, advanced *in vitro* evidence, including air-liquid interface, artificial pulmonary mucus, and lung-on-chip models; and Level 4, conventional *in vitro* or physicochemical characterization. This hierarchy distinguishes the degree of experimental and translational validation and does not constitute a risk-of-bias or methodological-quality assessment. Evidence from lipid nanoparticles, lipoplexes, and other non-liposomal systems was additionally classified as indirect mechanistic evidence and was not treated as equivalent to conventional-liposome evidence, irrespective of experimental level. Narrative reviews and regulatory or institutional documents were not assigned Levels 1–4 because they are not primary experimental evidence; they were treated as secondary or contextual evidence and were not used independently to establish formulation–effect relationships, clinical efficacy, or liposome-specific targets.

Within the 18-study illustrative subset in Suppl. material 1, 14 studies provide direct conventional-liposome evidence, and four are classified only as indirect mechanistic evidence, so non-liposomal comparators constitute a minority of the illustrative evidence base.

Pulmonary barriers and rationale for liposomal inhalation

Inhaled formulations must achieve regional deposition and then retain sufficient integrity for controlled release while encountering airway mucus or, after alveolar deposition, surfactant, epithelial surfaces, and macrophage clearance (Ferguson et al. 2023; Gholap et al. 2025). Surfactant proteins A (SP-A) and D (SP-D) can promote macrophage recognition of inhaled nanomaterials through cluster of differentiation 14 (CD14)-dependent mechanisms (Wang et al. 2021). In bronchoalveolar lavage fluid, protein-corona formation also altered carrier fate: liposomes were exocytosed from macrophages within 6 h, whereas cubosomes showed greater intracellular retention (Subramaniam et al. 2023); because cubosomes differ structurally from phospholipid-bilayer liposomes, that retention should not be generalized to conventional liposomes.

Liposomes are rational carriers for inhaled drug delivery because their bilayers can incorporate biocompatible phospholipids, including those found in endogenous pulmonary surfactant. However, compositional similarity does not guarantee functional compatibility with the pulmonary environment (Cañadas et al. 2026), and performance remains dependent on composition, vesicle characteristics, payload, aerosolization conditions, and disease context (Bashyal et al. 2025; Carrillo-Romero et al. 2026).

Liposome design parameters for inhalation

Lipid composition and membrane rigidity

Lipid composition is an upstream variable affecting bilayer stability, surfactant interaction, aerosolization, and drug release. In the specific context of inhaled salvianolic acid B delivery in an idiopathic pulmonary fibrosis model, Peng et al. (2024) found greater stability and permeability with saturated neutral and anionic liposomes than with unsaturated and cationic formulations, with improved outcomes in the optimized bleomycin model. These results are specific to the lipid compositions, payload, and disease model evaluated; saturated neutral or anionic phospholipids remain candidate compositions for product-specific testing, not generally preferred lipid classes.

Wen et al. (2025) used phospholipid complexing to improve baicalein solubility and loading; the resulting nebulized liposomes showed greater mucus penetration and lung deposition than comparator liposomes in acute lung injury, a strategy requiring confirmation across other drugs and lipid compositions. Lyophilized powders were produced by de Jesús Valle et al. (2026) from sildenafil-loaded liposomes containing resveratrol or cholesterol, showing preclinical feasibility of bilayer modification combined with solid-state processing.

Each presentation—nebulized suspension, reconstituted dried liposome, dry powder, or proliposome—requires platform-specific verification of liposome integrity, drug retention, aerosol performance, and storage stability (Bashyal et al. 2025; Zhu et al. 2025; de Jesús Valle et al. 2026).

Size, polydispersity, and mucus penetration

Carrillo-Romero et al. (2026) compared liposomes of approximately 100, 200, and 600 nm in pulmonary cell models and artificial pulmonary mucus. Under the conditions studied, the approximately 100 nm liposomes showed greater colloidal stability, lower cytotoxicity, and more prolonged migration through artificial mucus, whereas the approximately 600 nm liposomes showed greater mucus retention. Larger vesicles may accumulate in mucus-rich regions, but retention may also promote mucociliary clearance, and because the *in vitro* mucus model may not fully reproduce the viscoelastic properties, biochemical heterogeneity, and mucociliary-clearance dynamics of native mucus, the *in vivo* significance remains uncertain. Vesicle size and polydispersity should therefore be verified for the intended deposition site, payload, disease environment, and biological target, and the approximately 100–200 nm range remains a model-derived candidate whose benefit must be confirmed independently for each disease and formulation.

Because the aerodynamic size of the aerosol is distinct from vesicle size (see Practical application of the decision framework), evaluation should include mass median aerodynamic diameter (MMAD), emitted dose, and fine particle fraction (FPF), together with hydrodynamic diameter, polydispersity index (PDI), zeta potential, and encapsulation efficiency, before and after aerosolization (Elrufaie et al. 2026).

Surface charge and PEGylation

Surface charge and PEGylation influence liposome interactions with mucus, epithelium, surfactant, and alveolar macrophages, and their effects vary with lipid composition, vesicle size, cargo, and disease context (Peng et al. 2024; Piñol-Cancer et al. 2025; Carrillo-Romero et al. 2026).

Surface charge alters electrostatic interactions with mucus, cell membranes, and surfactant-associated proteins. Among the formulations of Zhang et al. (2025a), slightly negatively charged liposomes gave a favorable balance of mucus penetration, cellular uptake, drug activity, and biocompatibility, whereas in Peng et al. (2024), cationic formulations showed lower stability and permeability than saturated neutral and anionic ones. Cationic systems therefore warrant specific evaluation for aggregation and local pulmonary safety. The FAP-targeted, pH-responsive liposomes of Chen et al. (2025b) were strongly cationic (+29.2 ± 2.1 mV) and achieved myofibroblast delivery in a preclinical fibrosis model, but the study reported no dedicated local or systemic tolerability assessment: they show that a cationic surface need not preclude targeted delivery, not that it is well tolerated. This does not offset the charge-dependent cytotoxicity of Zhang et al. (2025a), where RAW264.7 viability fell from 95.2% at −2.5 mV to 76.4% at +2.6 mV and 69.3% at +21.5 mV, with hemolysis rising from 4.2% to 15.0% and 35.2%, respectively. Cationic surfaces should therefore be treated as a tolerability risk requiring explicit local pulmonary safety evaluation, with any targeting or pH-responsive strategy tested against a charge-matched non-targeted control, and surface charge assessed alongside targeting strategy and disease context rather than as an independent determinant of tolerability.

PEGylation may increase mucus transport and colloidal stability while reducing cellular uptake, with effects depending on PEGylation density, PEG molecular weight, and the PEG-lipid anchor (Ongun et al. 2024; Piñol-Cancer et al. 2025). In mRNA lipid nanoparticles, higher PEG-lipid content improved aerosol stability but reduced *in vitro* transfection efficiency, while pulmonary administration produced more durable protein expression than nasal administration in mice (Ongun et al. 2024); this indirect evidence of a stability–activity trade-off requires confirmation in conventional liposomes. In pulmonary liposomes, PEGylation has also altered surfactant interactions and reduced cellular internalization (Piñol-Cancer et al. 2025; Carrillo-Romero et al. 2026).

PEGylation may additionally reduce payload loading: in DPPC/lyso-PC pirfenidone liposomes, 4 mol% DSPE-PEG (2 kDa) shifted zeta potential from −2 ± 1 mV to −28 ± 5 mV at an essentially unchanged hydrodynamic diameter (125 ± 2 nm vs. 126 ± 2 nm) but lowered encapsulation efficiency from 45% to 27% and loading capacity from 8.9% to 6.6% (Piñol-Cancer et al. 2025). Thus, the improved mucus penetration observed after PEGylation may not have translated into better biodistribution or antifibrotic efficacy because the PEG corona can reduce cellular internalization and alter surfactant interactions, while the accompanying reduction in pirfenidone loading may further limit the effective dose reaching disease-relevant cells; these mechanisms remain plausible explanations rather than experimentally established causes. Such loading penalties should be quantified alongside any transport benefit rather than assumed negligible. Reduced macrophage uptake may favor extracellular residence, whereas intracellular infection may require uptake to be retained or enhanced. PEGylation should therefore be tested as a product-specific surface modification, with density, PEG molecular weight, and anchor confirmed before adoption.

Nebulization of aqueous liposomal suspensions

Nebulization can deliver aqueous liposome suspensions without requiring high inspiratory flow. Vibrating-mesh nebulizers may impose less mechanical stress than some jet nebulizers, and a strengths, weaknesses, opportunities, and threats (SWOT) analysis identified targeting and drug solubilization as strengths and leakage, pulmonary safety, and scale-up as challenges (Zhu et al. 2025). Vibrating-mesh nebulization nevertheless remains a candidate platform to be selected by direct formulation–device comparison rather than assumed preferable.

Studies of siRNA lipoplexes and lipid nanoparticles show that vibrating-mesh nebulization can generate respirable droplets, with aggregation, encapsulation, and delivery effects depending on carrier type (Neary et al. 2026). Because these observations were obtained with lipoplexes and lipid nanoparticles, they identify device-related variables only and require direct confirmation in the intended liposomal formulation, with integrity assessed in both reservoir and aerosol fractions using the endpoints in Table 3 (Zhu et al. 2025).

Dry powders, lyophilized liposomes, and proliposomes

Drying may improve stability and portability but can disrupt bilayers and increase drug leakage, requiring protective excipients and suitable processing conditions (Friis et al. 2023; de Jesús Valle et al. 2026). Lyophilized sildenafil liposomes containing resveratrol or cholesterol have been aerosolized, supporting the feasibility of inhalable solid liposomal formulations; proliposomes similarly require verification of reconstitution and pulmonary deposition.

Related non-liposomal systems provide only mechanistic context on drying, aerosolization, and storage and require direct confirmation in the intended liposomal formulation: spray-dried LNPs preserved mRNA function

Table 3. Quality attributes and development factors for inhalable liposomal systems.

Attribute classification	Examples	Role in development	Analytical or evaluation approach	Acceptance consideration
Drug-product CQA: liposome physicochemistry	Vesicle-size distribution, PDI, morphology or lamellarity, surface charge where relevant	Control finished-product identity, consistency, aggregation risk, and release-related behavior	DLS; nanoparticle tracking analysis (NTA) where appropriate; electron microscopy for morphology or lamellarity; zeta-potential measurement	Product-specific limits justified by links to stability, aerosol performance, and biological function (illustrative development target: PDI ≤ 0.2); no universal vesicle-size target
Drug-product CQA: drug association and release	Encapsulation efficiency, drug loading, free drug, leakage, and release profile	Control dose presentation, retention, and availability of the payload	HPLC or UPLC with an appropriate separation method; validated release testing	Product-specific limits based on stability and performance data; illustrative target: encapsulation efficiency ≥80% for retention-dependent products
Drug-product CQA: physicochemical and microbiological quality	Assay, impurities, pH, osmolality, sterility, endotoxin, and preservative content, where applicable	Control chemical, microbiological, and pulmonary-use quality	Validated compendial or product-specific methods	Dosage-form- and product-specific specifications
Drug-product CQA: stability	Storage stability, aggregation, leakage, degradation, redispersibility, or reconstitution, where applicable	Ensure quality throughout shelf life and after preparation for use	Stability-indicating assays; size, PDI, drug content, leakage, and release testing	Product-specific shelf-life and in-use criteria
Critical material attribute	Phospholipid identity and purity, cholesterol content, PEG-lipid characteristics, excipient grade, and payload properties	Identify input-material properties that may affect finished-product CQAs	Raw-material characterization and supplier or compendial controls	Risk-based material specifications linked to CQAs
Critical process parameter	Mixing, hydration, size reduction, loading, filtration, drying, sterilization, and filling conditions	Control manufacturing steps that may alter CQAs	Process monitoring, design-of-experiments studies, and in-process controls	Validated operating ranges linked to consistent finished-product quality
Device-performance attribute	Emitted or delivered dose, MMAD, FPF, fine particle dose, and deposition profile	Characterize performance of the integrated formulation–device system	Cascade impaction and delivered-dose testing using Ph. Eur. 2.9.18, USP <601>, or justified equivalents	Product- and device-specific criteria for deposition and dose reproducibility; illustrative targets: MMAD ≈1–5 μm and FPF ≥40%; none is established in FDA, EMA, or compendial guidance as a cross-product acceptance criterion, and the only approved inhaled liposomal product reports an aerosol MMAD of approximately 4.7 μm (FDA 2018d), above the range most frequently quoted
Biological endpoint	Mucus transport, epithelial or surfactant interactions, macrophage uptake, inflammation, and biological activity	Test the biological hypothesis and pulmonary safety; not a finished-product CQA unless formally justified	Disease-relevant *in vitro* or advanced models; *in vivo* studies where justified	No universal limits; use predefined, study-specific endpoints
Clinical-usability factor	Administration time, inspiratory-flow requirements, preparation steps, and dose reproducibility	Assess practical suitability and adherence-related risks	Human-factors, device-compatibility, and simulated-use studies	Product- and population-specific usability criteria

Abbreviations: CMA, critical material attribute; CPP, critical process parameter; CQA, critical quality attribute; FPF, fine particle fraction; MMAD, mass median aerodynamic diameter; NTA, nanoparticle tracking analysis; PDI, polydispersity index.

and improved storage stability, although administration was intratracheal (Friis et al. 2023), and drug–phospholipid porous microparticles achieved an MMAD of ~2.3 μm and an FPF of ~60% in murine acute lung injury (Chen et al. 2025a). A spray-freeze-dried ciprofloxacin-liposome/S-nitrosoglutathione formulation achieved an FPF of 36.5% and *in vivo* antibiofilm activity (Ran and Chai 2026).

DPI development should additionally cover powder flow, emitted dose, and de-agglomeration (Chen et al. 2025a; de Jesús Valle et al. 2026; Ran and Chai 2026).

Therapeutic applications

Respiratory infections

ALIS is the principal clinical benchmark for inhaled liposomal therapy. In the pivotal CONVERT study in treatment-refractory *Mycobacterium avium* complex (MAC) lung disease, culture conversion by month 6 was achieved in 65 of 224 patients (29.0%) receiving ALIS with guideline-based therapy vs. 10 of 112 (8.9%) receiving guideline-based therapy alone (reported odds ratio 4.22; 95% confidence interval 2.08–8.57), while respiratory adverse events were reported in 87.4% vs. 50.0% of patients (Griffith et al. 2018); the INS-312 extension supported exposure up to 20 months and later culture conversion in some patients (Winthrop et al. 2021). Nephrotoxicity and clinically relevant hearing impairment were infrequently reported, and real-world data suggested reduced respiratory healthcare use without establishing causality (Aksamit et al. 2022).

The approved product comprises amikacin encapsulated in dipalmitoylphosphatidylcholine (DPPC)/cholesterol liposomes, supplied as 590 mg of amikacin per 8.4 mL vial and delivered by a dedicated vibrating-mesh nebulizer, with a reported aerosol MMAD of approximately 4.7 μm (FDA 2018c, 2018d). This combination of a neutral saturated phospholipid, a comparatively large droplet size, and an integrated device demonstrates the feasibility of an integrated liposome–nebulizer product without predicting success for other formulations (Winthrop et al. 2021).

Preclinical evidence includes charge-optimized budesonide/baicalin liposomes (Zhang et al. 2025a; Kenaan et al. 2026). Lipid-based and polymeric antibacterial, antifungal, and antitubercular pulmonary delivery remains predominantly preclinical (Islam and Collet 2026; Martins et al. 2026; Saxena et al. 2026), and non-liposomal inhaled systems—rifampin-loaded β-glucan-chitosan-PLGA nanoparticles in murine tuberculosis (Kutscher et al. 2026) and bacteriophage powders (Encinas-Basurto et al. 2025)—are comparators, not direct evidence of liposomal efficacy.

Framework implication: for respiratory infection, the candidate composition is saturated neutral phospholipids with cholesterol; vesicle size and charge should preserve rather than suppress macrophage recognition where the pathogen is intracellular, and shielding PEGylation is not applied by default; active targeting is generally unnecessary where macrophage uptake is itself the delivery route; nebulization has clinical precedent; the governing CQAs are vesicle size and PDI, encapsulation efficiency, post-nebulization integrity, delivered dose, and aerodynamic particle-size distribution (APSD); the principal risks are accelerated clearance for extracellular targets, aminoglycoside-class toxicity, and respiratory adverse events; and the evidence base remains one formulation in one indication.

Pulmonary fibrosis and inflammatory lung injury

In preclinical fibrosis models, inhaled liposomal systems increased pulmonary exposure or improved antifibrotic outcomes. Intrapulmonary nintedanib-loaded liposomes increased exposure relative to oral free nintedanib (Ferguson et al. 2023); however, because route and formulation differed between groups, the benefit cannot be attributed to liposomal encapsulation alone. Salvianolic acid B liposomes improved outcomes in a bleomycin model (Peng et al. 2024); PEGylated neutral metformin/nintedanib liposomes prolonged pulmonary retention and reduced fibrosis (Li et al. 2023; that study characterizes phospholipid-bilayer liposomes and is treated as direct liposomal evidence, notwithstanding the use of the term lipid nanoparticles in its title); and fibroblast activation protein (FAP)-targeted, pH-responsive liposomes co-delivering nintedanib and interleukin-11 small interfering RNA (IL-11 siRNA) increased myofibroblast delivery and reduced collagen deposition (Chen et al. 2025b). PEGylated pirfenidone liposomes improved mucus penetration without clear gains in biodistribution or efficacy and were given by intratracheal instillation rather than by a clinically representative inhalation device (Piñol-Cancer et al. 2025).

The absence of a corresponding improvement in biodistribution or efficacy despite enhanced mucus penetration highlights the importance of sequential biological barriers rather than mucus transport alone: improved diffusion may increase access to the epithelial surface without increasing intracellular delivery or therapeutic exposure at the target site. PEGylation creates a steric barrier that reduces membrane interaction and cellular internalization, while altered interactions with pulmonary surfactant proteins may influence particle fate after deposition, so improved extracellular transport may be offset by reduced uptake, altered intracellular trafficking, or insufficient payload release. This supports a stability–activity trade-off in which optimization of mucus penetration must be balanced against cellular interaction and pharmacodynamic requirements. Framework implication: for pulmonary fibrosis, the candidate lipid selection is neutral or slightly anionic saturated compositions; vesicle size should be optimized for alveolar and interstitial access rather than mucus transport alone; PEGylation should be titrated rather than maximized because extended extracellular residence can coexist with reduced cellular uptake; targeting of disease-relevant cells, for example, fibroblast activation protein-positive myofibroblasts, is a candidate strategy where a validated ligand exists; nebulization has the most supporting preclinical data; the governing CQAs are pulmonary retention, post-aerosolization integrity, release behavior, and target-cell delivery; the principal risks are transport optimized without pharmacodynamic gain and route confounded with formulation; and all supporting evidence remains preclinical and model-dependent.

Lung cancer and metastatic disease

Local inhaled delivery may increase pulmonary tumor exposure while limiting systemic exposure (Fu et al. 2025; Ashraf et al. 2026). Preclinical liposomal systems include osimertinib/DNA co-delivery (Fu et al. 2025),

pH-responsive astragaloside IV/polyphyllin VII liposomes that increased lung accumulation and improved response to PD-1 inhibition (Liu et al. 2025), and aerosolized cyclic-dinucleotide liposomal nanoparticles that enhanced antitumor immunity and PD-L1 inhibition (Liu et al. 2023); clinical efficacy remains unestablished (Ashraf et al. 2026).

Mucus obstruction and immune suppression may additionally limit local therapy (Ashraf et al. 2026). Framework implication: for lung cancer, the intended local action must be defined before any formulation variable is fixed; lipid selection should support the payload class, whether cytotoxic, immunomodulatory, or gene-directed; vesicle size and charge should balance regional deposition against tumor penetration; extensive PEGylation risks reducing tumor-cell interaction and requires justification; pH-responsive or ligand-targeted designs are candidate strategies only; nebulization predominates in the available preclinical work; the governing CQAs are deposition profile, tumor accumulation, cellular uptake, biological activity, and systemic exposure; the principal risks are tumor heterogeneity, uneven ventilation, and extrapulmonary disease beyond the reach of local therapy; and no clinical efficacy evidence yet exist.

Nucleic acid delivery

In pulmonary nucleic acid delivery, ionizable lipid chemistry is an additional design variable beyond PEG-lipid content and aerosol stability. Ionizable lipids remain relatively neutral at physiological pH but become positively charged in acidic endosomes after cellular uptake. Protonation promotes interaction with endosomal membranes and may facilitate the endosomal escape required for cytosolic release of mRNA and related cargoes. Lipid structure, pKa, biodegradability, and tail architecture influence transfection, trafficking, and pulmonary safety.

LNP experience has increased interest in inhaled mRNA, siRNA, and plasmid DNA (Liu et al. 2024; Gabelmann et al. 2025). As set out in Transferability of evidence from non-liposomal lipid-based systems, LNP findings on lipid composition, cholesterol, PEG-lipid content, particle size, and aerosol stress may identify candidates for testing, whereas ionizable-lipid chemistry and endosomal escape cannot be generalized directly.

Charge-assisted stabilization preserved nebulized LNP performance and supported mucosal and systemic immune responses in preclinical vaccination (Liu et al. 2024), and PEG-lipid content altered aerosol stability and transfection efficiency (Ongun et al. 2024). These are indirect mechanistic findings requiring confirmation in conventional liposomes.

Framework implication: for nucleic acid delivery, lipid selection is dominated by the ionizable or cationic component and PEG-lipid content; vesicle size and charge govern aerosol stability and cellular uptake; PEGylation improves aerosol robustness at the cost of transfection efficiency, so both must be co-optimized; endosomal escape, not surface transport, is rate-limiting; vibrating-mesh nebulization has the most data, although carrier-dependent aggregation and encapsulation loss are documented; the governing CQAs are encapsulation efficiency, post-nebulization size and integrity, and *in vitro* potency; and the principal risk is that the evidence derives almost entirely from lipid nanoparticles and lipoplexes, so these observations are indirect and require confirmation in the intended liposomal architecture.

Evaluation and critical quality attributes

Size, PDI, aggregation, retention, and release should be measured before and after actuation because the pre-aerosolized formulation may not represent the emitted aerosol (Zhu et al. 2025; Neary et al. 2026). The quality attributes and development factors relevant to inhalable liposomal systems, covering formulation-, aerosol-, and device-level measures, are set out in Table 3 (FDA 2018a; EMA 2025a; Zhu et al. 2025; European Pharmacopoeia 2026).

Analytical procedures used for CQA assessment should be validated according to ICH Q2(R2) (ICH 2023a), addressing specificity or selectivity, accuracy, precision, detection and quantitation limits, and working range, as applicable to their intended use; procedure development should follow ICH Q14 (ICH 2023c) where relevant. Aerosol performance should be assessed with compendial methods such as European Pharmacopoeia (Ph. Eur.) 2.9.18 and United States Pharmacopeia (USP) <601> (European Pharmacopoeia 2026; United States Pharmacopeia 2026), together with formulation-specific measurements of post-aerosolization liposome integrity, drug retention, and release. The regulatory and compendial documents applicable to these requirements are summarized in Table 4.

Biological assessment should complement submerged cultures with air–liquid-interface, mucus-containing, and controlled aerosol-exposure systems where possible (Carius et al. 2021; Sakolish et al. 2022; Sengupta et al. 2023; Mitchell et al. 2024). Lung-on-chip, multicellular alveolar, artificial-mucus, and surfactant-corona models can reveal behavior not apparent in simple cultures, although none reproduces the complete *in vivo* lung environment (Piñol-Cancer et al. 2025; Carrillo-Romero et al. 2026; Rindchen et al. 2026).

Where cross-product regulatory or compendial consensus is absent, numerical values should be treated as development targets requiring product-specific justification rather than universal specifications. The illustrative targets most frequently applied in inhalable liposome development, covering PDI, encapsulation efficiency, MMAD, and FPF, are listed in Table 3 with their analytical basis and with the reasons none constitutes a cross-product acceptance criterion (Chen et al. 2025a; Wen et al. 2025; Zhu et al. 2025; Elrufaie et al. 2026). Table 5 collates the candidate strategies arising from these variables with their evidence type and confidence, their relevance to conventional liposomes and principal limitations, and the confirmatory testing required.

Table 3 separates finished-product CQAs from upstream critical material attributes (CMAs), critical pro-

Table 4. Principal guidance documents applicable to inhalable liposomal product development.

Document and identifier	Principal relevance	Access date
EMA Reflection Paper on nanotechnology-based medicinal products—EMA/CHMP/79769/2006 https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-nanotechnology-based-medicinal-products-human-use_en.pdf	Nanomedicine characterization and batch consistency.	17 September 2026
EMA Reflection paper on intravenous liposomal products—EMA/CHMP/806058/2009 Rev. 2 https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-data-requirements-intravenous-liposomal-products-developed-reference-innovator-liposomal-product-revision-2_en.pdf	Liposomal quality and comparability; intravenous-focused.	17 September 2026
EMA Guideline on pharmaceutical quality of inhalation and nasal medicinal products—EMEA/CHMP/QWP/49313/2005 Rev. 1 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-quality-inhalation-nasal-medicinal-products-revision-1_en.pdf	Quality and performance of nebulized products, pMDIs, and DPIs. Does not address liposomal carriers.	17 September 2026
FDA (CDER)—Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products—Quality Considerations; Draft Guidance for Industry, April 2018 (draft; not finalized as of 17 September 2026). Docket No. FDA-2018-D-1098 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/metered-dose-inhaler-mdi-and-dry-powder-inhaler-dpi-drug-products-quality-considerations	MDI/DPI quality and aerosol performance; draft and not liposome-specific.	17 September 2026
FDA (CDER)—Liposome Drug Products: Chemistry, Manufacturing, and Controls; Human Pharmacokinetics and Bioavailability; and Labeling Documentation; Guidance for Industry, April 2018 (final). Docket No. FDA-2016-D-2817 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/liposome-drug-products-chemistry-manufacturing-and-controls-human-pharmacokinetics-and	Liposome CMC, release, stability, pharmacokinetics, and labeling; not inhalation-specific.	17 September 2026
EMA therapeutic-equivalence guideline for orally inhaled products—CPMP/EWP/4151/00 Rev. 2 https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-demonstrating-therapeutic-equivalence-between-orally-inhaled-products-oip-asthma-chronic-obstructive-pulmonary-disease-copd-revision-2_en.pdf	Therapeutic equivalence for orally inhaled products. Not liposome-specific.	17 September 2026
ICH Q8(R2), Q9(R1), Q10, Q2(R2), and Q14 https://www.ich.org/page/quality-guidelines	QTPP, CQAs, CPPs, risk management, and analytical-procedure development and validation.	17 September 2026
Ph. Eur. 2.9.18 and USP <601> https://pheur.edqm.eu/ ; https://www.uspnf.com/	Aerodynamic particle-size and delivered-dose testing; USP <5> provides the corresponding general information and product quality tests.	17 September 2026

Note: EMA documents are identified by their official reference numbers. FDA guidance documents are identified by their full official titles, issuing center, and publication status because documents of this type are not assigned public reference numbers comparable to EMA reference numbers. All documents were accessed on 17 September 2026.

Abbreviations: CDER, Center for Drug Evaluation and Research; CHMP, Committee for Medicinal Products for Human Use; CMC, chemistry, manufacturing, and controls; CPMP, Committee for Proprietary Medicinal Products; CQA, critical quality attribute; DPI, dry powder inhaler; EMA, European Medicines Agency; EWP, Efficacy Working Party; FDA, US Food and Drug Administration; ICH, International Council for Harmonisation; MDI, metered-dose inhaler; OIP, orally inhaled product; Ph. Eur., European Pharmacopoeia; QTPP, quality target product profile; QWP, Quality Working Party; USP, United States Pharmacopeia.

cess parameters (CPPs), device-performance attributes, biological endpoints, and clinical-usability factors. Only attributes whose control is required to ensure the quality of the finished drug product are classified as CQAs. CMAs and CPPs are development inputs and process controls, whereas biological endpoints and usability factors provide evidence of performance or clinical suitability. Categories and acceptance criteria should be adapted to the formulation, aerosol platform, and intended use.

Safety and translational issues

Potential risks include irritation, cough, bronchospasm, immune activation, altered surfactant function, excessive macrophage uptake, and systemic exposure. Inflammation or fibrosis can alter mucus, epithelial permeability, immune activity, and ventilation, so healthy-lung behavior may not predict diseased-lung performance (Peng et al. 2024; Piñol-Cancer et al. 2025; Zhang et al. 2025a).

For selected flavonoids, liposomal delivery may improve pulmonary delivery and anti-inflammatory effects, although comparisons with polymeric or solid-lipid formulations remain composition-dependent and long-term safety evidence is limited (Prasher et al. 2026). Macrophage inflammatory activation by persistent non-liposomal nanomaterials cannot be generalized to biodegradable liposomes (Lim et al. 2025).

Translation also requires reproducible manufacturing and device compatibility: scale-up, shear, freeze–thaw cycles, and storage can alter liposomes; nebulized products must remain stable in the intended device, and dry powders must retain dispersibility and liposome integrity or form liposomes after hydration (Zhu et al. 2025).

Table 5. Evidence-informed candidate strategies, uncertainty, and confirmatory requirements.

Candidate strategy	Evidence and confidence	Interpretation and limitations	Required confirmation
Enhanced mucus transport	Levels 2–3; moderate confidence (Piñol-Cancer et al. 2025; Zhang et al. 2025a; Carrillo-Romero et al. 2026).	Direct but preclinical and model-dependent. Artificial mucus may not reproduce disease mucus, and PEGylation may reduce cellular uptake and payload loading.	Test disease-relevant mucus, deposition, pre- and post-aerosol integrity, and pulmonary safety; justify product-specific size and surface controls.
Reduced macrophage recognition	Levels 2–3; low confidence (Wang et al. 2021; Piñol-Cancer et al. 2025; Carrillo-Romero et al. 2026).	Direct evidence for liposome–macrophage interactions. Reduced uptake may impair intracellular delivery; whether uptake is desirable depends on the therapeutic objective.	Measure macrophage uptake, clearance, retention, inflammation, and safety; treat uptake as a biological endpoint.
Retention in mucus-rich airways or macrophage uptake	Levels 2–3; low confidence (Peng et al. 2024; Zhang et al. 2025a; Carrillo-Romero et al. 2026).	Direct but model-specific. Retention may increase local exposure or promote mucociliary clearance and sequestration.	Determine residence time, clearance, distribution, uptake, and tolerability with the intended device.
Bilayer stability and surfactant compatibility	Levels 2–4 plus contextual review evidence; moderate confidence (Peng et al. 2024; Wen et al. 2025; Cañadas et al. 2026 [review; not level-assigned]; de Jesús Valle et al. 2026).	Direct evidence for composition and stability, but compatibility remains product-specific. Compositional similarity alone does not establish functional compatibility.	Test surfactant interaction, leakage, release, stability, and post-aerosol integrity; control lipid identity, purity, and batch consistency.
Sustained pulmonary retention	Level 2; low confidence (Ferguson et al. 2023; Peng et al. 2024).	Direct but limited and preclinical. Simultaneous differences in route and formulation limit causal attribution, and excessive retention may impair clearance.	Use matched pulmonary and plasma pharmacokinetics, release, efficacy, and local and systemic safety studies.
Improved aerosol stability	Levels 2–4 plus indirect comparator evidence; moderate confidence (Ongun et al. 2024; Zhu et al. 2025; Neary et al. 2026).	Direct for liposomal aerosol testing, whereas LNP and lipoplex evidence is indirect. Strong carrier and device dependence, with possible aggregation, leakage, or loss of activity.	Test the intended device for size, PDI, encapsulation, leakage, release, delivered dose, APSD, and biological activity.
Improved storage stability	Levels 2–4; moderate confidence (Friis et al. 2023; Chen et al. 2025a; de Jesús Valle et al. 2026; Ran and Chai 2026).	Direct for liposomal and proliposome processing, although the phospholipid-complex microparticle evidence (Chen et al. 2025a) is indirect; strongly process-dependent. Drying may impair bilayers, drug retention, redispersion, or aerosol performance.	Conduct long-term and accelerated stability testing with moisture, reconstitution, integrity, retention, release, and aerosol endpoints.
Reduced systemic exposure	Level 2; low confidence (Ferguson et al. 2023; Li et al. 2023).	Direct but sparse and preclinical. Lower systemic exposure does not by itself establish efficacy, and route differences can confound comparisons.	Use matched pulmonary and plasma pharmacokinetics, efficacy, and local and systemic safety studies.
Co-delivery and nucleic-acid applications	Levels 2–4; low confidence (Liu et al. 2024; Ongun et al. 2024; Fu et al. 2025; Chen et al. 2025b).	Limited direct relevance; LNP and lipoplex evidence is mechanistic only. Ionizable-lipid chemistry and endosomal escape cannot be transferred directly to conventional liposomes.	Establish composition, encapsulation, aerosol stability, uptake, intracellular release, potency, efficacy, and safety in the intended liposomal architecture.
Integrated regulatory planning	ICH and FDA/EMA framework evidence; moderate confidence.	Directly relevant to development planning rather than to efficacy. No single guidance covers an integrated inhalable-liposome product.	Define the QTPP and CQAs early, demonstrate formulation–device compatibility, and seek regulatory scientific advice.

Note: Confidence levels represent narrative assessments of evidence type, directness, consistency, and translational relevance rather than quantitative scores. Moderate confidence indicates direct liposomal evidence with important preclinical or model-specific limitations; low confidence indicates limited, indirect, or strongly model-dependent evidence. No strategy received high confidence. These categories are not formal evidence grades or risk-of-bias assessments, and all strategies require prospective, product-specific validation.

Abbreviations: APSD, aerodynamic particle-size distribution; CQA, critical quality attribute; EMA, European Medicines Agency; FDA, US Food and Drug Administration; ICH, International Council for Harmonisation; LNP, lipid nanoparticle; PDI, polydispersity index; QTPP, quality target product profile.

Sterilization of inhalable liposomal products

Sterilization is an additional manufacturing challenge because processes that ensure microbiological safety may affect vesicle integrity. Terminal methods such as autoclaving can alter membrane structure, size distribution, and drug retention, whereas sterile filtration may be limited by vesicle size, aggregation tendency, or drug loss. Aseptic processing is therefore often considered for sensitive formulations, although the appropriate strategy depends on composition and product requirements. The impact of sterilization or aseptic processing should be evaluated through changes in vesicle size, polydispersity, encapsulation efficiency, drug leakage, release kinetics, and aerosol performance.

Regulatory considerations

No single guideline comprehensively addresses inhalable liposomes as integrated formulation–device products, so developers must combine requirements for liposomal medicines, inhaled products, and, where relevant, drug–device combinations: in the United States, Title 21 of the Code of Federal Regulations (21 CFR) Part 4 may apply, and in the European Union, Article 117 of Regulation (EU) 2017/745 may apply where the device is integral to the medicinal product (European Union 2017; FDA 2017). Existing liposome, nanomedicine, and inhalation guidance addresses these elements separately but not in combination; the scope, relevance, and limitations of each document are given in Table 4 (EMA 2006, 2013, 2025a, 2025b; FDA 2018a, 2018b). ALIS is approved in the United States and the European Union; US accelerated approval under the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) used sputum culture conversion as a surrogate endpoint, but LPAD is restricted to qualifying antibacterial and antifungal products for limited populations with serious or life-threatening infections (FDA 2018c).

Development should integrate ICH Q8(R2), Q9(R1), and Q10 with the compendial aerosol methods cited in Evaluation and critical quality attributes (ICH 2008, 2009, 2023b). Priorities include formulation–device robustness, pulmonary safety, batch comparability, and the relationship between release, pulmonary exposure, and clinical performance; early regulatory engagement is advisable.

Future perspectives

Future development should emphasize disease-specific design, with advanced pulmonary models preceding *in vivo* validation (Rindchen et al. 2026). Pulmonary nucleic acid delivery may expand lipid-carrier applications, but LNP and lipoplex evidence remains indirect for conventional liposomes, and aerosol stability, mucus transport, uptake, and intracellular release remain unresolved (Ongun et al. 2024; Fu et al. 2025; Neary et al. 2026). Translation requires clearer links among CQAs, pulmonary exposure, and outcomes (Griffith et al. 2018; Winthrop et al. 2021).

Limitations

This review has several limitations. First, the narrative search was designed for representative rather than exhaustive coverage, using one bibliographic database, one reviewer, and no formal risk-of-bias assessment or quantitative synthesis. The supporting evidence was not independently verified, and the proposed relationships require confirmation through systematic review and quantitative synthesis; mechanistic and preclinical findings should not be interpreted as equivalent to clinical evidence. The four-level hierarchy and narrative confidence categories describe translational proximity and interpretive certainty but do not replace formal evidence grading or risk-of-bias assessment. Second, clinical evidence for inhalable liposomal products remains limited, so many conclusions rely on preclinical models, related lipid-based nanocarriers, or principles extrapolated from non-inhaled liposomal formulations. Third, differences among pulmonary disease models in mucus composition, surfactant function, immune-cell recruitment, and epithelial permeability limit direct comparison and generalization. Fourth, non-liposomal lipid-based systems were included only as mechanistic comparators (see Transferability of evidence from non-liposomal lipid-based systems). Finally, the proposed decision chain is a literature-derived conceptual framework that has not been prospectively validated; independent development case studies are required before it can be considered a validated decision tool.

Conclusion

The reviewed evidence supports selecting lipid composition, vesicle size, surface charge, PEGylation, payload, and aerosolization method according to the therapeutic objective and disease-specific pulmonary barriers, and developing the formulation and device as an integrated process.

ALIS remains the main clinical benchmark, whereas evidence for pulmonary fibrosis, cancer, inflammatory disease, and nucleic acid delivery is predominantly preclinical. This imbalance highlights the need for predictive pulmonary models, reproducible manufacturing, and long-term safety evaluation.

The proposed decision chain should be tested prospectively in 3–5 independent inhalable-liposome case studies representing different payloads, pulmonary indications, and aerosol platforms. For each case, formulation choices and expected outcomes should be documented before experiments and compared with observed CQAs, including vesicle characteristics, aerosol performance, stability, and relevant biological outcomes. Agreement between predicted and observed profiles would indicate the framework's predictive accuracy, reveal limitations in the current criteria, and guide refinement.

References

Aksamit T, Wu J, Hassan M, Achter E, Chatterjee A (2022) Impact of initiation of amikacin liposome inhalation suspension on hospitalizations and other healthcare resource utilization measures: a retrospective cohort study in real-world settings. BMC Pulmonary Medicine 22: 461. https://doi.org/10.1186/s12890-022-02257-8

Ashraf A, ul Ain Q, Qamar A, Nisar A, Arshad S, Asim MH, Irfan HM (2026) Liposomal nano-formulations: advancement in lung

cancer treatment. Clinica Chimica Acta 582: 120813. https://doi.org/10.1016/j.cca.2025.120813

Baethge C, Goldbeck-Wood S, Mertens S (2019) SANRA—a scale for the quality assessment of narrative review articles. Research Integrity and Peer Review 4: 5. https://doi.org/10.1186/s41073-019-0064-8

Bashyal S, Suwal N, Thapa R, Bagale LR, Sugandhi VV, Subedi S, Idrees S, Panth N, Elwakil BH, El-Khatib M, Dua K, Paudel KR (2025) Liposomal drug delivery system for lung diseases: Recent advancement and future perspectives. Nanomedicine: Nanotechnology, Biology and Medicine 69: 102855. https://doi.org/10.1016/j.nano.2025.102855

Cañadas O, Hidalgo A, Pérez-Gil J (2026) The lung (surfing) dealer: pulmonary surfactant and drug delivery. Expert Opinion on Drug Delivery 23: 1019–1029. https://doi.org/10.1080/17425247.2026.2646545

Carius P, Dubois A, Ajdarirad M, Artzy-Schnirman A, Sznitman J, Schneider-Daum N, Lehr C-M (2021) PerfuPul—a versatile perfusable platform to assess permeability and barrier function of air exposed pulmonary epithelia. Frontiers in Bioengineering and Biotechnology 9: 743236. https://doi.org/10.3389/fbioe.2021.743236

Carrillo-Romero J, Fernández-Méndez L, de la Iglesia E, Katsumiti A, Germán L, Di Silvio D, Ruíz-Cabello J, Carregal-Romero S, Goñi-de-Cerio F (2026) *In vitro* evaluation of the effect of size and PEGylation on inhalable liposomes for pulmonary drug delivery. Nanomaterials 16: 200. https://doi.org/10.3390/nano16030200

Chen W-Y, Wei J-X, Yu C-Y, Liu C-Y, Liao Y-H (2025a) Inhalable spray-dried porous microparticles containing dehydroandrographolide succinate phospholipid complex capable of improving and prolonging pulmonary anti-inflammatory efficacy in mice. Drug Delivery and Translational Research 15: 670–687. https://doi.org/10.1007/s13346-024-01626-6

Chen Z, Yang J, Zhang Q, Zeng W, Liu Y, Hu W, Chen L, Shen J, Miao Y, Xiao Z, Wu Z, Wang H, Shen H, Ding C, Chen Q, Zhao J, Yang Y (2025b) Inhalable myofibroblast targeting nanoparticles for synergistic treatment of pulmonary fibrosis. Science Advances 11: eadv9571. https://doi.org/10.1126/sciadv.adv9571

de Jesús Valle MJ, Leo LC, Díaz DL, Navarro AS (2026) Inhalable dry powders from lyophilized sildenafil-loaded liposomes with resveratrol or cholesterol as a bilayer component. Pharmaceuticals 19: 129. https://doi.org/10.3390/ph19010129

Elrufaie AE, Khan SA, Hussain Z, Rawas-Qalaji M, Ahmed IS (2026) Nanotechnology-driven targeted pulmonary drug delivery: Innovations, insights, and clinical horizons. Colloids and Surfaces B: Biointerfaces 259: 115289. https://doi.org/10.1016/j.colsurfb.2025.115289

EMA [European Medicines Agency] (2006) Reflection paper on nanotechnology-based medicinal products for human use. European Medicines Agency, London. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-nanotechnology-based-medicinal-products-human-use_en.pdf [Accessed 17 September 2026]

EMA [European Medicines Agency] (2013) Reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product, Revision 2. European Medicines Agency, London. https://www.ema.europa.eu/en/data-requirements-intravenous-liposomal-products-developed-reference-innovator-liposomal-product-scientific-guideline [Accessed 17 September 2026]

EMA [European Medicines Agency] (2025a) Guideline on the pharmaceutical quality of inhalation and nasal medicinal products, Revision 1. European Medicines Agency, Amsterdam. https://www.ema.europa.eu/en/pharmaceutical-quality-inhalation-nasal-products-scientific-guideline [Accessed 17 September 2026]

EMA [European Medicines Agency] (2025b) Guideline on the requirements for demonstrating therapeutic equivalence between orally inhaled products (OIP) for asthma and chronic obstructive pulmonary disease (COPD). European Medicines Agency, Amsterdam. https://www.ema.europa.eu/en/requirements-demonstrating-therapeutic-equivalence-between-orally-inhaled-products-oip-asthma-chronic-obstructive-pulmonary-disease-copd-scientific-guideline [Accessed 17 September 2026]

Encinas-Basurto D, Martinez-Flores PD, García J, Lopez-Mata MA, García-González G, Rodea GE, Eedara BB, Mansour HM, Juarez J (2025) Latest advances in inhalable dry powder bacteriophage therapy for pulmonary infections. Pharmaceutics 17: 1077. https://doi.org/10.3390/pharmaceutics17081077

European Pharmacopoeia (2026) 2.9.18. Preparations for inhalation: aerodynamic assessment of fine particles. https://pheur.edqm.eu/ [Accessed 17 September 2026]

European Union (2017) L 117 Official Journal of the European Union Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, 175 pp. https://eur-lex.europa.eu/eli/reg/2017/745/oj [Accessed 17 September 2026]

FDA [US Food and Drug Administration] (2017) Current good manufacturing practice requirements for combination products: guidance for industry and FDA staff. US Food and Drug Administration, Silver Spring, MD. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/current-good-manufacturing-practice-requirements-combination-products [Accessed 17 September 2026]

FDA [US Food and Drug Administration] (2018a) Liposome drug products: chemistry, manufacturing, and controls; human pharmacokinetics and bioavailability; and labeling documentation. Guidance for Industry. US Food and Drug Administration, Silver Spring, MD. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/liposome-drug-products-chemistry-manufacturing-and-controls-human-pharmacokinetics-and [Accessed 17 September 2026]

FDA [US Food and Drug Administration] (2018b) Metered dose inhaler (MDI) and dry powder inhaler (DPI) drug products—quality considerations: draft guidance for industry. US Food and Drug Administration, Silver Spring, MD. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/metered-dose-inhaler-mdi-and-dry-powder-inhaler-dpi-drug-products-quality-considerations [Accessed 17 September 2026]

FDA [US Food and Drug Administration] (2018c) Multidiscipline review: Arikayce (amikacin liposome inhalation suspension), NDA 207356. US Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207356Orig1s000MultidisciplineR.pdf [Accessed 17 September 2026]

FDA [US Food and Drug Administration] (2018d) ARIKAYCE (amikacin liposome inhalation suspension), for oral inhalation use: highlights of prescribing information. US Food and Drug Administration, Silver Spring, MD. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207356s000lbl.pdf [Accessed 17 September 2026]

Ferguson LT, Ma X, Myerson JW, Wu J, Glassman PM, Zamora ME, Hood ED, Zaleski M, Shen M, Essien E-O, Shuvaev VV, Brenner

JS (2023) Mechanisms by which liposomes improve inhaled drug delivery for alveolar diseases. Advanced NanoBiomed Research 3: 2200106. https://doi.org/10.1002/anbr.202200106

Friis KP, Gracin S, Oag S, Leijon A, Sand E, Lindberg B, Lázaro-Ibáñez E, Lindqvist J, Whitehead KA, Bak A (2023) Spray dried lipid nanoparticle formulations enable intratracheal delivery of mRNA. Journal of Controlled Release 363: 389–401. https://doi.org/10.1016/j.jconrel.2023.09.031

Fu X, Shi Y, Wu H, Zhang Y, Liu Y, Wan X, Chen X, Zhou J, Qiu S, Zhao X, Tian Z, Li L, Zang H, Lin G (2025) Inhalable liposomal delivery of osimertinib and DNA for treating primary and metastasis lung cancer. Nature Communications 16: 3336. https://doi.org/10.1038/s41467-025-58312-5

Gabelmann A, Biesel A, Loretz B, Lehr C-M (2025) Exploring the future of mRNA delivery: beyond lipid nanoparticles. Biochemical and Biophysical Research Communications 778: 152347. https://doi.org/10.1016/j.bbrc.2025.152347

Gholap A, Pardeshi S, Giram P, Nangare S, Sodha S, Kapare H, More M, Sonar Y, Shukla R, Naik J, Reddy G, Damiri F, Dhas N, Berrada M, Bari D, Prajapati B, García MC, Pardeshi C (2025) Breathing new life nanomedicines for pulmonary drug delivery: targeting approaches, experimental models, and regulatory aspects. Beni-Suef University Journal of Basic and Applied Sciences 14: 65. https://doi.org/10.1186/s43088-025-00646-6

Griffith DE, Eagle G, Thomson R, Aksamit TR, Hasegawa N, Morimoto K, Addrizzo-Harris DJ, O'Donnell AE, Marras TK, Flume PA, Loebinger MR, Morgan L, Codecasa LR, Hill AT, Ruoss SJ, Yim J-J, Ringshausen FC, Field SK, Philley JV, Wallace RJ, van Ingen J, Coulter C, Nezamis J, Winthrop KL (2018) Amikacin liposome inhalation suspension for treatment-refractory lung disease caused by *Mycobacterium avium* complex (CONVERT). A prospective, open-label, randomized study. American Journal of Respiratory and Critical Care Medicine 198: 1559–1569. https://doi.org/10.1164/rccm.201807-1318OC

ICH (2008) ICH Q10: Pharmaceutical quality system. International Council for Harmonisation, Geneva. https://database.ich.org/sites/default/files/Q10_Guideline.pdf [Accessed 17 September 2026]

ICH (2009) ICH Q8(R2): Pharmaceutical development. International Council for Harmonisation, Geneva. https://database.ich.org/sites/default/files/Q8_R2_Guideline.pdf [Accessed 17 September 2026]

ICH (2023a) ICH Q2(R2): Validation of analytical procedures. International Council for Harmonisation, Geneva. https://database.ich.org/sites/default/files/ICH_Q2%28R2%29_Guideline_2023_1130.pdf [Accessed 17 September 2026]

ICH (2023b) ICH Q9(R1): Quality risk management. International Council for Harmonisation, Geneva. https://database.ich.org/sites/default/files/ICH_Q9%28R1%29_Guideline_Step4_2023_0118.pdf [Accessed 17 September 2026]

ICH (2023c) ICH Q14: Analytical procedure development. International Council for Harmonisation, Geneva. https://database.ich.org/sites/default/files/ICH_Q14_Guideline_2023_1116.pdf [Accessed 17 September 2026]

Islam N, Collet T (2026) Recent and future developments in inhaled formulations to overcome anti-bacterial drug resistance. Expert Opinion on Drug Delivery 23: 877–892. https://doi.org/10.1080/17425247.2026.2631043

Kenaan HT, Duncan RM, Al-Jamal WT, Jones DS, Andrews GP, Gilmore B, Yardley V, Farrington N, Stott KE, Lawrence D, Jarvis JN, Harrison TS, Robinson S, Ribeiro I, Hope W, Tian Y (2026) Liposomal antimicrobials in the fight against bacterial and fungal pathogens: Clinical successes and development challenges. International Journal of Pharmaceutics: X 11: 100478. https://doi.org/10.1016/j.ijpx.2025.100478

Kutscher HL, Tamblin M, Smith E, Shah A, Kenney PO, Reynolds JL (2026) Repeated pulmonary dosing of β-glucan-chitosan-PLGA nanoparticles controls *Mycobacterium tuberculosis* in mice. Antimicrobial Agents and Chemotherapy 70: e01480-25. https://doi.org/10.1128/aac.01480-25

Li D, Zhao A, Zhu J, Wang C, Shen J, Zheng Z, Pan F, Liu Z, Chen Q, Yang Y (2023) Inhaled lipid nanoparticles alleviate established pulmonary fibrosis. Small 19: 2300545. https://doi.org/10.1002/smll.202300545

Lim CS, Gu JK, Ma Q (2025) Multiwalled carbon nanotubes activate the NLRP3 inflammasome-dependent pyroptosis in macrophages. Molecular Pharmacology 107: 100031. https://doi.org/10.1016/j.molpha.2025.100031

Liu S, Wen Y, Shan X, Ma X, Yang C, Cheng X, Zhao Y, Li J, Mi S, Huo H, Li W, Jiang Z, Li Y, Lin J, Miao L, Lu X (2024) Charge-assisted stabilization of lipid nanoparticles enables inhaled mRNA delivery for mucosal vaccination. Nature Communications 15: 9471. https://doi.org/10.1038/s41467-024-53914-x

Liu Y, Crowe WN, Wang L, Petty WJ, Habib AA, Zhao D (2023) Aerosolized immunotherapeutic nanoparticle inhalation potentiates PD-L1 blockade for locally advanced lung cancer. Nano Research 16: 5300–5310. https://doi.org/10.1007/s12274-022-5205-6

Liu Y, An T, Que Z, Luo B, Shi W, Zhou Y, Tian J (2025) Inhalable herbal nano-liposomes co-delivering astragaloside IV and polyphyllin VII reprogram immunosuppressive microenvironment to overcome anti-PD-1 resistance in NSCLC. Biological Procedures Online 27: 43. https://doi.org/10.1186/s12575-025-00302-4

Martins YA, Anselmo-Lima WT, Tamashiro E, Ho E, Valera FC (2026) Next-generation drug delivery systems for aspergillosis: Overcoming barriers in antifungal therapy. Biomedicine & Pharmacotherapy 201: 119691. https://doi.org/10.1016/j.biopha.2026.119691

Mitchell SM, Meldrum K, Bateman JWP, Tetley TD, Doak SH, Clift MJD (2024) Development and characterisation of a novel complex triple cell culture model of the human alveolar epithelial barrier. In Vitro Models 3: 125–137. https://doi.org/10.1007/s44164-024-00075-2

Neary MT, Mulder LM, Leime CO, MacLoughlin R, Grassiri B, Baranowski Ł, Kowalski PS, Crean AM, Ryan KB (2026) Pulmonary delivery of siRNA lipoplexes and lipid nanoparticles using a vibrating mesh nebuliser. European Journal of Pharmaceutical Sciences 216: 107386. https://doi.org/10.1016/j.ejps.2025.107386

Ongun M, Lokras AG, Baghel S, Shi Z, Schmidt ST, Franzyk H, Rades T, Sebastiani F, Thakur A, Foged C (2024) Lipid nanoparticles for local delivery of mRNA to the respiratory tract: Effect of PEG-lipid content and administration route. European Journal of Pharmaceutics and Biopharmaceutics 198: 114266. https://doi.org/10.1016/j.ejpb.2024.114266

Peng J, Wang Q, Sun R, Zhang K, Chen Y, Gong Z (2024) Phospholipids of inhaled liposomes determine the *in vivo* fate and therapeutic effects of salvianolic acid B on idiopathic pulmonary fibrosis. Journal of Controlled Release 371: 1–15. https://doi.org/10.1016/j.jconrel.2024.05.026

Piñol-Cancer M, Fernández-Méndez L, Carrillo-Romero J, Urkola-Arsuaga A, Azkargorta M, Elortza F, Goñi-de-Cerio F, García-Mouton C, de Alejo CM-P, Ismalaj E, Cañadas O, Pérez-Gil J, Ruíz-Cabello J, Carregal-Romero S (2025) The role of PEGylation in the

pulmonary delivery of antifibrotic liposomal therapies. Journal of Controlled Release 386: 114134. https://doi.org/10.1016/j.jconrel.2025.114134

Prasher P, Sharma M, Fatima R, Vishwas S, Singh SK, Chakraborty A, Gupta G, Chellappan DK, Dureja H, Oliver BGG, Macloughlin R, Dua K, Hussain MS (2026) Nanocarriers for lung health: ameliorating inflammation and cell aging using flavonoid-based nano nutrients. Immunopharmacology and Immunotoxicology 48: 234–259. https://doi.org/10.1080/08923973.2026.2625042

Ran F, Chai G (2026) An inhalable dry powder co-delivery system of ciprofloxacin liposomes and S-nitrosoglutathione for synergistic treatment of *Pseudomonas aeruginosa* biofilm-associated pulmonary infections. Drug Delivery and Translational Research. https://doi.org/10.1007/s13346-026-02121-w

Rindchen A, Schneider-Daum N, Lehr C-M (2026) Microphysiological ("organ-on-a-chip") models of pulmonary infections for developing novel anti-infectives. Advanced Drug Delivery Reviews 236: 115917. https://doi.org/10.1016/j.addr.2026.115917

Sakolish C, Georgescu A, Huh DD, Rusyn I (2022) A model of human small airway on a chip for studies of subacute effects of inhalation toxicants. Toxicological Sciences 187: 267–278. https://doi.org/10.1093/toxsci/kfac036

Saxena A, Bhagra S, Das S, Kaushik N, Saha B (2026) Emerging therapeutic paradigms in tuberculosis: nanocarriers, host-directed strategies, and translational pharmacology. Microbial Pathogenesis 216: 108545. https://doi.org/10.1016/j.micpath.2026.108545

Sengupta A, Dorn A, Jamshidi M, Schwob M, Hassan W, De Maddalena LL, Hugi A, Stucki AO, Dorn P, Marti TM, Wisser O, Stucki JD, Krebs T, Hobi N, Guenat OT (2023) A multiplex inhalation platform to model *in situ* like aerosol delivery in a breathing lung-on-chip. Frontiers in Pharmacology 14: 1114739. https://doi.org/10.3389/fphar.2023.1114739

Subramaniam S, Joyce P, Donnellan L, Young C, Wignall A, Hoffmann P, Prestidge CA (2023) Protein adsorption determines pulmonary cell uptake of lipid-based nanoparticles. Journal of Colloid and Interface Science 641: 36–47. https://doi.org/10.1016/j.jcis.2023.03.048

United States Pharmacopeia (2026) Inhalation and nasal drug products: aerosols, sprays, and powders—performance quality tests. https://www.uspnf.com/ [Accessed 17 September 2026]

Wang Q, Wang Q, Zhao Z, Fan J, Qin L, Alexander DB, Tsuda H, Zhao D, Xu J (2021) Surfactant proteins A/D–CD14 on alveolar macrophages is a common pathway associated with phagocytosis of nanomaterials and cytokine production. Frontiers in Immunology 12: 758941. https://doi.org/10.3389/fimmu.2021.758941

Wen Z, Yu J, Meng Y, Du S, Shi Y, Jiang Y, Ye J, Liu Y, Xia X (2025) Nebulized inhalation of novel baicalein liposome based on phospholipid complex to alleviate acute lung injury. Drug Delivery 32: 2596168. https://doi.org/10.1080/10717544.2025.2596168

Winthrop KL, Flume PA, Thomson R, Mange KC, Yuen DW, Ciesielska M, Morimoto K, Ruoss SJ, Codecasa LR, Yim J-J, Marras TK, van Ingen J, Wallace RJ, Brown-Elliott BA, Coulter C, Griffith DE (2021) Amikacin liposome inhalation suspension for *Mycobacterium avium* complex lung disease: a 12-month open-label extension clinical trial. Annals of the American Thoracic Society 18: 1147–1157. https://doi.org/10.1513/AnnalsATS.202008-925OC

Zhang J, Huang Y, Shen W, Zeng Y, Miao Y, Feng N, Ci T (2025a) Effects of surface charge of inhaled liposomes on drug efficacy and biocompatibility. Pharmaceutics 17: 329. https://doi.org/10.3390/pharmaceutics17030329

Zhang X, Tu S, Tian J, Liang Y, An Y, Zhang T, Guan H, Xiong B, Qin L, Li Y, Gong L (2025b) Liposome-based nanoparticle delivery systems for lung diseases: Opportunities and challenges. International Journal of Nanomedicine 20: 12485–12509. https://doi.org/10.2147/IJN.S538382

Zhu J, Chen Q, Wang W, Wu C, Pan X, Huang Z (2025) Nebulized liposomal drug delivery: a SWOT analysis in drug development. International Journal of Pharmaceutics 683: 125962. https://doi.org/10.1016/j.ijpharm.2025.125962

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI.
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Author contributions

Venesa Lupçi: Conceptualization, investigation, formal analysis, writing—original draft; Aida Loshaj Shala: Investigation, data curation, writing—review and editing; Anita Lupçi: Investigation, data curation; Ufuk Bağcı: Validation, writing—review and editing; Mimoza Basholli Salihu: Validation, writing—review and editing; Toskë Kryeziu: Supervision, validation, writing—review and editing.

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Data availability

All of the data that support the findings of this study are available in the main text or Supplementary Information.

Supplementary material 1

Representative experimental studies informing the proposed inhalable-liposome decision framework

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Explanation note: Representative experimental studies informing the proposed inhalable-liposome decision framework. Evidence level: 1 = clinical study; 2 = *in vivo* animal study; 3 = advanced *in vitro* model, including air–liquid interface, artificial mucus or lung-on-chip systems; 4 = conventional *in vitro* or physicochemical characterization. Abbreviations: ALI acute lung injury; ALIS amikacin liposome inhalation suspension; DNA deoxyribonucleic acid; DPI dry powder inhaler; EE encapsulation efficiency; FAP fibroblast activation protein; FL-NI FAP-targeted nintedanib/siIL-11 liposomes; FPF fine particle fraction; IL-11 interleukin 11; IPF idiopathic pulmonary fibrosis; LLC-Luc luciferase-expressing Lewis lung carcinoma; L-NI non-targeted nintedanib/siIL-11 liposomes; LNP lipid nanoparticle; LPS lipopolysaccharide; MAC *Mycobacterium avium* complex; MMAD mass median aerodynamic diameter; mRNA messenger RNA; NO nitric oxide; NSCLC non-small cell lung cancer; PD-1 programmed cell death protein 1; PEG polyethylene glycol; SARS-CoV-2 severe acute respiratory syndrome coronavirus 2; siRNA small interfering RNA; TGF-β1 transforming growth factor beta 1; TKI tyrosine kinase inhibitor.

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