

Hydration Driven Nanocarrier Design for Enhanced Mucosal Drug Transport

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ABSTRACT

Mucosal drug delivery has emerged as a promising strategy for both local and systemic therapeutic administration due to its non-invasive nature and extensive absorptive surface area. However, the protective mucus barrier, composed of highly viscoelastic and adhesive mucin networks, significantly restricts the efficient transport of conventional nanocarriers. Traditional mucoadhesive systems, while improving retention, often suffer from limited diffusion and heterogeneous drug distribution across mucosal surfaces. In recent years, hydration driven nanocarrier design has gained substantial attention as an advanced approach to overcome mucus associated transport limitations. Surface hydration layers formed through the incorporation of highly hydrophilic polymers, zwitterionic materials, and biomimetic coatings create a water rich interfacial barrier that minimizes adhesive interactions between nanoparticles and mucin fibers. This hydration mediated lubrication facilitates rapid nanoparticle diffusion, enhances mucus penetration, and improves drug bioavailability. This review critically examines the fundamental mechanisms governing hydration layer formation and its role in modulating nanoparticle mobility across mucosal barriers. The physicochemical characteristics of mucus, including structural heterogeneity, rheological behavior, and disease induced alterations, are discussed to provide a comprehensive understanding of transport challenges. Various material engineering strategies for generating stable hydration layers, along with fabrication techniques and characterization methodologies, are systematically reviewed. Particular emphasis is placed on the translational potential of hydration driven nanocarriers in oral and pulmonary drug delivery, highlighting their ability to enhance drug stability, absorption, and targeted delivery. Additionally, safety considerations, regulatory challenges, and manufacturing limitations associated with hydration engineered nanocarriers are analyzed. The review concludes by outlining emerging trends such as adaptive surface engineering and personalized mucosal nanomedicine, underscoring the future potential of hydration based nanocarrier systems in overcoming biological barriers and improving therapeutic outcomes.

Keywords: Hydration Layer, Mucus Barrier Transport, Nanocarrier, Oral Drug Delivery, Pulmonary Drug Delivery.

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INTRODUCTION

Mucosal drug delivery has emerged as an important and rapidly advancing field in pharmaceutical sciences due to its potential to provide both localized and systemic therapeutic effects through non-invasive administration routes. Mucosal surfaces, including those of the gastrointestinal tract and respiratory system, offer extensive surface area, rich vascularization, and reduced enzymatic degradation compared to conventional delivery pathways (Hua, 2020). These characteristics make oral and pulmonary routes highly attractive for improving patient compliance and

therapeutic efficacy. Despite these advantages, efficient drug transport across mucosal barriers remains a significant challenge because mucus functions as a highly specialized protective layer designed to prevent the entry of foreign particles, pathogens, and environmental toxins.

Mucus is a complex hydrogel primarily composed of water, mucin glycoproteins, lipids, salts, and cellular debris that together form a viscoelastic and adhesive network (Abrami *et al.*, 2024). This network acts as a selective barrier by trapping particulate matter and facilitating its removal through physiological clearance mechanisms. While this protective function is essential for maintaining tissue homeostasis, it significantly restricts the penetration of drug carriers, particularly nanoparticle based delivery systems. Conventional nanoparticles often interact strongly with mucin fibers through hydrophobic, electrostatic, and hydrogen bonding interactions, leading to rapid immobilization and nonuniform drug distribution



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across mucosal surfaces (Subramanian *et al.*, 2022). As a result, many nanoparticle formulations fail to achieve optimal drug bioavailability despite demonstrating favorable physicochemical properties. In response to these limitations, the concept of mucus penetrating nanocarriers has gained considerable attention as a strategy to enhance nanoparticle mobility through mucosal barriers. Unlike traditional mucoadhesive systems that focus on prolonging retention at mucosal surfaces, mucus penetrating nanoparticles are specifically engineered to minimize adhesive interactions with mucin networks, allowing them to diffuse rapidly through mucus layers and reach underlying epithelial tissues (Watchorn *et al.*, 2022). This shift from adhesion-based retention to penetration based transport represents a significant paradigm change in mucosal drug delivery design. The ability of nanoparticles to effectively traverse mucus layer depends largely on their surface characteristics, including hydrophilicity, charge neutrality, and steric stabilization (Yan and Sha, 2023).

Among various surface engineering approaches, hydration driven nanocarrier design has emerged as a highly promising strategy for improving mucus penetration. This approach involves the incorporation of highly hydrophilic surface modifications that promote the formation of dense hydration layers around nanoparticle surfaces (Carlson *et al.*, 2018). These hydration shells create a water rich interfacial barrier that reduces direct contact between nanoparticles and mucin fibers, thereby minimizing adhesive interactions and facilitating lubrication mediated diffusion. The formation of stable hydration layers is typically achieved through the use of hydrophilic polymers, zwitterionic materials, and biomimetic coatings capable of strong water binding. By modulating nanoparticle surface properties through hydration layer engineering, it becomes possible to significantly enhance drug transport across mucus while maintaining nanoparticle stability and therapeutic payload integrity. The application of hydration driven nanocarrier systems has shown particular promise in oral and pulmonary drug delivery. In oral administration, such systems can improve drug stability in the gastrointestinal environment, enhance mucosal absorption, and facilitate the delivery of macromolecular therapeutics that traditionally suffer from poor bioavailability (Azman *et al.*, 2022). In pulmonary delivery, hydration engineered nanoparticles demonstrate improved penetration through airway mucus, enabling targeted delivery to respiratory epithelium and enhancing treatment outcomes for various pulmonary disorders. The growing interest in hydration mediated nanoparticle transport reflects a broader shift toward rational nanocarrier design guided by an improved understanding of biological barrier interactions.

Despite encouraging progress, several challenges remain in translating hydration engineered nanocarriers into clinical applications. Variability in mucus composition, dynamic physiological clearance mechanisms, and complexities associated with large scale manufacturing require further investigation

(Tufail *et al.*, 2025). Additionally, comprehensive evaluation of safety, long term biocompatibility, and regulatory compliance remains essential for successful clinical adoption. Addressing these challenges requires an integrated understanding of mucus biology, nanoparticle surface chemistry, fabrication methodologies, and translational considerations. This review aims to provide a comprehensive overview of hydration driven nanocarrier design for enhanced mucosal drug transport. The discussion begins with an overview of mucus structure and its barrier properties, followed by an analysis of nanoparticle transport limitations across mucosal environments. The review then focuses on the mechanistic principles of surface hydration layer formation and the materials used for engineering hydration enabled nanocarriers. Fabrication techniques, characterization methodologies, and therapeutic applications in oral and pulmonary drug delivery are systematically examined. Finally, safety considerations, translational challenges, and emerging research directions are discussed to highlight the future potential of hydration based nanocarrier systems in advancing mucosal drug delivery.

METHODOLOGY

An extensive and systematic literature survey was performed using major scientific databases, including PubMed, Scopus, and Google Scholar. A combination of targeted keywords, such as mucosal drug delivery, hydration layer, nanocarrier systems, mucus penetration, and zwitterionic polymers, was applied to retrieve pertinent peer reviewed articles published up to the year 2026. The scope of this review encompasses fundamental mechanistic insights, advanced material design strategies, and translational therapeutic applications, with particular emphasis on oral and pulmonary drug delivery systems.

MUCUS AS A BIOLOGICAL BARRIER

Mucus is a highly specialized biological secretion that plays a fundamental role in protecting mucosal tissues from environmental insults, pathogens, and particulate matter. It forms a dynamic and hydrated gel layer that lines various epithelial surfaces, including those of the gastrointestinal and respiratory tracts. The primary function of mucus is to act as a physical and biochemical defense barrier while simultaneously maintaining tissue lubrication and hydration (Petrou and Crouzier, 2018). Its structural complexity and continuous turnover enable it to efficiently trap and eliminate foreign substances through coordinated clearance mechanisms. While these protective properties are essential for maintaining physiological homeostasis, they also present a significant obstacle for drug delivery systems attempting to access underlying epithelial tissues. The structural framework of mucus is predominantly formed by mucin glycoproteins, which are large, heavily glycosylated macromolecules capable of forming extended and entangled polymeric networks (Fass and Thornton, 2023). These mucins contain densely packed carbohydrate side

chains that contribute to their hydrophilic nature and high water retention capacity. The mucin network is stabilized through various intermolecular interactions, including disulfide bonds, hydrogen bonding, and ionic interactions, resulting in a three dimensional mesh like architecture (Authimoolam and Dziubla, 2016). This hydrated matrix typically contains more than ninety percent water, along with lipids, proteins, enzymes, salts, and cellular debris. The presence of these components contributes to the viscoelastic nature of mucus and influences its permeability characteristics. The mesh size within the mucin network varies depending on anatomical location and physiological conditions, creating a heterogeneous barrier that selectively restricts the movement of particulate materials (Pednekar *et al.*, 2022).

The physicochemical and rheological properties of mucus are critical determinants of its barrier function. Mucus exhibits both viscous and elastic behavior, allowing it to deform under mechanical stress while maintaining structural integrity (Wagner *et al.*, 2018). This viscoelasticity facilitates effective trapping of foreign particles while enabling coordinated transport and removal through physiological clearance systems. The rheological behavior of mucus is influenced by factors such as mucin concentration, hydration level, ionic strength, and PH. Variations in these parameters can significantly alter mucus permeability and diffusion properties. Additionally, mucus displays selective permeability based on molecular size, charge, and hydrophobicity, enabling it to function as a biological filter that discriminates between endogenous molecules and potentially harmful exogenous agents (Kim *et al.*, 2024). Although mucus serves a universal protective function, its structural and functional characteristics vary significantly between different mucosal tissues. In the gastrointestinal tract, mucus forms a multilayered barrier that protects the epithelium from mechanical damage, enzymatic degradation, and microbial invasion (Şenel, 2021). The outer mucus layer is relatively loose and supports microbial colonization, while the inner layer is more densely packed and tightly adherent to the epithelial surface, providing enhanced protective capability. Gastrointestinal mucus is continuously secreted and renewed, resulting in dynamic thickness and turnover rates that vary along different regions of the digestive tract. These variations influence the residence time and transport behavior of drug delivery systems.

In contrast, pulmonary mucus is generally thinner and more mobile, facilitating efficient clearance through mucociliary transport mechanisms (Hill *et al.*, 2022). The respiratory mucus layer works in coordination with ciliary motion to remove inhaled particles and microorganisms from airway surfaces. Pulmonary mucus composition is optimized to balance protective function with the need to maintain airway patency and efficient gas exchange. The rate of mucus clearance in the respiratory system is typically faster than in the gastrointestinal tract, which presents unique challenges for sustained drug delivery. Furthermore,

pulmonary mucus hydration is tightly regulated to maintain optimal rheological properties necessary for effective mucociliary function (Abrami *et al.*, 2024). Key structural and functional differences between gastrointestinal and pulmonary mucus influencing drug transport are summarized in Table 1.

The barrier properties of mucus are highly sensitive to physiological and pathological changes. Factors such as inflammation, infection, and chronic disease conditions can alter mucus composition, increase mucin secretion, and modify hydration levels (Marriott and Gregory, 2024). These alterations often result in increased viscosity and reduced mucus permeability, further complicating drug transport across mucosal surfaces. Understanding the structural diversity and dynamic behavior of mucus across different anatomical regions is essential for designing effective drug delivery systems capable of overcoming mucosal barriers. A comprehensive understanding of mucus composition, structure, and functional variability provides a critical foundation for evaluating nanoparticle transport behavior in mucosal environments. By elucidating the physicochemical characteristics that govern mucus barrier function, it becomes possible to rationally design nanocarriers that can efficiently navigate through mucosal layers and achieve improved therapeutic performance.

BARRIERS TO NANOPARTICLE TRANSPORT ACROSS MUCUS

The efficient transport of nanoparticles across mucus is significantly restricted by the structural and biochemical complexity of the mucin network. Although nanoparticles are designed to enhance drug stability and targeting efficiency, their interaction with mucus often results in rapid immobilization, preventing them from reaching underlying epithelial tissues. The mucin matrix acts as a multifunctional barrier that limits nanoparticle diffusion through steric obstruction, adhesive interactions, and dynamic physiological clearance processes (Carlson *et al.*, 2018). These transport limitations are strongly influenced by the physicochemical properties of both mucus and nanoparticle surfaces, making mucus penetration a critical challenge in mucosal drug delivery. Steric obstruction represents one of the primary physical barriers to nanoparticle mobility within mucus. The entangled mucin fibers form a heterogeneous mesh structure with variable pore sizes that can restrict the movement of particulate carriers (Witten *et al.*, 2018). Nanoparticles that exceed the effective pore dimensions of the mucin network often experience physical entrapment, leading to reduced diffusion rates. Even nanoparticles smaller than the average mesh size may encounter restricted movement due to local variations in mucin density and crosslinking. The dynamic and irregular arrangement of mucin fibers further contributes to spatial heterogeneity within mucus, creating regions of varying permeability that can influence nanoparticle transport

behavior (Zhao *et al.*, 2024). In addition to steric hindrance, adhesive interactions between nanoparticles and mucin components play a crucial role in limiting particle mobility. Mucin glycoproteins possess diverse functional groups capable of forming multiple intermolecular interactions with nanoparticle surfaces. Hydrophobic interactions between mucin domains and hydrophobic nanoparticle coatings frequently result in strong binding and prolonged retention within mucus. Electrostatic interactions also significantly influence nanoparticle transport, as mucins typically carry a net negative charge due to the presence of sialic acid and sulfate groups (Bandi *et al.*, 2020). Positively charged nanoparticles tend to exhibit strong electrostatic attraction toward mucins, leading to rapid immobilization and restricted diffusion. Hydrogen bonding interactions between mucin carbohydrate chains and nanoparticle surface functional groups further contribute to adhesive entrapment, collectively reducing nanoparticle penetration efficiency.

The physicochemical characteristics of nanoparticles play a decisive role in determining their interaction with mucus. Particle size is a critical parameter influencing diffusion through mucin networks, with smaller nanoparticles generally demonstrating improved mobility compared to larger particles (Abdulkarim *et al.*, 2015). However, size alone does not guarantee efficient penetration, as surface properties such as hydrophobicity and surface charge significantly affect nanoparticle-mucus interactions. Highly hydrophobic nanoparticles are prone to adhesive binding with mucin fibers, whereas strongly charged particles may undergo electrostatic interactions that hinder their diffusion. Surface roughness and morphological features also influence particle mobility by affecting contact area and interaction potential with mucin components. Therefore, optimizing nanoparticle physicochemical attributes is essential for improving mucosal transport (Sumarokova *et al.*, 2018). Physiological clearance mechanisms further complicate nanoparticle retention and transport across mucosal surfaces. In the gastrointestinal tract, continuous mucus secretion and luminal fluid movement contribute to rapid clearance of trapped particles. Similarly, in the respiratory system, mucociliary clearance mechanisms facilitate the removal of inhaled particulate matter through coordinated ciliary motion and mucus transport toward the upper airway (Whitsett, 2018). These clearance processes reduce the residence time of nanoparticles within mucus, limiting their ability to release therapeutic payloads at target sites. Effective drug delivery systems must therefore balance the need for rapid mucus penetration with sufficient retention at the epithelial surface to ensure adequate drug absorption. Pathological alterations in mucus composition and structure can further influence nanoparticle transport behavior. Inflammatory and infectious conditions often lead to increased mucin production, altered glycosylation patterns, and reduced hydration levels, resulting in enhanced mucus viscosity and decreased permeability. Chronic respiratory disorders and gastrointestinal diseases frequently produce abnormally

thickened mucus layers that present additional diffusion barriers. This disease associated changes introduce variability in mucus barrier properties across patient populations, complicating the design of universally effective nanoparticle delivery systems (Liu *et al.*, 2021). Understanding these pathological variations is essential for developing nanocarriers capable of maintaining consistent performance under diverse physiological conditions. Collectively, steric entrapment, adhesive interactions, physicochemical incompatibility, and dynamic clearance mechanisms form a complex network of barriers that limit nanoparticle transport across mucus. Overcoming these challenges requires innovative nanoparticle design strategies that minimize mucin interactions while preserving drug delivery efficiency. A detailed understanding of these transport barriers provides the scientific basis for developing advanced nanocarrier systems specifically engineered to enhance diffusion through mucosal environments.

HYDRATION DRIVEN NANOCARRIER DESIGN PRINCIPLES

The limitations associated with nanoparticle transport across mucus have prompted the development of advanced surface engineering strategies aimed at minimizing adhesive interactions and enhancing particle mobility (Bayer, 2022). Among these approaches, hydration driven nanocarrier design has emerged as a highly effective strategy for facilitating rapid diffusion through mucosal barriers. This design concept is based on modifying nanoparticle surfaces with hydrophilic materials capable of forming dense and stable hydration layers that reduce direct contact between nanoparticles and mucin fibers. By introducing a water rich interfacial barrier, hydration engineered nanocarriers can significantly reduce intermolecular interactions that otherwise lead to particle entrapment, thereby improving transport efficiency across mucus layers (Babiuch *et al.*, 2012). Traditional mucosal drug delivery systems have largely relied on mucoadhesive mechanisms to prolong nanoparticle residence time at mucosal surfaces. While mucoadhesion enhances localized drug retention, it often results in heterogeneous drug distribution and limited penetration into deeper mucosal layers. In contrast, mucopenetrating nanocarriers are specifically designed to avoid strong adhesive interactions with mucus, allowing them to rapidly diffuse through the mucin network and reach epithelial tissues more effectively. Hydration driven nanoparticle design supports this penetration based strategy by creating surface environments that are highly resistant to protein adsorption and mucin binding (Guo *et al.*, 2023). This shift from adhesion-oriented retention to penetration-oriented delivery represents a significant paradigm change in mucosal nanomedicine.

The formation of surface hydration layers is primarily governed by the presence of highly hydrophilic functional groups capable of strong water binding (Xiao *et al.*, 2019). These groups attract

and organize surrounding water molecules into tightly bound hydration shells that act as steric barriers between nanoparticle surfaces and mucin components. The structured water molecules surrounding hydrated nanoparticles generate repulsive hydration forces that prevent close contact with mucin glycoproteins. This phenomenon reduces frictional resistance and promotes lubrication mediated particle transport through the mucus matrix. The stability of hydration layers depends on the density and arrangement of hydrophilic groups on the nanoparticle surface, as well as the ability of these groups to maintain strong hydration under physiological conditions. Molecular level interactions play a critical role in determining the effectiveness of hydration layer formation. Hydrophilic polymers and zwitterionic materials often contain functional groups capable of forming extensive hydrogen bonding networks with water molecules. These hydrogen bonding interactions stabilize hydration shells and contribute to long range steric repulsion that minimizes nanoparticle aggregation and mucin adhesion. Additionally, the presence of charge balanced ionic groups within zwitterionic materials enhances water retention through electrostatic solvation effects, further strengthening hydration layer stability. The cooperative interaction between hydrogen bonding, ionic solvation, and steric stabilization enables hydration engineered nanoparticles to maintain high mobility even within densely structured mucin environments (Le *et al.*, 2024). Another important aspect of hydration driven nanocarrier design involves optimizing surface charge neutrality. Nanoparticles with strong positive or negative surface charges tend to interact electrostatically with mucin glycoproteins, leading to immobilization. Hydration layer engineering often incorporates charge neutral or charge balanced surface modifications that minimize electrostatic attraction while maintaining nanoparticle stability in biological fluids. The combined effect of steric hydration barriers and charge neutrality significantly reduces nonspecific binding and enhances nanoparticle diffusion through mucus layers (Wang *et al.*, 2019).

Common hydrophilic materials used for generating hydration layers are summarized in Table 2.

Surface hydration also contributes to improved nanoparticle colloidal stability and reduced aggregation in biological environments. Aggregated nanoparticles often exhibit increased effective particle size, which can further restrict transport through mucin networks. Hydration layers provide steric stabilization that prevents particle aggregation by maintaining adequate interparticle distance. This stabilization enhances nanoparticle dispersibility and ensures consistent transport behavior across mucosal surfaces. Additionally, hydration engineered surfaces can protect encapsulated therapeutic agents from enzymatic degradation and premature drug release, thereby improving drug delivery efficiency (Guerrini, *et al.*, 2018). The effectiveness of hydration driven nanocarrier design is influenced by several physicochemical parameters, including the thickness of the hydration layer, surface polymer density, and molecular conformation of hydrophilic coatings. Dense and uniformly distributed hydration layers generally provide stronger steric repulsion and enhanced diffusion capability. However, excessive surface modification may compromise drug loading capacity or alter nanoparticle structural integrity. Therefore, achieving an optimal balance between hydration layer stability and nanoparticle functional performance is critical for successful nanocarrier design. Hydration mediated nanoparticle transport also demonstrates adaptability across different mucosal environments. Variations in mucus composition, hydration level, and ionic strength can influence nanoparticle mobility. Hydration engineered surfaces provide dynamic interactions with surrounding biological fluids, enabling nanoparticles to maintain diffusion efficiency under varying physiological conditions. This adaptability highlights the potential of hydration driven nanocarrier systems to provide consistent drug delivery performance across diverse mucosal tissues. Overall, hydration driven nanocarrier design represents a rational and mechanistically guided approach for overcoming

Table 1: Comparative structural and functional characteristics of gastrointestinal and pulmonary mucus and their influence on mucosal drug transport.

Parameter	Gastrointestinal Mucus	Pulmonary Mucus	Impact on Drug Delivery
Primary Function	Protects intestinal epithelium and regulates microbial interaction	Protects respiratory tract and supports mucociliary clearance	Determines nanoparticle residence and diffusion behavior
Major Components	Mucins, lipids, enzymes, electrolytes, microbial products	Mucins, surfactant proteins, immune mediators, electrolytes	Influences particle adhesion and mobility
Thickness	Highly variable depending on intestinal region	Relatively thinner but highly viscoelastic	Affects penetration depth of nanocarriers
Turnover Rate	Rapid renewal due to continuous secretion and shedding	Cleared through mucociliary movement	Influences retention time of drug carriers
pH Environment	Variable across gastrointestinal tract	Near neutral	Affects nanoparticle stability and drug release
Barrier Properties	Dense mucin network and enzymatic degradation	Highly hydrated gel with dynamic clearance	Regulates drug diffusion and bioavailability

Table 2: Representative hydrophilic materials employed for generating surface hydration layers and their roles in enhancing mucosal nanoparticle transport.

Material	Key Characteristics	Mechanism of Hydration Layer Formation	Advantages in Mucus Penetration
Polyethylene glycol	Hydrophilic and flexible polymer	Forms steric hydration barrier via water molecule binding	Reduces mucoadhesion and improves nanoparticle diffusion
Zwitterionic polymers	Possess balanced positive and negative charges	Strong electrostatically induced hydration shell	Provides ultra low protein and mucin adsorption
Polysaccharides	Natural hydrophilic biopolymers	Hydrogen bonding with water molecules	Enhances biocompatibility and mucus permeability
Peptide based coatings	Biomimetic and structurally tunable	Formation of ordered hydration interfaces	Supports targeted mucosal transport
Lipid based hydrophilic coatings	Amphiphilic surface stabilization	Enhances surface water retention and flexibility	Improves nanoparticle stability and penetration efficiency

mucus associated transport barriers. By integrating hydrophilic surface engineering, molecular hydration stabilization, and steric repulsion mechanisms, this strategy enhances nanoparticle mobility while preserving drug delivery functionality (Sultana *et al.*, 2020). The continued advancement of hydration based nanocarrier systems is expected to play a crucial role in improving mucosal drug transport and expanding the therapeutic potential of nanoparticle mediated drug delivery platforms.

MATERIALS FOR ENGINEERING SURFACE HYDRATION LAYERS

The choice of materials that can form stable and dense layers of hydration over the surfaces of nanoparticles is a key element in the successful implementation of hydration driven nanocarrier design. The materials should have a high-water binding capacity, biocompatibility and be stable in their structure in the physiological conditions. Synthetic and naturally occurring hydrophilic materials of different classes have been studied in the context of engineering surface hydration layers and each has different physicochemical properties which affect the transport behavior of nanoparticles across the mucosal barriers (Yu *et al.*, 2016). The material largely controls the thickness of the hydration layer, stability, and mucin interaction resistance, and therefore has a direct impact on diffusion efficiency of nanoparticles. Hydrophilic synthetic polymers are among the most researched classes of materials to be used in the hydration layer formation. These polymers have adopted flexible chain structures which have high hydrophilic functional groups that can form strong association with water molecules. Synthetic hydrophilic polymers have a high capacity to form sterically stabilized hydration shells, and therefore they are very suitable in minimizing nonspecific biological interactions. Their chemical versatility enables fine control of the properties of the hydration layers through the precise control of molecular weight, chain density and surface coverage. Synthetic polymers also tend to be highly physiochemically stable and can be readily functionalized to add targeting ligands

or even functional groups that are responsive (Siafaka *et al.*, 2016). Nevertheless, too high polymer chain density sometimes disrupts the efficiency of drug loading or nanoparticle cellular uptake, and thus requires the optimization of polymer coating parameters. Zwitterionic materials have received significant interest as sophisticated hydration layer forming agents owing to their dynamic water retention potential and anti-protein adsorption resistance. These materials have equal positive and negative ionic groups on the same molecular structure forming powerful electrostatically induced hydration shells. The strongly bound water molecules interactive with zwitterionic surfaces form a very strong and dense hydration shell that essentially reduces nonspecific interaction of the molecules. The presence of zwitterionic coatings can also be superior in antifouling properties than standard hydrophilic polymers, and in complex biological contexts, this leads to zwitterionic coatings being the most appropriate in keeping nanoparticles in suspension. Moreover, the use of zwitterionic materials increases the stability over a wide ionic strength and pH range, a property that is believed to explain their reproducible behavior in a wide variety of mucosal settings (Lu and Cheng, 2025). Natural and biomimetic hydrophilic substances have also been broadly examined in the fabrication of hydration layer facilitated nanocarriers. Biological poly saccharides are rich in hydroxyl and carbohydrate functional groups that allow high binding of hydrogen bonds with water molecules. The materials are biocompatible, biodegradable, and less immunogenic in nature, and they are considered desirable in the application of mucosal delivery of drugs. The compatibility of nanoparticles with biological systems can also be improved by the structural similarity of some types of polysaccharides with existing mucosal components that are found in nature. Also, peptide based and protein inspired surfaces have been considered to recreate the naturally hydrated biological surfaces and provide dynamic and adaptive hydration layers under the response to physiological microenvironments. These biomimetic materials tend to assist in the development of multifunctional nanoparticles that enhance hydration stability as well as target cell interactions

(Mu *et al.*, 2014). Experimental techniques used for evaluating mucus penetration efficiency are summarized in Table 3.

Amphiphilic polymeric materials are also becoming good alternatives to hydration layer engineering. The materials have hydrophilic and hydrophobic units which enable the material to self-assemble into nanostructures whilst exposing hydrophilic units on the surface of the particles. The hydrophilic groups are involved in the formation of a hydration layer and the hydrophobic domains are used to ensure structural stability and encapsulation of drugs. The amphiphilic properties of the polymers allow the creation of nanocarriers that can compromise between hydration mediated mucus penetration, as well as, to achieve, successful drug loading and controlled release properties (Sato *et al.*, 2023). The versatility of these structures enables the amphiphilic materials to be extremely useful in the creation of multifunctional drug delivery systems. Besides polymer-based materials, new nanomaterial-based coating that involves the use of hydrophilic inorganic and hybrid organic-inorganic materials have also demonstrated promise in stabilizing hydration layer. This will allow these materials to increase nanoparticle mechanical strength and offer other surface functionalization opportunities without compromising the integrity of hydration layers (Niranjana *et al.*, 2025). Inorganic compounds combined with organic polymers in Taiwanese Hybrid materials tend to combine the stability of inorganic materials and the elasticity of various organic polymers to form surfaces that can maintain hydration in complicated physiological environments. This type of hybrid technique is progressively being pursued to enhance the stability of nanoparticles and their long-term functionality in mucosal conditions (Ren *et al.*, 2021).

A number of factors affect the effectiveness of hydration layer forming material, they comprise the flexibility of the molecular chains, the capacity to hold water, the density of the coating and the resistance to biological degradation. More flexible polymeric chains of materials usually permit improved accommodation of water molecules, which results in a higher stability of the hydration

shell. In the same way, high density of grafting on surfaces enhances uniformity of the hydration layer but needs optimization to prevent steric hindrance that can lead to loss of nanoparticle functionality (Dahal *et al.*, 2018). To select the appropriate hydration layer materials, a trade-off between physicochemical stability, drug delivery performance, and biological compatibility is thus needed. The development of material science still continues to increase the choice of hydrophilic surface modifiers to design hydration driven nanocarrier. The combination of synthetic, natural and hybrid materials provide the possibilities of the adjustment of nanoparticle surface characteristics to particular mucosal conditions and therapeutic requirements (Atmakuri *et al.*, 2020). A thorough knowledge of material dependent hydration behavior is crucial towards developing nanocarriers that can realize efficient mucus penetration without compromising the ideal drug delivery functionality.

FABRICATION STRATEGIES FOR HYDRATION ENGINEERED NANOCARRIERS

Engineered nanocarriers fabrication entails use of the surface modification method that allows the incorporation of hydrophilic materials onto the surface of the nanoparticles. The efficiency of the hydration layer formed is not only based on the choice of material but also on the accuracy and effectiveness of the fabrication plans to create homogeneous and consistent coatings. Different engineering strategies have been designed such that controlled surface hydration is attained without interrupting the structural integrity of nanoparticles and drug encapsulation activity, and biological activity (Wang *et al.*, 2016). Nanoparticle composition, required hydration layer thickness and intended therapeutic use determine the choice of a suitable fabrication method. Surface grafting methods can be seen as one of the most popular methods of forming hydration layer coated nanoparticles. These methods consist of the covalent or noncovalent coupling of hydrophilic polymers to the existing nanoparticle surfaces. Covalent grafting offers robust and stable attaching of polymer,

Table 3: Experimental techniques used to characterize mucus penetration and transport behavior of hydration engineered nanocarriers.

Technique	Principle	Information Obtained	Application Relevance
Multiple particle tracking	Monitors nanoparticle movement in mucus matrix	Diffusion coefficient and mobility patterns	Determines mucus penetration efficiency
Fluorescence microscopy	Visualizes nanoparticle distribution in mucus layers	Spatial penetration and localization	Evaluates real time nanoparticle transport
Rheological analysis	Measures mucus viscoelastic properties	Interaction of nanoparticles with mucus microstructure	Predicts formulation performance in mucus environment
<i>In vitro</i> mucus diffusion models	Simulates physiological mucus barrier	Drug release and permeability characteristics	Screens formulation effectiveness
<i>Ex vivo</i> mucosal tissue studies	Uses isolated biological tissues	Penetration depth and tissue interaction	Provides physiologically relevant transport data
<i>In vivo</i> imaging techniques	Tracks nanoparticle distribution in living systems	Biodistribution and therapeutic targeting	Validates clinical translational potential

which leads to the permanence of physiological grafting of hydration layers. This enables a close regulation of polymer chains density and molecular orientation which respectively affect the stability of the hydration shell and the diffusion pattern of nanoparticles. Other noncovalent grafting techniques such as adsorption and electrostatic attachment provide less complicated fabrication processes and less chemical processing. Whereas noncovalent interactions can be less long term stable than covalent modification, they offer flexibility to tune surface properties and are often applicable to situations where it is necessary to have a reversible surface modification (Desai *et al.*, 2025).

Simple fabrication techniques have been of considerable interest as self-assembly techniques since they are simple and capable of producing uniform hydration enabled nanostructures. Under these strategies, the amphiphilic materials are spontaneously assembled into nanoscale during exposure to the suitable solvent environments. Hydrophilic parts of these materials are directed to the external aqueous environment and make surfaces that are hydrated, and hydrophobic parts make the structure stable and to encapsulate drugs. Self-assembly in nanotechnology enables the nanoparticle to be formed at the same time as the surface hydration transformation, and this enables easier processing and enhanced scale up (Kashapov *et al.*, 2020). Also, the techniques allow flexibility in modulating nanocarrier structure through changing of polymer composition and solvent conditions. Multilayered hydration coating on nanoparticle surfaces is a highly regulated technique of surface modification done in layer-by-layer. This method consists in the sequential deposition of oppositely charged material or chemically compatible material onto nanoparticles and leads to the formation of structured surface-layers with adjustable thickness and composition. The layer-by-layer assembly gives partial and exact control of the density of the hydration layers and the possibility to incorporate several functional materials into the coating. This technique enables optimization of hydration stability, targeting ability and drug release properties simultaneously because it is modular in nature, which allows customization of nanoparticle surface properties. The numerous processing cycles in the process can however make this process more time consuming in fabrication and need to be optimized carefully to achieve uniform coating (Ariga *et al.*, 2022). The modulation of surfaces with stimuli responsiveness strategies have also been researched in order to increase the versatility of hydration engineered nanocarriers. These systems utilize surface material that can change the hydration characteristics following environmental cues like the change of pH, ionic strength, or enzyme activity. The use of stimuli responsive coating on nanoparticles allows the nanoparticles to exhibit a stable state of hydration when penetrating the mucus and also allows the surface characteristics of the nanoparticles to be controlled when the nanoparticles reach target tissues. These adaptive surface engineering methods increase the specificity of drug delivery and therapeutic efficiency, since they allow

site selective behavior of nanoparticles (Canaparo *et al.*, 2019). Multi-surface engineering methods, whereby a combination of various fabrication methods is used to produce hydration layers, have proven to be viable in terms of optimization of the stability of hydration layers and the multifunctionality of nanoparticles. These techniques combine covalent grafting with self-assembly or multilayer coating approaches to produce composite surface formats that have the potential to offer better hydration, enhanced loading of drugs and target delivery properties. Mixed strategies also permit the use of both synthetic and natural hydrophilic compounds and realize nanocarriers of enhanced biological safety and mechanical strength. Combination of several fabrication methodologies tends to improve the performance of nanoparticles by overcoming the shortcomings of the single modification methods (Zhao *et al.*, 2022).

The outcome of the hydration engineered nanocarrier fabrication depends on a number of critical parameters such as polymer grafting density, uniformity of the coating, nanoparticle surface curvature, and processing conditions such as temperature and solvent composition. To obtain maximum surface coverage without interfering with the stability of the nanoparticles or the rate of drug encapsulation, it is necessary to optimize the procedure. Further, the method of fabrication should provide reproducibility and scalability in order to accommodate possible clinical translation and industrial manufacture (Chancellor *et al.*, 2019). Nanofabrication technologies are currently being enhanced to make the engineering of hydration layers more precise and efficient. The innovation of automated coating methods, microfluidic fabrication systems and scalable processes of conjugation of polymers have increased the capacity to fabricate hydration engineered nanocarriers that are of high quality and performance (Alexandre *et al.*, 2024). It is anticipated that further development of fabrication approaches can simplify the translation of hydration based nanocarrier systems to the clinical setting to aid the development of mucosal drug delivery technologies.

CHARACTERIZATION AND EVALUATION OF MUCUS PENETRATION

Engineered nanocarrier hydration development is anticipated to occur as a result of thorough characterization methods to assess their physicochemical characteristics and movement behavior across mucosal barriers. Mucus penetration needs to be accurately measured in order to predict *in vivo* performance and improve nanoparticle design. Different methods of analysis, imaging and modeling have been established to investigate nanoparticle mobility, contact with mucin network and overall efficiency of transport in mucus environment (Liu *et al.*, 2021). These testing techniques can give useful information on the efficiency of hydration layers formation and their contribution in improving the diffusion of nanoparticles. Preliminary screening

assays into nanoparticle mucus transport are often done using *in vitro* diffusion models. The models are usually based on artificial or purified mucin gels that are meant to replicate the structural and rheological properties of the natural mucus. The common methods to measure nanoparticle movement across mucus layers with time include diffusion chambers and membrane based permeation systems (Sedaghat *et al.*, 2023). With the aid of these experimental arrangements, the thickness of the mucus, level of hydration and the concentration of the nanoparticles can be manipulated in a controlled way so that the behavior of transport can be evaluated systematically. Despite the reproducible and cost effective analysis offered by *in vitro* diffusion models, *in vitro* diffusion models may not adequately estimate the complex composition and dynamic turnover properties of physiological mucus (Wright *et al.*, 2021).

The techniques of particle tracking have also become very sensitive techniques of direct observation of nanoparticle mobility in mucus matrices. These methods include the fluorescent or optical labelling of nanoparticles and measuring their dynamics by using advanced microscopic platforms. The measurement of quantitative parameters like diffusion coefficient, velocity of particles, and heterogeneity of transport can be achieved by tracing individual trajectories of the nanoparticles (Yildiz *et al.*, 2015). Particle tracking offers specific details about the interactions between nanoparticles and mucus on a microscale

level and can be used to compare the efficiency of transport of various surface modifications. The capability to visualize real time movement of nanoparticles in real time has contributed immensely to the realization of the interaction of hydration layers on diffusion of particles on mucin network. The structural and mechanical properties of mucus also extensively rely on the rheological and microrheological evaluation methods in the study of the interaction of nanoparticles during nanoparticle interaction (Huck *et al.*, 2019). Bulk rheological measurements determine the viscosity, elasticity, and strength of gels of mucus before and after the addition of nanoparticles. Such measurements aid to reveal whether nanoparticles modify the structure of mucus or cause aggregation that can result in changing the efficiency of transport. Microrheological methods, which are the study of the motion of probe particles in mucus, give local data of mucus microstructure and mechanical resistance to which nanoparticles are exposed. The techniques provide useful data about the gel point of hydration engineered nanocarriers and mucus rheology (Mao *et al.*, 2022).

Ex vivo mucus permeation models offer a more physiologically relevant model on nanoparticle transport. The models are based on freshly obtained mucus samples or excised mucosal tissues of biological origins. *Ex vivo* systems maintain native mucus composition, mucin diversity, enzyme content, and cellular composition, and as such provide a better predictive ability of *in*

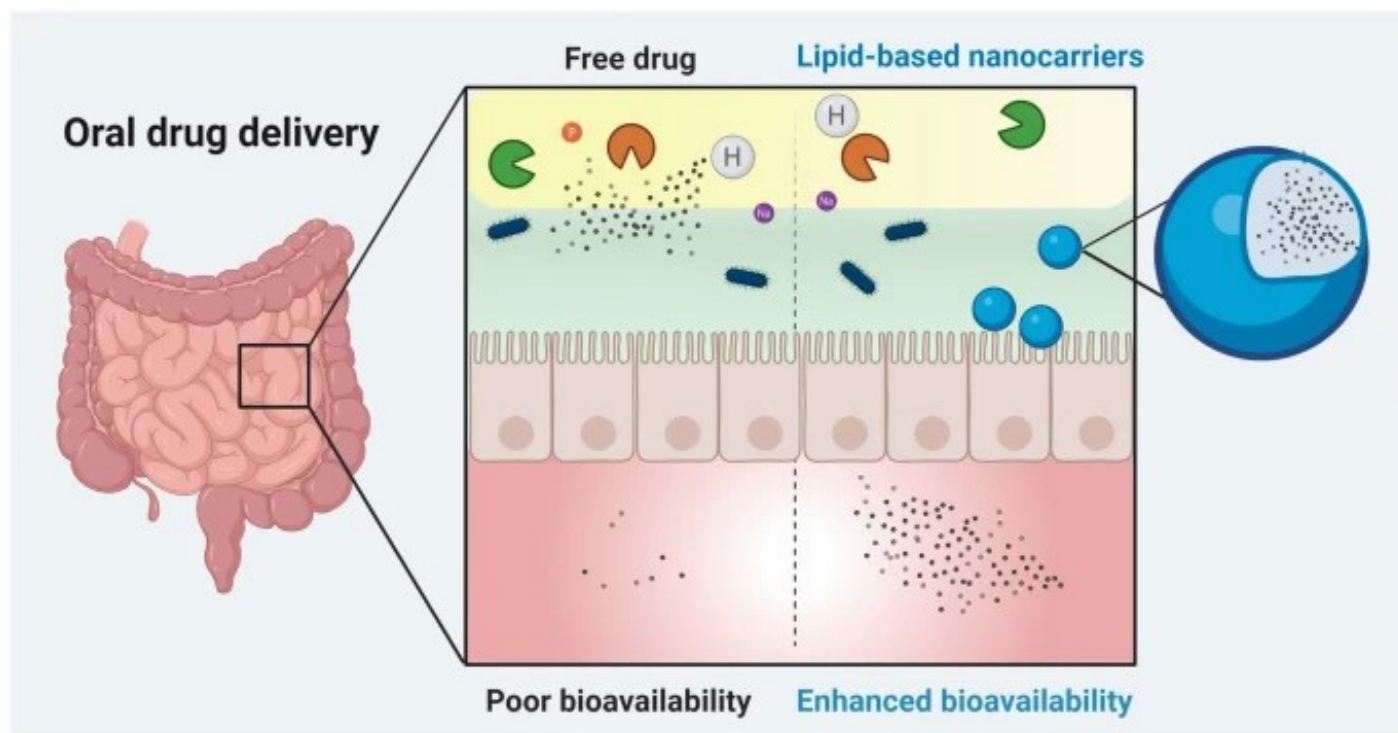


Figure 1: Schematic comparison of oral delivery of free drug versus lipid based nanocarriers. The left panel depicts conventional free drug administration, where drug molecules undergo degradation in the gastrointestinal environment and demonstrate limited epithelial permeation, resulting in poor bioavailability. The right panel illustrates lipid based nanocarriers encapsulating the drug within a lipid matrix, protecting it from degradation, enhancing membrane interaction, and promoting improved absorption across the intestinal epithelium, thereby increasing systemic bioavailability. Reproduced from the source (Plaza *et al.*, 2021).

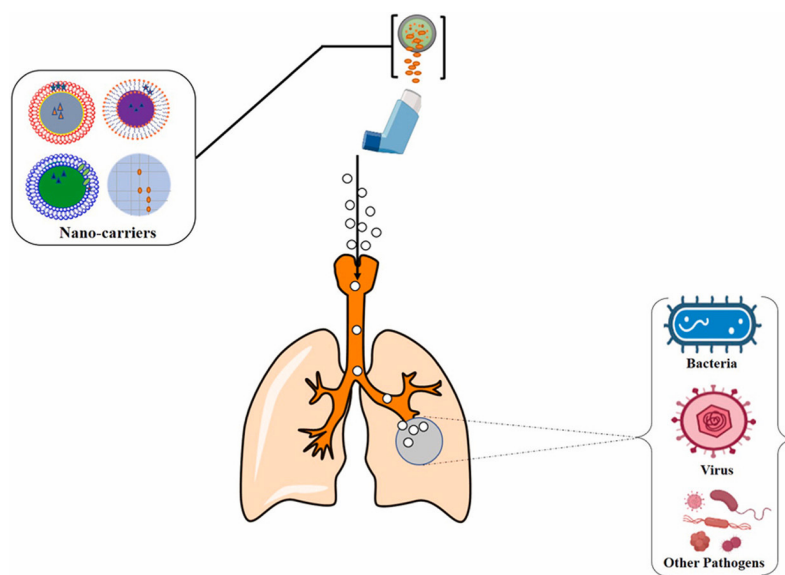


Figure 2: Schematic representation of nano-carrier based pulmonary drug delivery via inhalation. Aerosolized drug-loaded nanocarriers deposit within bronchial and alveolar regions of the lungs, where they release therapeutic agents at sites of infection or inflammation. The illustration highlights targeted delivery to respiratory pathogens, enabling improved local drug concentration and enhanced pulmonary therapeutic outcomes. Reproduced from the source (Kumar *et al.*, 2023).

vivo performance. The tissue based permeation models enable the assessment of nanoparticle diffusion within the mucus followed by epithelial transportation to be conducted simultaneously (Wright *et al.*, 2023). Although *ex vivo* models can be physiologically relevant, there can be variability in *ex vivo* models because of the difference in mucus composition of biological samples, and this necessitate critical experimental standardization. Developed imaging modalities have also enabled a great deal of visualization and analysis of transport of nanoparticles through mucus layers. The use of high-resolution microscopy also allows the distribution of nanoparticles, their depth of penetration and the mucin structure interaction to be observed in detail. Confocal imaging could be used to reconstruct nanoparticles movement in mucus matrices to create three-dimensional images which could give spatial distribution information that could be used in the analysis of diffusion. Also, nanoparticle mobility may be measured using fluorescence recovery techniques, which involve measuring the redistribution of a fluorescence after local photobleaching. Those imaging methods offer visual confirmation of hydration layer-mediated nanoparticle penetration and can be used to evaluate quantitatively the transport (Meziu, 2025).

The use of computational modeling and simulation studies has proved useful in the prediction of nanoparticle behavior in the mucus environment. The diffusion of nanoparticles under different physiological conditions can be estimated by mathematical models that involve parameters of particle size, surface chemistry and mesh structure of mucus. Computational methods can also speedily screen design parameters of nanoparticles and give mechanistic understanding of particle transport dynamics that would otherwise be challenging to acquire experimentally (Roy and Bhattacharjee, 2025). Combining experimental data

with computational modeling can prevent biases in prediction and rational design of hydration engineered nanocarriers. To achieve a complete characterization of mucus penetration the combination of various analytical methods is necessary in order to have credible and physiologically significant results. Diffusion, particle tracking, rheological analysis, imaging analysis, and computational modeling are combined to have a comprehensive view of nanoparticle transport mechanisms. This type of evaluation which is multidimensional is required to maximize hydration-driven nanocarrier systems and to achieve reliable performance in various mucosal environments. The further development of analytical technologies is likely to further enhance the possibilities to analyze nanoparticle-mucus interactions and facilitate the establishment of highly efficient platforms to deliver drugs to the mucosal surface (Jia *et al.*, 2021).

THERAPEUTIC APPLICATIONS

Engineered nanoparticles (hydrated) have shown great possibilities in the enhancement of drug delivery across the mucosal surfaces through the diffusion of nanoparticles and the efficiency of drug absorption. The capacity of hydration layers to reduce mucin interactions can permit such nanocarriers to attain enhanced tissue accessibility, controlled drug release as well as improved therapeutic performance. Oral and pulmonary drug delivery are amongst other prominent avenues of mucosal drug delivery that hydration-based nanoparticles systems have offered massive benefits. The delivery pathways pose unique physiological threats that are easily addressed by means of hydration based surface engineering solutions (Liu *et al.*, 2021). The route of administration that is most preferable is oral drug delivery because of its convenience, patient suitability, and cost

efficiency. Nevertheless, the gastrointestinal environment poses several challenges, among which are enzymatic degradation, unpredictable pH conditions, mucus mediated transport barriers, which restrict drug absorption. Hydrated nanocarriers can improve oral delivery of drugs through increased diffusion across gastrointestinal layers of mucus and hence accessibility to epithelial absorption sites (Azman *et al.*, 2022). The shell of hydration around nanoparticles causes less nonspecific interactions with mucin glycoproteins and allows free distribution across mucosal surfaces. This increased drug residence at the epithelial interface which contributes to higher drug absorption and bioavailability Figure 1 illustrates a comparative schematic representation of conventional free drug administration and lipid based nanocarrier mediated delivery in the gastrointestinal tract. In the free drug scenario, the drug molecules are exposed to the harsh luminal microenvironment, including acidic pH, enzymatic degradation, and limited membrane permeability, resulting in premature degradation and poor epithelial transport. The dispersed drug particles exhibit low stability and minimal interaction with the absorptive epithelium, ultimately leading to reduced systemic bioavailability. In contrast, lipid based nanocarriers encapsulate the drug within a protective lipid matrix, shielding it from chemical and enzymatic degradation. These nanocarriers facilitate enhanced interaction with the epithelial membrane, promote improved permeability, and enable controlled drug release at the absorption site. Consequently, improved epithelial transport and enhanced bioavailability are achieved.

Nanocarrier systems under hydration are especially useful in delivery of drugs and macromolecule therapeutics that are not readily soluble and possess low permeability across gastrointestinal barriers (Talegaonkar and Bhattacharyya, 2019). Hydration of nanoparticles by encapsulation preserves sensitive therapeutic molecules by preventing degradation by the digestive tract enzymes and chemical instability. Also, improved mucus penetration capacity of hydration engineered nanoparticles includes higher transportation of biologics including peptides, proteins and nucleic acid based therapeutics, which conventionally have low bioavailability orally. The enhanced stability and diffusion properties of systems offered by the hydration layers, as well as lead to sustained drug release and improved systemic therapeutic effects after oral administration. Another application field available of hydration engineered nanocarriers is pulmonary drug delivery, especially in respiratory disease treatment (Cojocaru *et al.*, 2024). The respiratory tract offers high absorptive surface area and high potential systemic absorption hence makes an attractive route of local and systemic therapy. But airway mucus provides a dynamic protection which quickly entraps and removes the inhaled particles due to mucociliary clearance processes. The engineered nanoparticles which are hydrated, show increased penetration through the airways mucus by decreasing the adhesive forces and increasing

rapid diffusion into the underlying tissues of the epithelia. This enhanced the mucus transport and, as a result, enhances an efficient deposition of drug at the target sites in the respiratory tract. Hydration-based nanocarrier pulmonary drugs delivery has high therapeutic benefits in controlling respiratory diseases that are associated with excessive secretion of mucus and abnormal rheology. Increased mucus penetration increases the ability to distribute drugs throughout the airway tissues improving the treatment of inflammatory and infectious pulmonary disease. The delivery efficiency of aerosolized drug formulations can also be promoted by hydrated nanoparticles which stabilize nanoparticles and prevent aggregation of nanoparticles during inhalation (Muralidharan *et al.*, 2014). In addition, enhanced hydration engineered nanoparticles mobility facilitates deep lung deposition as well as extended retention time of drugs at disease sites, which has helped to increase therapeutic efficacy Figure 2 illustrates the nano-carrier mediated pulmonary drug delivery process following aerosol administration. Drug-loaded nano-carriers are dispersed through an inhalation device and transported into the respiratory tract, where they deposit within bronchial and alveolar regions. After deposition, the nanocarriers localize at infected or inflamed lung tissues and release encapsulated therapeutics in close proximity to respiratory pathogens such as viruses and bacteria. The schematic emphasizes targeted pulmonary delivery, enhanced local drug concentration, and improved therapeutic efficiency while minimizing systemic exposure.

Nanoparticle system based on hydration also allow targeted drug delivery approaches since they allow them to interact with particular epithelial receptors after mucus penetration. This has enabled the creation of versatile drug delivery systems incorporating mucus permeation with cellular targeting and regulated drug delivery. These combined methods lead to increased accuracy of therapeutic treatments, reduced exposure of off target drugs, and, consequently, to better safety and efficacy of treatments. Such versatility is evidenced by the flexibility of hydration engineered nanocarriers throughout various mucosal environments to meet a wide variety of therapeutic needs. Although hydration engineered nanocarriers have shown promising therapeutic results, there is still research to be done to streamline the efficacy of drug loading, dosing, and long-term safety. The mucus varies between patients and disease conditions, which can affect the efficiency and safety of nanoparticles in transport and therapy. Further investigation into the properties of patient specific mucus and the development of nanoparticles that are patient-specific at the molecular level is likely to enhance the clinical usefulness of mucosal drug delivery systems that rely on hydration. Altogether, hydration engineered nanocarriers have a great potential to enhance treatment results in oral and pulmonary drug delivery (Kim *et al.*, 2025). Their capacity to increase the nanoparticles movement, protect therapeutic cargo, and improve the absorption of drugs makes them noticeable in

overcoming significant constraints related to traditional mucosal drug delivery methods. The further developments in the field of hydration-based nanoparticles engineering are likely to increase the clinical possibilities of mucosal nanomedicine considerably.

SAFETY, REGULATORY AND TRANSLATIONAL CONSIDERATIONS

Surface hydration based nanocarriers have become superior platforms of improving drug delivery across mucosal barriers because of their capacity to reduce adhesive mucus glycoprotein interactions and speedy diffusion through mucosal networks. Hydrated nanoparticles used in oral drug delivery can entrap therapeutic molecules to prevent enzymatic degradation and adverse intestinal environments and enhance penetration of the mucus and absorption by the intestinal epithelia (Ejazi *et al.*, 2023). This method comes in handy especially with drugs that have limited solubility, low permeability and stability in the gastrointestinal tract, hence, increasing systemic bioavailability and therapeutic efficacy. Also, hydration-mediated surface modification improves the homogeneous distribution of intestinal mucosa and the controlled release of the drugs, which further increases the treatment outcome. Hydrated nanocarriers are useful in pulmonary drug delivery to allow transport across the viscoelastic airway mucus barrier and to allow increased deposition and distribution by the lung tissues. These systems have shown promise towards enhancing therapeutic efficacy of respiratory disorders due to their ability to enable enhanced retention of drugs, targeted delivery and prolonged release of drugs. In addition to this, hydration-based surface engineering lessens mucociliary clearance and increases cellular uptake, thus promoting better local and systemic therapeutic responses. Altogether, hydration mediated nanocarrier design is a potentially important approach to overcoming mucosal transport barriers and improving next generation drug delivery vehicles (Jawadi *et al.*, 2022).

FUTURE DIRECTIONS

Future investigations should prioritize understanding the heterogeneity of mucus composition among different patient populations and pathological conditions, as such variability presents substantial challenges in designing broadly effective nanocarrier systems. Addressing this complexity will require the rational development of stimuli responsive hydration interfaces capable of dynamically adapting to physiological and microenvironmental fluctuations. In parallel, comprehensive long term toxicological assessments are essential to establish the safety profile of emerging zwitterionic and biomimetic materials intended for clinical use. Moreover, the translation of these advanced surface engineered nanoparticles from laboratory scale to industrial production demands the establishment of robust,

reproducible, and economically viable manufacturing strategies, which currently represent a major bottleneck in clinical implementation.

CONCLUSION

Hydration driven nanocarrier design represents a transformative advancement in mucosal drug delivery by addressing the inherent limitations associated with mucus mediated drug transport. By engineering nanoparticle surfaces capable of forming stable hydration layers, it is possible to significantly reduce adhesive interactions with mucin networks and facilitate enhanced diffusion across complex mucosal barriers. This strategy has demonstrated considerable promise in both oral and pulmonary drug delivery, where improved drug stability, enhanced epithelial uptake, prolonged residence time, and controlled drug release collectively contribute to superior therapeutic performance. The incorporation of hydrophilic and zwitterionic surface modifications has further expanded the functional versatility of mucus penetrating nanocarriers, enabling improved delivery of a wide range of therapeutic agents including small molecules, peptides, proteins, and nucleic acid-based therapeutics. Despite these advancements, several challenges remain, including the need for improved understanding of long-term safety, large scale manufacturing feasibility, and regulatory standardization for clinically viable formulations. Additionally, variability in mucus composition under physiological and pathological conditions continues to present formulation challenges that require further investigation. Future research focusing on stimuli responsive hydration layers, personalized nanocarrier design, and integration of advanced characterization techniques is expected to accelerate clinical translation. Overall, hydration mediated surface engineering offers a robust and scientifically validated approach for enhancing mucosal drug transport and holds substantial potential for the development of next generation drug delivery systems with improved patient outcomes.

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ABBREVIATIONS

GIT: Gastrointestinal tract; **MPT:** Multiple particle tracking; **MW:** Molecular weight; **PEG:** Polyethylene glycol; **PEO:** Polyethylene oxide.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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