

Mucosal Drug Delivery Systems: Recent Advances in Nanocarriers and Bioadhesive Technologies

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Graphical Abstract:

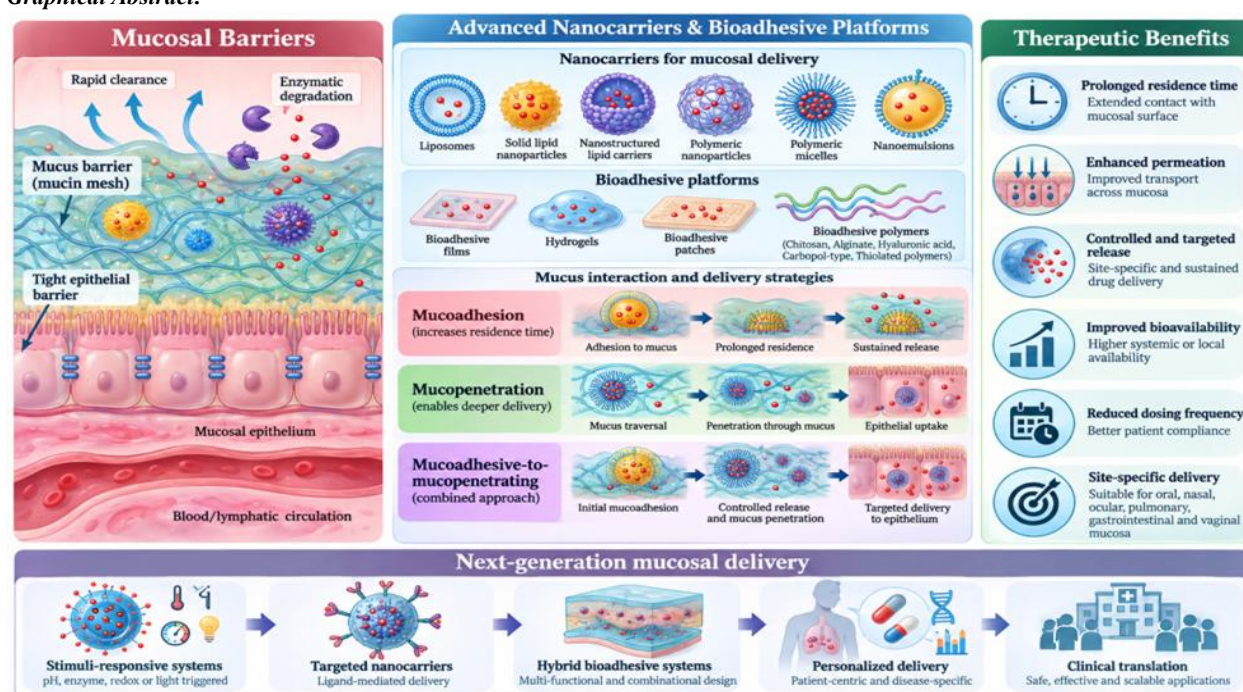


Figure 1. Integrated Nanocarrier and Bioadhesive Strategies for Advanced Mucosal Drug Delivery.[2]

Abstract—Mucosal drug delivery offers an effective strategy for improving drug absorption and therapeutic performance while enabling both local and systemic treatment. However, mucus turnover, enzymatic degradation, limited epithelial permeability, and rapid physiological clearance can restrict drug retention and bioavailability. Recent developments in nanotechnology and polymer science have introduced advanced delivery platforms capable of addressing these limitations. Nanocarriers such as liposomes, lipid nanoparticles, polymeric nanoparticles, micelles, and nanoemulsions can enhance drug solubility, protect unstable molecules, regulate release, and improve interaction with mucosal tissues. Bioadhesive systems incorporating chitosan,

alginate, hyaluronic acid, and thiolated polymers can increase formulation residence at mucosal sites. Combining mucoadhesion with mucopenetration provides opportunities for prolonged retention and improved epithelial access. Stimuli-responsive, targeted, hybrid, and multifunctional systems further enhance delivery precision. This review summarizes recent advances, mechanisms, benefits, limitations, and translational challenges associated with nanocarrier-based and bioadhesive mucosal drug delivery systems.

Index Terms—Mucosal drug delivery; Nanocarriers; Bioadhesion; Mucoadhesion; Mucopenetration; Nanoparticles; Bioadhesive polymers; Targeted drug delivery; Controlled release; Mucosal barriers.

I. INTRODUCTION

Mucosal surfaces form a large and physiologically active interface between the body and the external environment. The oral, buccal, nasal, ocular, pulmonary, gastrointestinal, rectal and vaginal sites have all been investigated as portals for therapeutic delivery because they can support local treatment and, in selected circumstances, systemic absorption. Compared with conventional oral or parenteral

administration, mucosal routes may provide non-invasive dosing, faster onset at selected sites, avoidance of gastrointestinal degradation for some products and partial or substantial reduction of hepatic first-pass exposure. Their value is nevertheless dependent on the physiology of the individual mucosal site, the physicochemical properties of the drug and the ability of the formulation to remain at, traverse or interact productively with the mucosal interface [1].

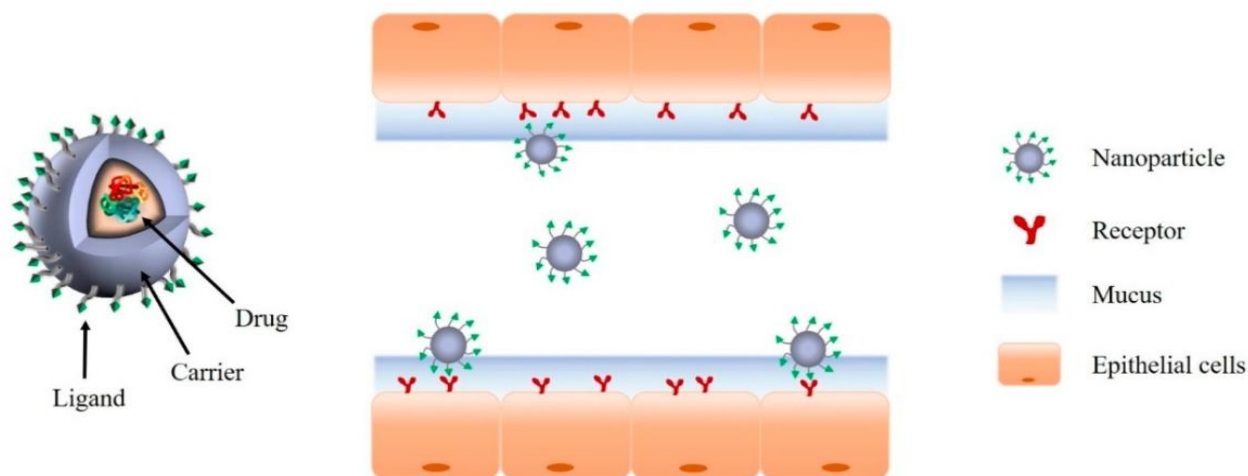


Figure 2. Mucosal barrier and carrier-transport design strategies.[3]

Modern mucosal delivery research has therefore moved beyond the simple placement of a drug on a mucosal surface. The formulation is increasingly treated as an engineered interface whose residence time, interaction with mucus, transport through the epithelial barrier and release kinetics must be designed together. Mucoadhesive systems seek to increase contact with mucus, whereas mucus-penetrating systems are designed to reduce adhesive interactions and move through the mucus mesh. Nanotechnology adds another level of control because particle size, morphology, surface composition, charge and hydration can be adjusted independently or in combination [2].

The central challenge is that mucus is both an opportunity and a barrier. It can concentrate a formulation close to the target epithelium, but it also traps many conventional particles and removes them through continuous mucus turnover. The appropriate design strategy therefore depends on whether prolonged residence within mucus, rapid passage through mucus, epithelial uptake, or a sequential

combination is the desired outcome. Recent literature increasingly supports hybrid approaches in which an initial adhesive interaction is followed by controlled mucus penetration or tissue-directed transport [4].

II. BIOLOGICAL BASIS OF MUCOSAL DRUG DELIVERY

Mucus is a hydrated, viscoelastic secretion composed predominantly of water together with mucins, proteins, lipids, salts and cellular components. Gel-forming mucins create a dynamic polymer network whose mesh structure, charge distribution and biochemical environment vary by anatomical location. These characteristics influence the diffusion of small molecules and nanoparticles and can change with hydration, pH, disease, inflammation, secretion rate and local enzymatic activity. Consequently, a carrier optimized in one mucosal compartment may not behave equivalently in another [8].

The epithelial layer represents a second major barrier. Depending on the tissue, therapeutic molecules may

need to cross mucus first and then pass through either transcellular or paracellular pathways. Tight junctions, membrane transporters, metabolic enzymes and endocytic mechanisms all influence uptake. For biological macromolecules and nucleic acids, degradation and limited membrane permeability can be especially restrictive. Formulation strategies therefore combine physical protection with permeation enhancement, receptor targeting, endosomal escape or controlled release when required [14].

Clearance mechanisms are highly site dependent. Salivary flow and swallowing affect buccal formulations, mucociliary transport removes material from the nasal and respiratory tract, tear turnover clears ophthalmic formulations, and vaginal self-cleaning reduces residence of conventional dosage forms. The gastrointestinal tract combines mucus

turnover with motility, dilution and enzymatic exposure. These processes mean that residence time is not simply a property of the dosage form; it is the result of a dynamic interaction between formulation and tissue [19].

An important consequence is that 'mucosal delivery' should not be treated as a single formulation problem. A carrier intended for ocular delivery may prioritize high precorneal residence and minimal irritation, whereas a pulmonary system may need a balance between aerosol performance, mucus penetration and macrophage interactions. Nasal delivery may emphasize rapid epithelial access and, for some indications, nose-to-brain transport. Buccal systems may prioritize retention despite saliva and mechanical movement. Such route-specific requirements are summarized in Table 1 [27].

Table 1. Route-specific barriers and formulation priorities in mucosal delivery [28]

Mucosal route	Principal barriers	Preferred design considerations	Representative opportunities
Buccal/oral	Saliva, mechanical movement, enzymes, limited permeation	Mucoadhesive films/gels; nanoparticle-loaded matrices; permeation control	Local therapy and systemic delivery
Nasal	Mucociliary clearance, enzymatic activity, limited epithelial transport	Mucoadhesive or mucus-penetrating nanoparticles; in situ gels	Systemic delivery and nose-to-brain research
Ocular	Tear turnover, blinking, corneal barrier, drainage	Mucoadhesive nanocarriers; liposomes; in situ gels	Anterior-segment therapy and prolonged ocular exposure
Pulmonary	Mucociliary clearance, mucus rheology, macrophages, aerosol deposition	Mucoadhesive or mucus-penetrating particles; inhalable nanosystems	Local respiratory therapy and systemic absorption
Gastrointestinal	Variable pH, enzymes, bile, mucus turnover, motility	Surface-engineered nanoparticles; lipid carriers; mucoadhesive matrices	Poorly soluble drugs, peptides and controlled absorption
Vaginal	Mucus turnover, fluid changes, self-cleaning	Mucoadhesive gels/films; nanoparticles; hybrid systems	Local anti-infective, contraceptive and systemic therapy

III. MUCOADHESION AND BIOADHESION: PRINCIPLES AND MECHANISMS

Mucoadhesion refers to the ability of a material or dosage form to establish and maintain interaction with the mucus layer or mucosal surface. The process is often described as a sequence involving initial contact, wetting or spreading, polymer hydration and

interpenetration, followed by consolidation of adhesive interactions. No single theory fully explains all systems; adsorption, diffusion, wetting, fracture, electronic and mechanical concepts can contribute depending on the polymer and biological environment [13].

At the molecular level, mucoadhesion can involve hydrogen bonding, electrostatic attraction,

hydrophobic interactions, van der Waals forces, chain entanglement and, for selected functional polymers, covalent disulfide bonding with cysteine-rich domains of mucins. The magnitude of adhesion is affected by molecular weight, chain flexibility, degree of hydration, functional-group density, cross-linking, surface charge and polymer concentration. Excessive hydration may weaken an adhesive matrix through dilution, while insufficient hydration may prevent effective chain mobility and interpenetration [7].

First-generation mucoadhesive materials generally rely on nonspecific interactions and include cellulose derivatives, polyacrylates, carbomers, alginates and chitosan. Second-generation materials introduce more specific functional groups, including thiols, catechols or other reactive moieties, to strengthen interactions with mucus. These materials can be incorporated into films, tablets, hydrogels, in situ gels, microparticles and nanoparticles, allowing adhesion to be combined with controlled release or targeting [10,11].

Bioadhesion becomes particularly useful when the formulation must remain at the administration site long enough to generate a therapeutic concentration. Increasing residence can reduce drug loss, support sustained release and improve local exposure. However, strong adhesion is not automatically beneficial. If a nanoparticle becomes irreversibly trapped in superficial mucus, it may be cleared before reaching the epithelium. The optimal degree of adhesion is therefore determined by the intended transport pathway rather than by maximizing adhesive strength alone [12].

IV. MUCOPENETRATION AND THE MUCOADHESION-MUCOPENETRATION BALANCE

Mucopenetration is based on a different design principle: the carrier should minimize adhesive interactions with the mucus mesh so that it can diffuse toward the epithelial surface before clearance. Early work with densely PEG-coated biodegradable nanoparticles demonstrated that surface chemistry can dramatically alter particle mobility in human mucus. A hydrated, sterically shielding surface reduces nonspecific binding to mucin fibers and allows more rapid transport through the mucus network [9].

Particle size is important because the mucus mesh imposes steric constraints, but size alone does not determine performance. Surface charge, hydrophobicity, ligand density and polymer conformation can either promote immobilization or facilitate diffusion. In addition, protein adsorption and the formation of a biomolecular corona can modify the effective surface properties after administration. This makes the biological interface more complex than the initial formulation composition suggests [6].

Current research increasingly recognizes that mucoadhesion and mucopenetration can be integrated sequentially. A formulation may first interact with mucus to avoid immediate loss and then alter its surface characteristics, hydration state or charge to facilitate deeper transport. Mucoadhesive-to-mucopenetrating nanoparticles represent an emerging example of this concept, with the aim of combining residence and epithelial access rather than optimizing only one property [18].

Such hybrid behavior can be achieved through reversible interactions, cleavable surface coatings, environment-responsive charge switching, ligand masking or spatially separated functionalities. The concept is particularly attractive for tissues where mucus turnover is rapid but the therapeutic target is located near or within the epithelium. The challenge is to control the timing of each transition reliably under physiological conditions [12].

V. NANOCARRIERS FOR MUCOSAL DELIVERY

Lipid-based nanocarriers remain important because their composition can support encapsulation of poorly water-soluble compounds and, in some systems, hydrophilic or macromolecular cargo. Liposomes can interact with cellular membranes and can be modified with mucoadhesive polymers or hydrophilic surface layers.

Solid lipid nanoparticles and nanostructured lipid carriers offer alternative lipid matrices with opportunities for controlled release and improved stability. Nanoemulsions and related self-emulsifying systems can improve solubilization and may exhibit favorable mucus transport properties depending on their composition [5,21].

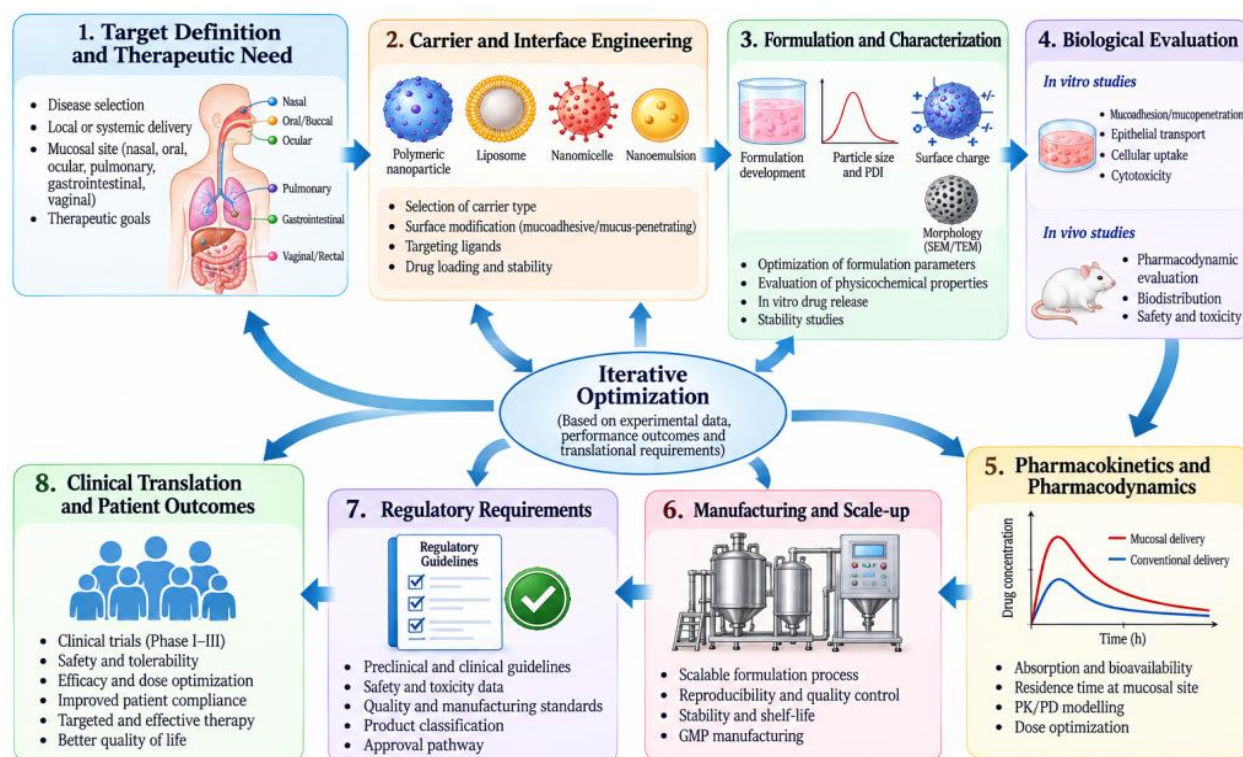


Figure 3. Iterative Development Pathway for Advanced Mucosal Drug Delivery.[20]

Polymeric nanoparticles provide broad control over degradation, drug loading, surface chemistry and release kinetics. Poly (lactic-co-glycolic acid), chitosan, alginate, hyaluronic acid and other polymers can be used as matrices or surface components. Chitosan is especially attractive because of its cationic character, biodegradability and ability to interact with negatively charged mucosal components, while chemical modification can improve its solubility and adhesive performance under physiological conditions [11,17].

Polymeric micelles and nanogels provide additional options for solubilizing hydrophobic molecules, protecting sensitive cargo and incorporating stimuli-responsive behavior. Their small size can support transport through mucus, but surface chemistry remains critical.

A system that is highly interactive with mucin may exhibit prolonged retention yet limited penetration, whereas a highly inert surface may penetrate efficiently but be cleared before sufficient tissue exposure occurs. Formulation development therefore

requires explicit definition of the desired transport phenotype [15].

Nanocarriers can also serve as multifunctional platforms. Targeting ligands may be added for receptor-mediated uptake, enzyme-sensitive linkers can regulate release, and pH- or redox-responsive components can respond to the local environment. These features are especially relevant to nucleic acids, peptides, proteins, vaccines and drugs requiring intracellular delivery. However, increasing complexity also increases manufacturing burden and the number of critical quality attributes that must be controlled [30].

Table 2 compares major nanocarrier families according to their principal design characteristics, potential benefits and limitations. The most appropriate system is not necessarily the most technologically complex one; rather, it is the platform that provides the required stability, release, mucosal interaction and safety profile with acceptable manufacturability [16].

Table 2. Major nanocarrier platforms for mucosal drug delivery [17]

Nanocarrier class	Key design features	Potential advantages	Important limitations
Liposomes	Phospholipid bilayer; surface modification possible	Biocompatibility; hydrophilic/lipophilic cargo; membrane interaction	Physical instability; leakage; scale-up complexity
Solid lipid nanoparticles	Solid lipid matrix	Protection; controlled release; lipid compatibility	Drug expulsion during storage; limited loading for some drugs
Nanostructured lipid carriers	Mixed solid/liquid lipid matrix	Higher loading flexibility; controlled release	Composition-dependent stability and processing
Polymeric nanoparticles	Biodegradable polymer matrix; tunable surface	Protection; sustained release; functionalization	Manufacturing complexity; residual solvent concerns
Polymeric micelles	Amphiphilic self-assembly	Solubilization of poorly soluble drugs; small size	Dilution stability; premature drug release
Nanoemulsions	Fine dispersed lipid/oil droplets	Solubilization; scalable processing options	Surfactant burden; physical stability
Nanogels	Cross-linked hydrophilic polymer network	High water content; stimuli response; macromolecule loading	Cross-linking and sterilization challenges
Hybrid nanocarriers	Combination of lipid/polymer/functional layers	Multiple functions in one platform	Greater formulation and regulatory complexity

VI. BIOADHESIVE POLYMERS AND ADVANCED FUNCTIONALIZATION

Chitosan is among the most studied polymers for mucosal delivery because it combines biodegradability, relatively favorable biocompatibility, film-forming behavior and mucoadhesive interactions. Its cationic amino groups can interact with negatively charged mucins and may also influence epithelial permeability. However, native chitosan has limited solubility near neutral pH and its adhesive performance can be highly dependent on molecular weight and degree of deacetylation, encouraging the development of functional derivatives [22].

Functionalized chitosans include thiolated, trimethylated, carboxymethylated, acrylated, catechol-modified and other derivatives. Thiolation is particularly important because sulfhydryl groups can form disulfide bonds with cysteine-rich regions of mucus, increasing residence. Other modifications can improve aqueous solubility, provide stronger interfacial interactions or introduce stimuli-responsive cross-linking. The challenge is to maintain a favorable balance among adhesion, hydration, stability, toxicity and release [29].

Hyaluronic acid is another useful mucosal polymer because it is naturally occurring, hydrophilic and

biologically interactive. Thiolated hyaluronic acid can form disulfide-linked interactions and may exhibit improved gelation, adhesion, enzyme inhibition and controlled-release behavior. This makes it attractive for ocular, buccal and vaginal systems as well as for hybrid nanocarriers [10].

Thiomers represent a broader class of polymers in which thiol groups are incorporated into a polymer backbone to enhance mucoadhesion. Their performance depends on thiol density, accessibility, polymer architecture, oxidation state and local pH. More advanced preactivated or protected thiol systems have been developed to improve stability and maintain reactive groups until administration [23].

Other bioadhesive materials include alginate, pectin, carbomers, cellulose derivatives, polycarbophil and selected synthetic copolymers. Natural polymers can offer favorable biocompatibility and biodegradation, whereas synthetic polymers often provide more reproducible molecular properties and processing behavior.

In practice, blended or chemically modified systems are increasingly used to combine complementary characteristics [33]. Table 3 summarizes representative bioadhesive polymers and their principal mechanisms. The selection of a polymer should be based on the target mucosa, required residence time, drug compatibility, desired release

mechanism, sterilization or processing requirements and the intended

regulatory pathway rather than on adhesive strength alone [31].

Table 3. Representative bioadhesive polymers and functional materials [32]

Bioadhesive material	Principal interaction	Major strengths	Key considerations
Chitosan	Electrostatic interaction; hydrogen bonding; permeability effects	Biodegradable; versatile; modifiable	Solubility and performance depend on pH and molecular characteristics
Thiolated chitosan	Disulfide bonding with mucin cysteine groups	Strong mucoadhesion; controlled release potential	Oxidation and stability of thiol groups
Hyaluronic acid	Hydrogen bonding and biological interactions	Biocompatibility; hydration; gel formation	Rapid clearance unless appropriately engineered
Thiolated hyaluronic acid	Disulfide bonding plus hydrogel formation	Enhanced adhesion and functional versatility	Chemical stability and substitution control
Alginate	Hydrogen bonding; ionic interactions; gelation	Mild processing; useful for hydrogels	Mechanical strength and ion-dependent behavior
Carbomers/polycarbophil	Hydrogen bonding and polymer interpenetration	High swelling and adhesion	Irritation and viscosity constraints
Cellulose derivatives	Hydrogen bonding and chain entanglement	Established pharmaceutical use; film formation	Adhesion varies with substitution and hydration
Functional synthetic polymers	Tailored charge, ligands or reactive groups	High design flexibility and reproducibility	Safety, degradation and regulatory assessment

VII. ROUTE-SPECIFIC APPLICATIONS

Buccal delivery is attractive for both local and systemic therapy because the buccal mucosa is relatively accessible, well vascularized and less exposed to the extreme pH and enzymatic conditions of the gastrointestinal tract. The main formulation challenge is maintaining contact in the presence of saliva, tongue movement, swallowing and mechanical stress. Nanoparticle-loaded films, hydrogels and mucoadhesive matrices can address these issues by combining retention with controlled release [24].

Nasal delivery offers rapid access to the systemic circulation and is also being investigated for nose-to-brain transport. However, mucociliary clearance and limited epithelial permeability can shorten residence. Modern approaches include mucoadhesive polymers, mucus-penetrating surface coatings, in situ gels, nanoformulations and stimuli-responsive systems. Recent work emphasizes that repeated-dose safety, nasal tolerability and reliable performance under physiological mucus conditions remain important translational considerations [19].

Ocular delivery is constrained by blinking, tear turnover, nasolacrimal drainage and the corneal barrier. Conventional eye drops therefore often provide short exposure and require repeated dosing. Mucoadhesive nanoparticles, liposomes, nanostructured lipid carriers, in situ gels and other nanocarriers can increase precorneal residence and improve drug partitioning toward ocular tissues. At the same time, excessive adhesion or irritation can compromise tolerability, so ocular formulations require careful optimization of surface chemistry and osmolality [22].

Pulmonary delivery offers direct access to the respiratory tract but is strongly influenced by mucus, mucociliary clearance, macrophage uptake and aerosol deposition. Mucoadhesive particles can increase local retention, whereas mucus-penetrating particles are designed to move through airway secretions and reach the epithelial surface. In disease states such as cystic fibrosis and chronic obstructive pulmonary disease, mucus rheology and mesh structure can differ substantially from healthy

conditions, making disease-relevant testing particularly important [26].

Vaginal delivery can provide localized therapy with reduced systemic exposure and can also support systemic administration for selected drugs. The formulation must remain in a dynamic environment affected by mucus, fluid turnover and self-cleaning. Nanoparticles, hydrogels, films and thermoresponsive systems have therefore been investigated to prolong residence and regulate release. Recent developments increasingly consider both mucoadhesion and mucus penetration because local therapeutic targets may reside within or beneath the mucus layer [25].

Oral gastrointestinal delivery represents one of the largest opportunities for mucosal nanomedicine but also one of the most difficult environments. The formulation must survive dilution, variable pH, enzymes, bile components, mucus turnover and intestinal motility. Mucoadhesive systems can prolong contact, while mucopenetrating systems can improve access to the epithelial surface. Surface engineering, lipid digestion behavior, polymer selection and carrier stability are therefore central determinants of performance [15,16].

VIII. MUCOSAL VACCINES AND MACROMOLECULAR THERAPEUTICS

Mucosal delivery is particularly relevant to vaccines because the mucosal immune system can provide localized protection at portals of pathogen entry. Nanoparticles can protect antigens from degradation, enhance uptake by antigen-presenting cells and support co-delivery of adjuvants. Mucoadhesive materials may prolong antigen exposure, while mucus-penetrating systems may improve access to epithelial or immune-cell compartments depending on the target [29].

Proteins, peptides, nucleic acids and other macromolecules also benefit from carrier protection because they are vulnerable to enzymatic degradation and often exhibit poor membrane permeability. Nanocarriers can provide physical shielding and can be engineered for endocytic uptake, intracellular trafficking and controlled release. Nevertheless, increased delivery efficiency must be balanced against potential immunogenicity, local inflammation and long-term safety, especially for repeated administration [15].

IX. FORMULATION DESIGN AND CRITICAL QUALITY ATTRIBUTES

Successful formulation development begins with definition of the intended biological pathway. Critical variables include particle size distribution, polydispersity, morphology, surface charge, surface hydration, polymer molecular weight, ligand density, drug loading, encapsulation efficiency and release kinetics. For bioadhesive systems, swelling, hydration, adhesive strength and residence time are additional attributes. The optimal target values are route specific and should be justified using mechanistic evidence rather than selected solely from generic nanoparticle specifications [13].

Surface engineering is particularly important because the surface is the first component that encounters mucus. Cationic surfaces may enhance adhesion through electrostatic interactions, whereas dense hydrophilic coatings such as PEG can reduce nonspecific binding and facilitate mucus diffusion. However, PEG density, chain length and surface organization influence performance, and excessive shielding may reduce cellular interactions. These trade-offs demonstrate why formulation optimization should consider the entire transport sequence rather than one isolated assay [9].

Release design should be matched to the therapeutic objective. A rapidly acting local treatment may benefit from fast release after deposition, while chronic therapy may require sustained release. Stimuli-responsive systems can exploit pH, enzymes, redox conditions or temperature, but the stimulus must be sufficiently distinct at the target site to prevent premature activation. The complexity of responsive formulations also creates additional stability and manufacturing requirements [32].

X. EVALUATION AND CHARACTERIZATION STRATEGIES

Mucoadhesion can be evaluated by tensile or detachment testing, rheological measurements, texture analysis, wash-off methods and residence studies. These methods provide complementary information but do not necessarily predict in vivo performance. Mucus composition, hydration, temperature, pH and mechanical stress should therefore be controlled or reported when comparing formulations. A single

numerical adhesion value should not be interpreted as a universal indicator of clinical effectiveness [33].

Mucopenetration is commonly studied using fluorescence-based particle tracking, diffusion measurements, microscopy, penetration depth analysis and mucus models. Multiple-particle tracking can quantify heterogeneity in particle motion and identify subpopulations that are immobilized or mobile. Importantly, native mucus, purified mucin, cultured epithelial models and animal tissues differ in composition and structure; model selection can therefore influence the apparent transport behavior [33].

Biological evaluation should progress from physicochemical characterization to mucus interaction, epithelial transport, tissue distribution, pharmacokinetics and pharmacodynamics. Ex vivo tissues can provide useful intermediate evidence, whereas in vivo models are required to account for secretion, clearance and immune responses. Increasingly, disease-relevant mucus and advanced in vitro platforms are being considered to improve translation and reduce overinterpretation of simplified laboratory systems [34].

XI. SAFETY, MANUFACTURING AND TRANSLATIONAL CHALLENGES

Despite strong preclinical progress, translation remains limited by the complexity of the mucosal interface and variability between individuals and disease states. A formulation that performs well in a standardized mucus model may behave differently in inflamed, dehydrated or enzyme-rich mucus. Repeated administration may also change the mucosal environment or produce local irritation. Long-term safety assessment must therefore include tissue compatibility, inflammation, microbiome effects where relevant and clearance of carrier components [35].

Manufacturing complexity is another major challenge. Nanocarriers with several functional components require tight control of particle size, surface composition, drug loading and residual solvents or reagents. Scale-up can change mixing, nucleation, encapsulation and coating behavior. Bioadhesive polymers may also exhibit batch-to-batch variability related to molecular weight, degree of substitution or

source material. Robust analytical methods and clearly defined critical quality attributes are necessary for reproducible production [5,16].

Regulatory translation requires a clear understanding of whether the product is classified primarily as a drug, device, combination product or another category. The more multifunctional the formulation becomes, the greater the need for well-defined composition, mechanism, manufacturing controls and safety data. Demonstrating meaningful improvement over conventional dosage forms will ultimately require comparative clinical evidence rather than reliance on laboratory adhesion or permeability metrics alone [36].

XII. FUTURE PERSPECTIVES

The next generation of mucosal delivery systems is likely to emphasize adaptive interfaces rather than permanently adhesive or permanently inert particles. Mucoadhesive-to-mucopenetrating systems illustrate this direction by attempting to separate the functions of retention and tissue access in time. Similar concepts can be achieved through reversible bonds, cleavable coatings, charge switching and stimulus-sensitive surface transformations [18].

Hybrid systems that combine nanoparticles with hydrogels, films, nanofibers or in situ gelling matrices may provide a useful compromise between handling, residence and nanoscale transport. Such architectures can create a macroscopic dosage form that retains a nanoscale therapeutic carrier. They may also allow local release of multiple agents or spatial separation of incompatible components [19].

Targeting is expected to become more precise as receptor biology, ligand engineering and disease-specific biomarkers are integrated into mucosal delivery design. For example, ligand-functionalized particles can be designed to favor uptake by selected epithelial or immune-cell populations. However, targeting should be considered after the more fundamental problems of residence, mucus transport, epithelial access and safety have been addressed [29]. Personalized mucosal delivery is another emerging opportunity. Variations in mucus composition, hydration, disease state, microbiota, age and anatomical physiology can influence carrier

performance. Future formulation platforms may therefore be selected or optimized using patient-relevant biological measurements, mechanistic models and predictive computational tools. This approach could reduce the gap between average laboratory conditions and the heterogeneous environment encountered in clinical practice [33].

Overall, the field is moving from single-function systems toward integrated delivery architectures in which nanocarrier composition, polymer chemistry and tissue physiology are considered simultaneously. The most clinically successful platforms are likely to be those that deliver a clear therapeutic advantage while remaining sufficiently simple, stable and reproducible for large-scale manufacture. The combination of rational interface engineering, disease-relevant testing and clinically meaningful endpoints should be prioritized over complexity for its own sake [37].

XIII. CONCLUSION

Mucosal drug delivery has progressed from conventional bioadhesive dosage forms toward sophisticated nanocarrier-based and multifunctional platforms capable of manipulating residence, mucus transport, epithelial interaction and drug release. Nanoparticles, liposomes, micelles, nanoemulsions and hybrid systems can protect therapeutic cargo and modify its disposition, while chitosan, hyaluronic acid, thiomers, alginates and related polymers provide versatile tools for bioadhesion and controlled release. The key design principle is increasingly the controlled balance between retention and penetration rather than maximizing either property in isolation [38].

Future progress will depend on better understanding of tissue-specific mucus biology, improved predictive models, standardized characterization, robust manufacturing and carefully designed clinical studies. Mucoadhesive-to-mucopenetrating systems, stimuli-responsive interfaces, targeted carriers and hybrid dosage forms offer particularly promising directions. If these technologies can be translated with consistent quality and acceptable safety, mucosal delivery may provide a practical route to improve local therapy, systemic exposure, patient convenience and treatment adherence across multiple therapeutic areas [37]

REFERENCES

- [1] Y. Song, Y. Wang, R. Thakur, V. M. Meidan, and B. Michniak, "Mucosal drug delivery: Membranes, methodologies, and applications," *Critical Reviews in Therapeutic Drug Carrier Systems*, vol. 21, no. 3, pp. 195–256, 2004, doi: 10.1615/CritRevTherDrugCarrierSyst.v21.i3.20.
- [2] N. Salamat-Miller, M. Chittchang, and T. P. Johnston, "The use of mucoadhesive polymers in buccal drug delivery," *Advanced Drug Delivery Reviews*, vol. 57, no. 11, pp. 1666–1691, 2005, doi: 10.1016/j.addr.2005.07.003.
- [3] S. K. Lai, Y. Y. Wang, and J. Hanes, "Mucus-penetrating nanoparticles for drug and gene delivery to mucosal tissues," *Advanced Drug Delivery Reviews*, vol. 61, no. 2, pp. 158–171, 2009, doi: 10.1016/j.addr.2008.11.002.
- [4] E. Fröhlich and E. Roblegg, "Mucus as barrier for drug delivery by nanoparticles," *Journal of Nanoscience and Nanotechnology*, vol. 14, no. 1, pp. 126–136, 2014, doi: 10.1166/jnn.2014.9015.
- [5] A. Sosnik, J. das Neves, and B. Sarmento, "Mucoadhesive polymers in the design of nano-drug delivery systems for administration by non-parenteral routes: A review," *Progress in Polymer Science*, vol. 39, no. 12, pp. 2030–2075, 2014, doi: 10.1016/j.progpolymsci.2014.07.010.
- [6] S. Dünhaupt, O. Kammona, C. Waldner, C. Kiparissides, and A. Bernkop-Schnürch, "Nano-carrier systems: Strategies to overcome the mucus gel barrier," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 96, pp. 447–453, 2015, doi: 10.1016/j.ejpb.2015.01.022.
- [7] S. Duggan, W. Cummins, O. O'Donovan, H. Hughes, and E. Owens, "Thiolated polymers as mucoadhesive drug delivery systems," *European Journal of Pharmaceutical Sciences*, vol. 100, pp. 64–78, 2017, doi: 10.1016/j.ejps.2017.01.008.
- [8] X. Murgia, B. Loretz, O. Hartwig, M. Hittinger, and C. M. Lehr, "The role of mucus on drug transport and its potential to affect therapeutic outcomes," *Advanced Drug Delivery Reviews*, vol. 124, pp. 82–97, 2018, doi: 10.1016/j.addr.2017.10.009.
- [9] J. T. Huckaby and S. K. Lai, "PEGylation for enhancing nanoparticle diffusion in mucus," *Advanced Drug Delivery Reviews*, vol. 124, pp. 125–134, 2018, doi: 10.1016/j.addr.2017.09.011.

- [10] J. Griesser, G. Hetényi, and A. Bernkop-Schnürch, "Thiolated hyaluronic acid as versatile mucoadhesive polymer: From the chemistry behind to product developments—what are the capabilities?" *Polymers*, vol. 10, no. 3, Art. no. 243, 2018, doi: 10.3390/polym10030243.
- [11] T. M. M. Ways, W. M. Lau, and V. V. Khutoryanskiy, "Chitosan and its derivatives for application in mucoadhesive drug delivery systems," *Polymers*, vol. 10, no. 3, Art. no. 267, 2018, doi: 10.3390/polym10030267.
- [12] P. Schattling, E. M. Taipaleenmäki, Y. Zhang, and B. M. Städler, "A polymer chemistry point of view on mucoadhesion and mucopenetration," *Macromolecular Bioscience*, vol. 17, no. 9, Art. no. 1700060, 2017, doi: 10.1002/mabi.201700060.
- [13] A. Kumar, P. K. Naik, D. Pradhan, G. Ghosh, and G. Rath, "Mucoadhesive formulations: Innovations, merits, drawbacks, and future outlook," *Pharmaceutical Development and Technology*, vol. 25, no. 7, pp. 797–814, 2020, doi: 10.1080/10837450.2020.1753771.
- [14] R. Kulkarni, S. Fanse, and D. J. Burgess, "Mucoadhesive drug delivery systems: A promising non-invasive approach to bioavailability enhancement. Part I: Biophysical considerations," *Expert Opinion on Drug Delivery*, vol. 20, no. 3, pp. 395–412, 2023, doi: 10.1080/17425247.2023.2181331.
- [15] H. Sato, K. Yamada, M. Miyake, and S. Onoue, "Recent advancements in the development of nanocarriers for mucosal drug delivery systems to control oral absorption," *Pharmaceutics*, vol. 15, no. 12, Art. no. 2708, 2023, doi: 10.3390/pharmaceutics15122708.
- [16] R. Kumar, T. Islam, and M. Nurunnabi, "Mucoadhesive carriers for oral drug delivery," *Journal of Controlled Release*, vol. 351, pp. 504–559, 2022, doi: 10.1016/j.jconrel.2022.09.024.
- [17] R. Sharma, S. Kumar, R. Malviya, B. G. Prajapati, D. Puri, S. Limmatvapirat, and P. Sriamornsak, "Recent advances in biopolymer-based mucoadhesive drug delivery systems for oral application," *Journal of Drug Delivery Science and Technology*, vol. 91, Art. no. 105227, 2024, doi: 10.1016/j.jddst.2023.105227.
- [18] B. Zheng, D. Liu, X. Qin, D. Zhang, and P. Zhang, "Mucoadhesive-to-mucopenetrating nanoparticles for mucosal drug delivery: A mini review," *International Journal of Nanomedicine*, vol. 20, pp. 2241–2252, 2025, doi: 10.2147/IJN.S505427.
- [19] N. N. Porfiryeva, R. I. Moustafine, and V. V. Khutoryanskiy, "Advances in mucoadhesive and mucus-penetrating materials, nano-formulations, and in situ gelling systems for nasal drug delivery," *Expert Opinion on Drug Delivery*, vol. 23, no. 5, pp. 797–822, 2026, doi: 10.1080/17425247.2026.2628612.
- [20] R. S. Dave, T. C. Goostrey, M. Ziolkowska, S. Czerny-Holownia, T. Hoare, and H. Sheardown, "Ocular drug delivery to the anterior segment using nanocarriers: A mucoadhesive/mucopenetrative perspective," *Journal of Controlled Release*, vol. 336, pp. 71–88, 2021, doi: 10.1016/j.jconrel.2021.06.011.
- [21] H. Han, S. Li, M. Xu, Y. Zhong, W. Fan, J. Xu, T. Zhou, J. Ji, J. Ye, and K. Yao, "Polymer- and lipid-based nanocarriers for ocular drug delivery: Current status and future perspectives," *Advanced Drug Delivery Reviews*, vol. 196, Art. no. 114770, 2023, doi: 10.1016/j.addr.2023.114770.
- [22] S. Ahmed, M. M. Amin, and S. Sayed, "Ocular drug delivery: A comprehensive review," *AAPS PharmSciTech*, vol. 24, no. 2, Art. no. 66, 2023, doi: 10.1208/s12249-023-02516-9.
- [23] A. S. Macedo, P. M. Castro, L. Roque, N. G. Thomé, C. P. Reis, M. E. Pintado, and P. Fonte, "Novel and revisited approaches in nanoparticle systems for buccal drug delivery," *Journal of Controlled Release*, vol. 320, pp. 125–141, 2020, doi: 10.1016/j.jconrel.2020.01.006.
- [24] D. D. Desai, J. Manikkath, H. Lad, M. Kulkarni, A. Manikkath, and R. Radhakrishnan, "Nanotechnology-based mucoadhesive and mucus-penetrating drug-delivery systems for transbuccal drug delivery," *Nanomedicine*, vol. 18, no. 21, pp. 1495–1514, 2023, doi: 10.2217/nnm-2023-0180.
- [25] M. T. M. Subi, N. Selvasudha, and H. R. Vasanthi, "Vaginal drug delivery system: A promising route of drug administration for local and systemic diseases," *Drug Discovery Today*, vol. 29, no. 6, Art. no. 104012, 2024, doi: 10.1016/j.drudis.2024.104012.
- [26] R. Pangen, T. Meng, S. Poudel, D. Sharma, H. Hutsell, J. Ma, B. K. Rubin, W. Longest, M.

- Hindle, and Q. Xu, "Airway mucus in pulmonary diseases: Muco-adhesive and muco-penetrating particles to overcome the airway mucus barriers," *International Journal of Pharmaceutics*, vol. 634, Art. no. 122661, 2023, doi: 10.1016/j.ijpharm.2023.122661.
- [27] M. Huang, M. Zhang, H. Zhu, X. Du, and J. Wang, "Mucosal vaccine delivery: A focus on the breakthrough of specific barriers," *Acta Pharmaceutica Sinica B*, vol. 12, no. 9, pp. 3456–3474, 2022, doi: 10.1016/j.apsb.2022.07.002.
- [28] R. Anggraeni, I. D. Ana, and H. Wihadmadyatami, "Development of mucosal vaccine delivery: An overview on the mucosal vaccines and their adjuvants," *Clinical and Experimental Vaccine Research*, vol. 11, no. 3, pp. 235–248, 2022, doi: 10.7774/cevr.2022.11.3.235.
- [29] K. Zhao, Y. Xie, X. Lin, and W. Xu, "The mucoadhesive nanoparticle-based delivery system in the development of mucosal vaccines," *International Journal of Nanomedicine*, vol. 17, pp. 4579–4598, 2022, doi: 10.2147/IJN.S359118.
- [30] K. Mfoafo, R. Mittal, A. Eshraghi, Y. Omid, and H. Omidian, "Thiolated polymers: An overview of mucoadhesive properties and their potential in drug delivery via mucosal tissues," *Journal of Drug Delivery Science and Technology*, vol. 85, Art. no. 104596, 2023, doi: 10.1016/j.jddst.2023.104596.
- [31] M. Surendranath, M. R. Rekha, and R. Parameswaran, "Recent advances in functionally modified polymers for mucoadhesive drug delivery," *Journal of Materials Chemistry B*, vol. 10, no. 31, pp. 5913–5924, 2022, doi: 10.1039/D2TB00856D.
- [32] J. Y. Lock, T. L. Carlson, and R. L. Carrier, "Mucus models to evaluate the diffusion of drugs and particles," *Advanced Drug Delivery Reviews*, vol. 124, pp. 34–49, 2018, doi: 10.1016/j.addr.2017.11.001.
- [33] C. Zandanel, G. Ponchel, M. Noiray, and C. Vauthier, "Nanoparticles facing the gut barrier: Retention or mucosal absorption? Mechanisms and dependency to nanoparticle characteristics," *International Journal of Pharmaceutics*, vol. 605, Art. no. 121147, 2021, doi: 10.1016/j.ijpharm.2021.121147.
- [34] C. T. Nordgård and K. I. Draget, "Co-association of mucus modulating agents and nanoparticles for mucosal drug delivery," *Advanced Drug Delivery Reviews*, vol. 124, pp. 175–183, 2018, doi: 10.1016/j.addr.2018.01.001.
- [35] H. Sato, "Development of nanoparticle-based mucosal drug delivery systems for controlling pharmacokinetic behaviors," *Biological and Pharmaceutical Bulletin*, vol. 48, no. 6, pp. 759–768, 2025, doi: 10.1248/bpb.b25-00071.
- [36] A. Ludwig, "The use of mucoadhesive polymers in ocular drug delivery," *Advanced Drug Delivery Reviews*, vol. 57, no. 11, pp. 1595–1639, 2005, doi: 10.1016/j.addr.2005.07.005.
- [37] V. F. Patel, F. Liu, and M. B. Brown, "Advances in oral transmucosal drug delivery," *Journal of Controlled Release*, vol. 153, no. 2, pp. 106–116, 2011, doi: 10.1016/j.jconrel.2011.01.027.
- [38] J. Leal, H. D. C. Smyth, and D. Ghosh, "Physicochemical properties of mucus and their impact on transmucosal drug delivery," *International Journal of Pharmaceutics*, vol. 532, no. 1, pp. 555–572, 2017, doi: 10.1016/j.ijpharm.2017.09.018.