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Review Article

An Overview of Mucoadhesive Drug Delivery Systems: Design, Evaluation, and Therapeutic Potential

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ABSTRACT

Mucosal drug delivery systems (MDDS) are groundbreaking drug delivery systems which deliver prolonged drug retention in the mucosa, improved bioavailability, and pharmacologic effect targeting. The systems utilize unique properties of the mucus gel layer—viscoelastic protective covering for epithelial membranes lining different areas of the body—to ensure close contact of the drug delivery system and target membranes. The current paper aims at describing the principles of pharmacology and science of MDDSs in detail, namely the anatomy and physiology of the systems, currently available mechanisms, novel approaches, and pharmacotechnology principles for polymers and formulations selections. A variety of mucoadhesive polymers, from traditional hydrophilic polymers such as HPMC and carbopol to innovative ones like thiomers, lectins, and stimuli-sensitive co-polymers, depending on their adhesive ability, applicability, and efficacy, are described. Drug delivery systems discussed in the paper include buccal tablets, in situ gel formulations for nasals, ocular inserts, bioadhesive rings for vaginals, suppositories for the rectum, and nanoparticles for the gastrointestinal tract. Tests for determination of mucoadhesion properties include rheometry, texture profile analysis, tensile strength measurements, wash-off method, ex vivo permeation studies, and imaging. The application of mucoadhesives in treating several diseases like vaccine delivery using oral mucosa, peptide absorption via nasal route, eye inflammation management, reproduction, and colorectal cancer chemotherapy using chemotherapeutic drugs is highlighted. Besides, the latest developments concerning mucoadhesive nanoparticles, 3D bioadhesive printing, artificial intelligence-assisted drug discovery process, and use of CRISPR technology as gene delivery vehicles for mucosal membranes are also presented. Regulatory issues, challenges in scaling up manufacturing, and the commercialization status of mucoadhesives are addressed. Finally, important knowledge gaps and future outlooks are described.

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INTRODUCTION

The search for drug delivery technologies that can solve the challenges in terms of pharmacokinetics of conventional oral and parenteral medications has led to significant research in the development of bioadhesive and mucoadhesive drug delivery methods. In fact, mucoadhesion, which is understood as a phenomenon of adhesion between the drug delivery device and mucous membrane on the basis of physical-chemical or biological mechanisms, is one of the promising methods that provides flexibility and feasibility in improving drug bioavailability, increasing its retention time, achieving a targeted effect, and ensuring patient compliance. [1,2]

The mucoadhesion phenomenon was first studied systemically in the 1980s through significant studies conducted by Nagai and Machida, who demonstrated that bioadhesive polymeric substances could effectively be used for delivering drugs to the buccal and rectal membranes. The last forty years have seen tremendous progress in developing mucoadhesive systems due to the advances in polymer science, nanotechnology, mathematical modeling, and increased knowledge regarding the properties of the mucus barrier. Now mucoadhesive devices are far more than just simple tablets or gels; they can include advanced nanoparticulate systems, programmable hydrogels, mucoadhesive microemulsions, and other bioresponsive delivery systems [4,5].

The reasons for developing mucoadhesive drug delivery are complex. On one hand, the mucosal membranes, consisting of the buccal, nasal, ocular, vaginal, rectal, and GI membranes, present a large (approximately 400 m2) accessible surface suitable for drug absorption, bypassing the first-pass effect [6]. On the other hand, many of the pathologies affecting the mucous surfaces, including ulceration of the mouth cavity, inflammatory diseases of the digestive tract, dry eye syndrome, and sexually transmitted infections benefit from mucoadhesive drug delivery, providing local drug concentration [7]. Finally, the growing prevalence of chronic diseases requiring prolonged pharmacotherapy makes it necessary to find dosage forms with a minimal number of administrations, which would not cause systemic toxicity.

Mucus consists of a complex hydrogel structure with water (95%), mucin glycoprotein (0.5-5%), lipids, electrolytes, enzymes, immunoglobulin sIgA, and dead cells [8]. The major constituents of mucus are mucin glycoproteins, which are high molecular weight compounds (0.5-40 MDa) with numerous carbohydrates side-chains. Knowledge of the biophysics of mucin-polymer interaction became crucial in development of mucoadhesive formulations; however, constant renewal of mucus (4-5 h in the gastrointestinal tract) remains a challenging task [9].

The purpose of this review is to collate the existing information on mucoadhesive delivery systems in terms of their mechanism of action, technology, and clinical use. Through the analysis of polymers used, the design of dosage forms, analytical techniques, and pharmacological applications, an attempt has been made to develop a systematic reference source for investigators, formulation scientists, and healthcare professionals involved in drug delivery research. Special emphasis has been laid on innovative technologies such as nanomucoadhesive systems, smart biopolymers, intelligent formulation through artificial intelligence, and 3D printing of mucoadhesive dosage forms. [10,11].

2. Anatomy and Physiology of Mucosal Surfaces

2.1 General Architecture of Mucosal Membranes

Mucosa membranes are special types of epithelial lining that form the boundary between the body and the outside world. Though mucosal membranes differ anatomically, they have a common organizational structure consisting of the mucus layer, the epithelium of different thicknesses and compositions, a well-vascularized lamina propria containing much connective tissue and immune cells, and the muscularis mucosae [12]. The mucus layer secreted by the goblet cells and special glands forms a viscoelastic gel matrix, which acts as a lubricant for the epithelial layer, diffusion barrier, and part of the innate immunity.

The mucus layer is organized as a dynamic bilayer structure in most anatomical locations, where the outer layer is loosely attached to the luminal side and the inner layer is tightly bound to the epithelial layer. The physical and chemical characteristics of the mucus layer, such as its viscosity (about 100–10,000 mPa·s), gel strength, and pore size (about 100–500 nm in the intestine), are highly variable depending on anatomy, health conditions, age, and hormones. They are essential for developing mucoadhesive drug delivery systems [13].

2.2 Buccal Mucosa

The buccal mucosa forms the inner part of the cheeks, which is lined with a non-keratinized stratified squamous epithelium of about 500-600 µm thickness that rests on a basement membrane and highly vascular lamina propria. Lipid-based permeability barriers are highly expressed in buccal tissue, characterized by the presence of membrane structures rich in ceramide and glycosylceramide in the uppermost layers of cells, despite being a non-keratinized epithelium having relatively higher permeability than keratinized mucosa of hard palate and gingiva [14]. The high flow rate of saliva, estimated to be around 0.5-2 L/day, and the forces of mouth opening/closing actions make it difficult to achieve good retention using mucoadhesives; however, the buccal delivery system provides a way out to avoid first-pass effect by delivering the drugs directly into the bloodstream via internal jugular vein [15].

2.3 Nasal Mucosa

Nasal cavity, covering an area of about 150-180 cm2, is mainly covered with pseudostratified ciliated columnar epithelium in the respiratory area and a layer of mucus around 10-15 µm thick in the nasal mucosa, which is continuously replaced in 10-15 min through mucociliary transport process. Olfactory area of the nasal mucosa offers a special route for drug passage to brain from nose through olfactory neurons and trigeminal nerve without encountering the BBB—a particular drug delivery strategy with great pharmaceutical significance for brain drug delivery [16]. The nasal mucosa is well perfused with blood through nasal arterial plexus, providing fast systemic uptake of the drug after penetrating the epithelial barrier. Goblet cell distribution and mucus composition may be significantly affected in some diseases like rhinitis, sinusitis, and cystic fibrosis, requiring a reformulation strategy accordingly.[17]

2.4 Ocular Mucosa

The mucous membranes in the eyes that include conjunctiva, corneal epithelium, and internal lid membranes form a complex and very sensitive area of administration. The conjunctiva is one of the mucous membranes that have goblet cells that secrete the ocular mucin that forms a layer in the PTF that is about 7 to 10 microns. The PTF is regenerated every 2 to 10 minutes while nasolacrimal drainage eliminates about 75% of the applied eye drops within 5 to 10 minutes; hence,

ophthalmic preparations have been proved to be very inefficient [18]. Mucoadhesive ocular drug delivery systems seek to increase the residence time of the PTF, increase corneal contact, and increase bioavailability which would be crucial for cases like glaucoma, dry eye condition, and ocular infections. The conjunctival epithelium unlike the corneal epithelium is not well organized and allows both transcellular and paracellular absorptions making it a preferred target area for mucoadhesive inserts and hydrogels [19].

2.5 Vaginal Mucosa

The vagina is lined with a non-keratinized squamous epithelium that is about 200-400 µm thick and coated with mucus whose nature, consistency, and pH vary considerably within the menstrual cycle, pregnancy, and menopause periods. The pH of the vagina can be between 3.5-4.5 for women of reproductive age (due to lactobacilli-dependent lactic acid production) and 6.0-7.0 for post-menopausal women, affecting the ionization of polymers and mucoadhesion properties [20]. The high vascularity of the vagina contributes to systemic absorption and local immune response to drugs, making this route of administration useful in contraception, hormone replacement therapy, antifungal drug delivery, and pre-exposure HIV prophylaxis. The cyclic change of luminal fluid content (about 1-5 mL), together with the effect of enzymes such as proteases and glycosidases [21].

2.6 Gastrointestinal Mucosa

The GI tract constitutes the heterogenous mucosal surface available for drug delivery, with its esophagus, stomach, small intestine, and large intestine each featuring different structures of the epithelium, composition of mucus, pH level, presence of enzymes, and concentration of lymphoid tissues. With the villi and microvilli contributing to its surface area of 200-400 m^2, the small intestinal mucosa becomes the primary organ responsible for absorption of nutrients and drugs. Intestinal mucus gel is represented as the bilayer in the colon (tight inner layer of 100 µm and loose outer layer of 700 µm) as well as the single loose layer in the small intestine; turnover of mucin occurs via MUC2 secretion by goblet cells [22]. Diseases including Crohn's disease and ulcerative colitis have impact on the properties of the mucus, which influences the behavior and rationale of mucoadhesives in the mouth [23].

3. Mechanisms and Theories of Mucoadhesion

3.1 Stages of Mucoadhesion

The conventional model for Mucoadhesion can be described in terms of two consecutive phases, namely the contact phase and the consolidation phase [24]. In the contact phase, the mucoadhesive system is physically brought into contact with the mucosa through mechanical insertion (buccal tablets), gravity (eye drops), or peristalsis (oral preparations). In the consolidation phase, water acts as a trigger for the mucoadhesive system, facilitating penetration by the polymer and mucin chains. The consolidation phase is energy-driven, involving simultaneous interactions, the importance of which varies according to the chemical structure of the polymer and the nature of the environment.

3.2 Electronic Theory

According to the electronic theory, mucoadhesion occurs due to electrostatic interaction between the mucoadhesive substance and the mucosa as long as they have different electrical charges [25]. Since mucus has a negative charge due to sulfate and carboxylate residues of mucin glycoprotein, mucoadhesion between cationic polymers, like chitosan, and mucosa can be strong. However, this

theory fails to explain how neutral polymers adhere, since mucoadhesion depends not only on electrostatic interaction but also on other physical factors, including mechanical contact time and humidity.

3.3 Adsorption Theory

The mucoadhesive behavior, according to the adsorption theory, depends on the creation of secondary bonds between the material and mucosal surface [26]. Such secondary bonds involve hydrogen bonding, van der Waals bonding, hydrophobic interactions, and electrostatic interactions. In particular, the hydroxyl groups of polyols (PVA, cellulose-based polymers), as well as carboxylic groups of polyacrylates (carbopol), create hydrogen bonds with the oligosaccharide side chain of the mucin due to high content of hydroxyl groups.

3.4 Diffusion Theory

According to the diffusion mechanism described by Peppas and Buri, mucoadhesion occurs due to the interaction between the interdiffusing chains of the polymer with the mucin glycoprotein chains, forming an entangled network structure of physical interactions which cannot be separated easily [27]. The degree of interpenetration (l) can be defined as follows: $l \approx (D \cdot t)^{0.5}$, where D – diffusion coefficient and t is time of contact. The maximum interdiffusion occurs when solubility parameters of both the adhesive polymer and mucin have similar values, as well as the high mobility of molecules. This mechanism works best for flexible and linear polymers.

3.5 Wetting Theory

Wetting theory is a theory that uses analysis of contact angle and surface energy to determine the adhesion process on the basis of thermodynamic principles. In general, adhesion would be spontaneous in situations where the work of adhesion, which is the amount of energy required to create an interface separation, exceeds the cohesive energy of one of the substances involved [28]. Surface energy compatibility between the polymer and mucus can be achieved through surfactant and plasticizer addition, leading to reduced interfacial tension. However, this theory is somewhat lacking in practicality.

3.6 Fracture Theory

The fracture theory is especially significant in terms of analyzing the mechanical strength of mucoadhesion and serves as the foundation for texture profile analysis and determination of tensile strength [29]. According to this theory, adhesive strength refers to the stress needed to separate an adhesive substance from the mucosal membrane after establishing the connection between them. Fracture strength (σ f) can be determined by its correlation with the elastic modulus and critical crack length of the interface. Such a parameter allows one to compare different formulations of drug delivery systems effectively.

3.7 Mucoadhesion at the Nanoscale: Emerging Perspectives

Significant developments in atomic force microscopy (AFM), quartz crystal microbalance with dissipation monitoring (QCM-D), and molecular dynamics simulations have provided unique insights into the mucoadhesion process on a nanomolecular level [30]. The QCM-D studies have revealed that the viscoelastic properties of adsorbed mucin layers contribute significantly to polymer-mucin binding energy, whereas AFM force spectroscopy has allowed for determination of adhesion force in the range of piconewtons between individual polymer chains and mucin glycoproteins. Molecular dynamics simulation has

shed light on the thermodynamic processes involved in hydrogen bond formation between chitosan polymers and mucin proteins and also explained the role of water molecules as bridging agents [31].

4. Mucoadhesive Polymers: Classification and Properties

4.1 Classification Overview

The mucoadhesive polymers form the basis of bioadhesive formulations, which can be divided into categories based on their source (natural, semi-synthetic, and synthetic), charge (anionic, cationic, and nonionic), mode of adhesion (physical or conventional, thio-polymers/covalent, and receptors/lectins), and generation (generation one: non-specific, generation two: functionalization on surface, generation three: stimuli-responsive) [32,33]. The choice of appropriate polymers is based on various aspects like mucoadhesivity, swelling capability, pharmacological activity, biocompatibility, biodegrade

Table 1. Classification and Key Properties of Major Mucoadhesive Polymers

Polymer	Type	Charge	Mucoadhesive Mechanism	Key Applications
Carbopol (PAA)	Synthetic	Anionic	H-bonding, chain entanglement	Buccal, vaginal, ophthalmic
HPMC	Semi-synthetic	Nonionic	H-bonding, swelling	Oral, buccal, ophthalmic
Chitosan	Natural	Cationic	Electrostatic, H-bonding	Nasal, buccal, ocular, GI
Sodium Alginate	Natural	Anionic	H-bonding, ionic crosslinking	GI, buccal, wound
Hyaluronic Acid	Natural	Anionic	H-bonding, receptor-mediated	Ocular, nasal, vaginal
Thiolated Chitosan	Semi-synthetic	Cationic+thiol	Disulfide bonds, covalent	Buccal, nasal, GI
Thiolated PAA	Synthetic	Anionic+thiol	Disulfide bonds, H-bonding	Buccal, vaginal, ocular
Gantrez (PMVE/MA)	Synthetic	Anionic	H-bonding, anhydride reactivity	Buccal, oral
Lectin-conjugated polymers	Synthetic/ natural hybrid	Variable	Receptor-mediated (carbohydrate)	Intestinal, lung, nasal
PVP	Synthetic	Nonionic	H-bonding, hydration	Ophthalmic, buccal
Pectin	Natural	Anionic	H-bonding, chain entanglement	Colonic, buccal
Xanthan gum	Natural	Anionic	H-bonding, swelling	Ophthalmic, buccal, GI

4.2 First-Generation Mucoadhesive Polymers

4.2.1 Polyacrylic Acids (Carbopol/Carbomer)

Polyacrylic acids, available commercially under the trademarked name of Carbopol (and called Carbomer according to the USP classification system), are some of the best studied and most utilized mucoadhesive polymers. These polymers, which are cross-linked derivatives of acrylic acid, are extremely hydrophilic, and adopt highly swelled and coiled configurations at physiological pH, which allows maximum availability of their hydrogen bond donor sites (carboxylate groups) for binding to mucin [34]. The most commonly used commercial formulations are Carbopol 934P, 971P, and 974P. Some major drawbacks include dose-related toxicity in large amounts, interference

with intestinal P-glycoprotein transport, and susceptibility to electrolyte-dependent viscosity changes, making it difficult to incorporate into formulations with ionic compounds [35].

4.2.2 Cellulose Derivatives

Hydroxypropyl Methylcellulose (HPMC), Hydroxypropyl Cellulose (HPC), Hydroxyethyl Cellulose (HEC), and Sodium Carboxymethyl Cellulose (NaCMC) represent examples of semi-synthetic cellulose ethers that have already been proved for their mucoadhesive behavior through hydrogen bonding interaction between hydroxyl groups of the polymer and oligosaccharide moieties of mucin [36]. Hydroxypropyl Methylcellulose is commonly utilized as a component of buccal tablets owing to its swelling-controlled drug delivery, biocompatibility, and abundant use in orally administered preparations with approval by regulatory bodies. Sodium Carboxymethyl Cellulose is often found in composite mucoadhesive formulations due to its ionic nature and gelling abilities.

4.2.3 Chitosan

Amongst cationic polysaccharides, chitosan, which is a deacetylated form of chitin derived from the exoskeletons of crustaceans and, more recently, fungi, is the one that has been widely studied in the context of mucoadhesion. Due to the presence of primary amines (pKa ≈ 6.2 – 6.5), chitosan gets protonated under conditions of low pH (< 6.5) in mucus, which results in the attraction between the positively charged chitosan and the anionic groups of sialic acid and sulfates in mucin [37]. Besides its mucoadhesive properties, chitosan can increase mucosal permeability via reversible disruption of tight junctions facilitated by interaction with claudins-4 and occludin proteins. The increased permeability of peptide drugs, vaccines, and genetic material was observed with nano- and micro-chitosan formulations when tested on buccal, nasal, and intestinal membranes in animal studies [38].

4.3 Second-Generation: Thiomers (Thiolated Polymers)

Thiomers constitute an innovative step in mucoadhesive polymers synthesis, developed by Andreas Bernkop-Schnürch et al. Thiomers are generated via covalent conjugation of thiol-containing ligands including cysteine, thioglycolic acid, N-acetylcysteine, and 4-mercaptobenzoic acid to backbone of polymers including chitosan, polyacrylates, sodium alginate, carboxymethyl cellulose, and pullulan [39]. Thiomers' thiol groups establish covalent disulfide linkage with cysteine-rich sequences on mucins resulting in mucoadhesive interactions up to 2–140-fold stronger than those generated by unconjugated forms based on tensile strength measurements. The formation of a covalent linkage between thiomers and mucins gives them a special

In addition to mucoadhesivity, thiomers also show permeation facilitation by inhibiting protein tyrosine phosphatase and efflux pump inhibitors (P-gp and MRP2) through non-glutathione pathways, thereby achieving 2-10 times increase in mucosal permeability of hydrophilic macromolecules like calcitonin, insulin, and low molecular weight heparin in preclinical studies [41]. S-protected thiomers—containing S-sulfo or S-nitrosothiols as protecting groups to avoid unwanted disulfide bond formation—are also found to show better stability and mucoadhesion. However, the regulatory pathway for thiomers is still being debated, considering that certain thiol-conjugated polymers need toxicity assessment in preclinical studies to ensure adequate safety margin for prolonged mucosal interaction.

4.4 Third-Generation: Stimuli-Responsive and Smart Polymers

The most recent advancement in mucoadhesive polymers includes environmental responsiveness in their design, which allows them to undergo controlled gelation, swelling, surface exposure, or drug release in the presence of a particular stimulus found in the targeted mucosal site [43]. Temperature-responsive polymers (e.g., poloxamers, PNIPAM, PLGA-PEG-PLGA triblock copolymers) change state from solution to gel phase when exposed to body temperature, allowing easy delivery as liquids with the formation of gels on mucosal membranes. pH-responsive polymers (e.g., Eudragit L/S series, chitosan-PAA polyelectrolyte complexes) show swelling-dependent mucoadhesiveness, which is customizable for particular regions of the GI tract or an acidic tumor environment [44]. Redox-responsive thiomers and ROS-activated formulations provide stimulus-specific drug delivery for inflamed mucosal sites. The combination of two stimuli-responsive polymers (e.g., temperature- and pH-responsive PNIPAm-g-chitosan) increases specificity. Research is now focusing on light-responsive mucoadhesive systems based on photoswitches such as azobenzene or spiropyran moieties [45].

5. Formulation Design Strategies

5.1 Principles of Mucoadhesive Formulation Design

A rational approach to designing mucoadhesive formulations demands the optimal balance between the mucoadhesive properties of the formulation, the physicochemical properties of the drug substance, the mechanism of drug release, the tolerability at the targeted mucosa, and manufacturability [46]. The formulator needs to have a comprehensive understanding of the nature of the mucosal target site in terms of the nature of the mucin present and the mucus secretion rate, the nature of the mucosal epithelium, the pH of the medium, the enzymes present in the medium, and the volume of the medium—the factors that play a significant role in determining the behavior of the polymer and its permeation across the mucosa.

The polymer concentration is one of the most important formulation factors that must be determined in a particular formulation and mucosal route combination. Below the critical level of polymer concentration, there will be insufficient entanglements of chains as well as insufficient interactions at the surface interface to form a bond, whereas above the critical level, there will be excessive cross-linking density, which will make the polymers immobile, making it difficult for the polymers to diffuse into the mucin molecules. This optimum range varies between 0.5–4% w/w for carbopol, 1–5% for HPMC, and 0.1–1% for chitosan. The plasticizers such as polyethylene glycols and propylene glycols are usually added in some formulations to manipulate the glass transition temperature of the polymers. [48].

5.2 Mucoadhesive Nanoparticulate Systems

Various nanoparticulate mucoadhesive carriers such as polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), dendrimers, and nanoemulsions have gained much attention from researchers due to their ability to overcome several challenges faced by mucosal delivery such as insolubility of the drugs, fast mucosal clearance, enzymatic degradation, and poor permeation through the epithelium [49]. The use of mucoadhesive polymers to coat or functionalize nanoparticulate carriers exploits both the drug loading and the permeation potential offered by nanoparticulate technology along with the retention capacity of

mucoadhesion. For instance, chitosan-coated PLGA nanoparticles show 3-8-fold increase in GI residence time as well as oral bioavailability of peptides and proteins [50].

The key difference is between mucoadhesive formulations, which bind to the mucus layer, and mucus penetrating particles (MPPs) that are engineered to have low binding affinity and therefore diffuse through the mucus layer rapidly to reach the underlying epithelium [51]. The conventional mucoadhesive nanoparticles may get entrapped in the loose mucus layer covering the epithelium and be removed with it, thus possibly limiting their effectiveness as an epithelial absorption system. On the other hand, MPPs, usually with high PEG coating density to reduce hydrophobic and electrostatic interactions with mucins, penetrate effectively to reach the epithelium but lack the retention property of mucoadhesive formulations. Combination of both approaches can provide a good solution to the problem. [52].

5.3 Composite and Multilayer Systems

Multilayer mucoadhesive systems aim to release the drug uni-directionally towards the mucosal surface by reducing the drug loss to the oral cavity, an idea extensively used in the buccal administration of drugs [53]. An example of such is the bilayer system where the outer layer is hydrophobic (ethylcellulose or hydroxypropyl cellulose acetate succinate), preventing diffusion of the drug towards the oral cavity. The inner layer is a mucoadhesive layer loaded with drugs (HPMC/carbopol matrix). Other layers include drug reservoir and lag-time layers. Polyelectrolyte multilayers (LbL assembly) utilize a coating technology based on the deposition of an alternating anionic (alginate, hyaluronic acid) and cationic (chitosan, protamine) polyelectrolytes onto nanoparticle or tablet cores, thus offering high degree of control over the film properties including thickness and permeability. [54].

5.4 In-Situ Gelling Systems

Significant clinical interest has been shown for nasal, ocular, and rectal delivery of drugs using in-situ forming gels, owing to their easy administration as solutions having low viscosity that undergo rapid gel formation when they come into contact with the physiological environment [55]. The commonly used mechanisms for inducing gelation include: thermosensitivity (poloxamer 407, PLGA-PEG-PLGA triblocks, gel at body temperature and liquid at room temperature); pH sensitivity (systems based on carbopol, viscous at physiological pH but low viscosity at the processing acid pH); and ionic interactions (gellan gum and sodium alginate, gelation by contact with Ca^{2+} and Na^{+} ions in the physiological fluid). In situ poloxamer 407 formulations have proven useful for nasal drug delivery, showing prolonged residence times in the nasal cavity and increased bioavailability of peptides in several preclinical studies [56]. For ocular delivery, a well-established in-situ forming gel is Timoptic-XE consisting of 0.5-1% gellan gum, and chitosan and HPMC ophthalmic gels are at advanced developmental stages [57].

6. Dosage Forms in Mucoadhesive Drug Delivery

6.1 Buccal Dosage Forms

Buccal drug delivery is the most clinically established application of mucoadhesive technology, with several commercialized formulations indicating the potential of the route for systemic drug delivery. Buccal delivery systems can be in the form of tablets, films, patches, discs, strips, gels, and in situ bioadhesive lozenges [58]. Buccal tablets made by direct

compression or wet granulation of mucoadhesive polymer matrices are still the most reliable and dominant delivery systems due to the ease of manufacturing, dosage uniformity, patient compliance, and precedence in regulatory approval. Rapid-dissolution buccal tablets, such as the fentanyl buccal tablet (Fentora®), utilize the quick dissolving and fast absorption property for breakthrough pain treatment in cancer patients, whereas sustained-release formulations, such as the bilayer HPMC-carbopol tablets for testosterone and buprenorphine, release drugs over an extended period of 4 to 12 hours.Mucoadhesive buccal films have become the modern choice of preference over tablets due to their thin, flexible, and transparent nature. [59].

The preparation of buccal films is carried out by means of solvent casting, hot melt extrusion, or electrospinning methods using film-forming polymers including HPMC, HPC, PVP, pullulan, and sodium alginate in pure form or combinations. The market success of the product known as ondansetron orally disintegrating film (Zuplenz®) and also the research being conducted for buccal fentanyl film (Breakyl®, Onsolis®) demonstrate that buccal film is clinically very effective. Mucoadhesive nanofibrous electrospun films, prepared from polymer solution under high electrical potential jet processing, have high surface area to volume ratio and fast dissolution rate. [60].

6.2 Nasal Drug Delivery Systems

Mucoadhesive intranasal drug delivery formulations include solutions, sprays, gels, powders, microspheres, and nanoparticles administered intranasally to exert either local or systemic effects [61]. The nasal route is particularly important for the delivery of peptide/protein drugs such as calcitonin, desmopressin, insulin, and GLP-1 analogs due to their low bioavailability when given orally as a result of enzymatic degradation and non-permeability across the GI tract barrier. Clinical pharmacokinetic data have shown that mucoadhesive nasal microsphere formulations based on HPMC, carbopol, and chitosan offer 3- to 6-fold increases in drug bioavailability relative to nasal solutions.

The nose-to-brain (N2B) drug delivery pathway based on olfactory axon transport and trigeminal nerve routes for circumventing the BBB represents a revolutionary nasal delivery system for treating CNS diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and psychiatric disorders [62]. Mucoadhesive nanoparticles and in situ gelling drug delivery systems targeting the olfactory mucosa have resulted in improved N2B drug delivery efficiency in animal models and primates. Chitosan-based mucoadhesive nasal formulations have achieved enhanced brain delivery of rivastigmine, donepezil, and siRNA drugs in Alzheimer's disease preclinical models, along with early-phase clinical trials [63].

6.3 Ocular Formulations

Mucoadhesive ocular drug delivery systems take advantage of the conjunctival mucous coating and tear film to prolong precorneal retention time to enhance bioavailability – an issue since topical eye drops offer poor ocular bioavailability, typically around 5% [64]. Mucoadhesive ocular hydrogel formulations using polymers like hyaluronic acid, carbopol, xanthan gum, and gellan gum have proven effective at increasing corneal drug uptake two- to fivefold relative to aqueous drug formulations in preclinical studies. In commercially available ophthalmic gels utilizing hyaluronic acid (Hylocare®, Blink Tears®), the mucoadhesion is achieved via the binding of hyaluronic acid with CD44 receptors present on

the ocular surface—a receptor-mediated mucoadhesive strategy [65].

Mucoadhesive ophthalmic inserts such as the Lacrisert®, which is a hydroxypropyl cellulose rod insert for dry eye, can release drugs over a period of 24 hours and minimize the number of doses, thus promoting better patient compliance—an especially important feature in diseases that need daily eye drops administration. Mucoadhesive contact lenses using drug-laden nanoparticles, hydrogels, or polymer film with embedded drug molecules form the next generation of ophthalmic mucoadhesive devices [66].

6.4 Vaginal and Rectal Systems

Mucoadhesive vaginal dosage forms like gels, rings, films, tablets, capsules, and microspheres offer a wide range of therapies, such as antifungal treatment (miconazole, clotrimazole), contraceptive drugs (progesterone vaginal ring), hormone replacement therapy (estradiol vaginal tablets), antiviral drug pre-exposure prophylactic therapy (tenofovir gel), and anti-inflammatory treatment [67]. Mucoadhesive vaginal ring is a toroid-shaped dosage form made up of a silicone or polyurethane material that contains a mucoadhesive polymer coating for drug release for weeks and months continuously and remains in contact with the tissue. Dapivirine vaginal ring (Dapivirine Ring-004, authorized in Europe by EMA in 2020) for HIV protection is one of the most advanced mucoadhesive vaginal rings products, showing 27–56% efficacy [68].

Rectal mucoadhesive formulations such as suppositories, enemas, foams, and gels have been developed to prolong the retention time of the drug in the rectum and the sigmoid colon for both local and systemic delivery of the drug (e.g., mesalamine in ulcerative proctitis and diazepam, morphine, and ondansetron in pediatric populations). Mucoadhesive rectal gels using carbopol and polycarbophil exhibit better distribution and retention than traditional suppository dosage forms, whereas thermoreversible mucoadhesive hydrogels offer benefits of both liquids and gels in intracolonic drug distribution [69].

6.5 Gastrointestinal Mucoadhesive Systems

Mucoadhesive oral systems designed to target the GI mucosa include gastroretentive dosage forms, mucoadhesive intestinal tablets and pellets, colon-specific drug delivery systems, and mucoadhesive nanoparticulate systems for oral peptides/proteins administration [70]. Gastroretentive Mucoadhesive Systems (GRMS) employ high-swellable matrix systems, floating devices, or bioadhesive polymeric coating layers that increase the retention time of drugs with a narrow window of absorption (levodopa, furosemide, metformin) in the stomach by increasing retention time from 2–4 hours to 6–8 hours and enhancing drug bioavailability by 40–150% based on clinical pharmacokinetics data. The challenge with GRMS, the variation of gastric emptying depending on the fed/fasted status, is still under investigation [71].

7. Evaluation and Characterization Techniques

7.1 In Vitro Mucoadhesive Strength Testing

Measurement of mucoadhesive strength is crucial for dosage form development and comparison between different polymer systems. Tensile strength determination involves the use of a texture analyzer (TA.XT Plus) fitted with mucus-coated probes that measure the force required to separate hydrated mucoadhesive formulations from a standard mucus substrate (porcine intestinal/mouth/abdominal mucosa or mucin-coated glass plates freshly excised) [72]. Important

considerations include the peak detachment force (maximum adhesive strength), work of adhesion (area under the force-distance plot), and detachment time. The rotating cylinder and flow-through models are used to test the effect of hydrodynamic conditions, similar to physiological shear forces, on mucoadhesive strength. It is important to bear in mind the freshness of the substrate, hydration, and temperature when interpreting results, as these factors affect the consistency of mucoadhesion measurements. [73].

7.2 Wash-Off and Retention Studies

Ponchel et al. invented the wash-off test, which measures the percentage of the formulation left on a mucosal surface after certain time intervals under fluid movement conditions simulating physiological conditions [74]. This test is performed using radiolabelled, fluorescently labelled, or gravimetrical monitoring of the formulations placed on the mucosa within an experimental device, where the fluid is pumped in a continuous or intermittent manner depending on whether the physiological movement simulates peristaltic movement of the GI tract, mucociliary clearance of the nasal mucosa, or drainage of tears.

7.3 Rheological Characterization

The rheological method, which involves the use of oscillatory shear rheology (dynamic mechanical analysis, DMA) or rotational viscometry, is used to assess the viscoelasticity of mucoadhesive gels as well as the interaction between the gel and mucin [75]. Synergy factor (Syn), which is calculated by subtracting the viscosity of the polymer-mucin mixture from the predicted viscosity based on the additive theory, represents the mucoadhesive interaction intensity. If the Synergy Factor is positive, there are molecular interactions that improve the viscoelasticity of the network. On the other hand, a negative value indicates steric incompatibility. [76].

7.4 Mucin Particle Size and Zeta Potential Analysis

Dynamic light scattering and laser Doppler electrophoresis techniques are utilized to measure variations in the particle size and zeta potential of mucin when mixed with polymers, offering indirect proof of the interaction between the polymer and mucin [77]. An increase in the hydrodynamic size of mucin after the addition of polymer suggests either the adsorption or entanglement of the chain, whereas variations in zeta potential (which is often in line with that of the polymer) suggest electrostatic interactions.

7.5 Drug Permeation and Absorption Studies

The ex vivo permeation tests conducted in Franz diffusion cells or Side-Bi-Side cells using freshly isolated mucosa tissues like porcine buccal, porcine/ovine nasal, bovine ocular, and porcine/human intestinal tissue are useful in providing pharmacokinetic information regarding drug flux and permeability coefficient values (Papp) along with the impact of mucoadhesive polymers and permeation promoters on drug absorption [78]. The CLSM technique, when applied using fluorescent analogues of drugs or nanoparticles, is helpful in assessing the depth of penetration and distribution of drugs into mucosal membranes.

7.6 Spectroscopic and Microscopic Characterization

A complete kit for characterization of mucoadhesive formulation comprises X-ray powder diffraction (XRPD) to study crystallinity, differential scanning calorimetry (DSC) to assess the compatibility between the drug and polymer

and to determine the glass transition temperature, FTIR and Raman spectroscopy to evaluate the chemical interaction between the drug and polymers, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) to characterize surface morphology and nanostructures, and atomic force microscopy (AFM) to evaluate nanomechanical properties and adhesion forces [80]. For nanoparticulate mucoadhesive formulations, characterization by nanoparticle tracking analysis (NTA), BET surface area determination, and XPS is mandatory.

Table 2. Evaluation Techniques for Mucoadhesive Drug Delivery Systems

Technique	Parameter Measured	Application	Limitations
Texture Analysis (TA.XT)	Detachment force, work of adhesion	All dosage forms	Substrate variability
Rheology (Oscillatory)	G', G", Syn index	Gels, hydrogels	Not route-specific
Wash-off Test	% retained vs. time	All forms	Non-standardized
DLS / Zeta Potential	Size change, charge interaction	Nanoparticles, polymers	Indirect measure
Franz Cell Permeation	Flux, Papp, bioavailability	All mucosal routes	Ex vivo limitations
FTIR / Raman	Chemical interactions	Polymer-drug, polymer-mucin	Qualitative only
DSC	Tm, Tg, compatibility	Solid dosage forms	Limited to thermal
SEM/TEM	Morphology, nanostructure	Particles, films	Vacuum artifacts
AFM Force Spectroscopy	Adhesion force (pN-nN)	Polymers, nanoparticles	Low throughput
QCM-D	Adsorption mass, viscoelasticity	Thin films, monolayers	Specialized equipment
CLSM	Penetration depth, distribution	Nanoparticles, films	Fluorescent label req.
In vivo Scintigraphy	GI residence, distribution	Tablets, pellets	Radiation, expensive

8. Therapeutic Applications

8.1 Pain Management and CNS Disorders

The buccal and nasal drug delivery routes have proven successful as alternatives to intravenous and oral administration of analgesics and psychotropic medications that require fast-acting properties [81]. The two buccal opioids that have received FDA approval for breakthrough cancer pain management and opioid addiction treatment include Actiq®, Fentora®, and Onsolis® fentanyl and Belbuca® buprenorphine, respectively. These two drug delivery routes offer a superior pharmacokinetic profile, including faster drug onset (Tmax at about 45-90 min compared to 1-2 h for oral administration), with better bioavailability (around 65-80% vs. 35% oral), leading to better therapeutic outcomes for analgesic purposes. For CNS-related conditions, an intranasal drug delivery route has been developed for the fast-acting antidepressant esketamine (Spravato® nasal spray), which received FDA approval in 2019 [82].

8.2 Diabetes and Metabolic Disorders

Insulin-like peptides (GLP-1 analogs, GIP, glucagon) is one of the most difficult and intensively studied areas of drug delivery by means of the mucosa [83]. Insulin-containing mucoadhesive nasal microspheres (based on chitosan or cross-linked starch using STMP) have shown 10-15% bioavailability compared to subcutaneous administration but still significantly insufficient for the latter type of delivery method.

However, this level of bioavailability may be enough to manage postprandial glycaemia under certain conditions. In the market, we can find such preparations like Nasulin® and Oral-Lyn®, demonstrating the possibility of using insulin without subcutaneous delivery. However, these medications still failed to become popular because of variable bioavailability compared to subcutaneously administered forms.

8.3 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, is a prime example of an indication that would benefit from colonic mucoadhesive drug delivery due to the access provided by the mucosal inflammation and reduced side effects of the drugs in question. Mucoadhesive mesalamine-based medications, including Asacol®, Lialda®, and Pentasa®, use pH-sensitive polymer coatings to provide colonic targeting of the drug release; on the other hand, the use of mucoadhesive microspheres and nanoparticles has proven superior to enemas in terms of providing better distribution, tissue uptake, and anti-inflammatory effect in mouse models of colitis. The increased expression of CD44 receptors, lectins, and inflammatory cytokines in IBD mucosa offers more targets for mucoadhesive targeting.

8.4 Infectious Diseases and Vaccines

In particular, mucosal vaccination using either buccal, intranasal, vaginal, or rectal modes of delivery is an extremely promising approach for eliciting both local sIgA and systemic humoral immune responses—an immune double-barreled approach that cannot be delivered using injectable vaccines [87]. Mucoadhesive nanoparticulate vaccines utilizing chitosan, PLGA, and lipid nanoparticles have shown significant results for inducing mucosal immunity against influenza virus through the nasal route, against HIV through the vaginal route, and against enteric pathogens through the oral route in experimental settings. With the onset of the COVID-19 pandemic, much attention has been paid to developing nasal SARS-CoV-2 vaccines based on chitosan and lipid nanoparticles [88].

8.5 Ocular Diseases

Several types of mucoadhesive ocular delivery systems are currently available to treat many different ocular disorders such as glaucoma, dry eye disease, uveitis, ocular infections, allergic conjunctivitis, and post-operative inflammation [89]. Mucoadhesive ocular delivery system containing timolol maleate in gellan or xanthan gels is proven to be equally effective in lowering IOP levels as conventional eye drops used twice per day, but applied only once per day. Ocular mucoadhesive drug delivery system with hyaluronic acid achieves sustained effects in ocular lubrication with once per day or twice a week dosing regimen.

9. Recent Advances and Novel Technologies

9.1 Nanomedicine-Based Mucoadhesive Platforms

The fusion between nanotechnology and mucoadhesion technology has led to more complex carriers during the period 2021-2025 [90]. The development of hybrid nanoparticles that combine the advantages of lipid shells and polymeric cores (lipid-polymer hybrid nanoparticles, LPHNs) has allowed the modification of their structure by introducing mucoadhesive polymer molecules such as thiolated hyaluronic acid, chitosan oligosaccharide, and PEGylated carbopol. Mucoadhesive nanovesicles mimicking exosomes secreted by mucosal cells have shown their

tropism for mucosal tissues and may be used for the treatment of inflammation of the mucosa and malignancies through mucosal and intracellular drug delivery [91]. The application of mucoadhesive molecules to surface-modified carbon nanotube (CNT) and graphene oxide nanocomposites is being considered for the photodynamic treatment of oral and esophageal carcinomas [92].

9.2 3D Printing and Advanced Manufacturing

The field of additive manufacturing, which includes technologies such as fused deposition modeling (FDM), stereolithography (SLA), selective laser sintering (SLS), extrusion-based printing, and inkjet printing, has created new opportunities for the production of individualized, geometrically complicated mucoadhesive dosage forms [93]. It is possible to make use of FDM-printed buccal films and tablets made with HPMC, PVA, and carbopol using exact spatial distributions for patient-specific dosing and customized release kinetics not attainable through conventional processes. Preclinical research shows that SLA-created mucoadhesive ocular inserts with regulated porosity, geometry, and surface characteristics have increased ocular residence periods compared to standard formulations. The combination of hot melt extrusion (HME) with 3D printing allows amorphization of the active pharmaceutical ingredient, optimization of miscibility between polymers and drugs, and fabrication of the dosage forms using a continuous manufacturing process [94].

9.3 Artificial Intelligence in Mucoadhesive Formulation Design

The use of artificial intelligence (AI) and machine learning (ML) strategies is becoming more prevalent in order to expedite mucoadhesive formulations development, as DoE cannot address effectively the multivariate optimization problem at hand [95]. In silico QSPR models based on datasets of physicochemical properties of polymers have been used to predict mucoadhesive properties, drug delivery, and permeability enhancement with remarkable accuracy (R^2 >0.85 in cross-validation). Neural networks-based models taking into account types of polymers, their molecular weight, concentrations, drug-related features, and mucosal routes characteristics have been successfully used to develop new formulations for specific pharmacokinetic profiles with an anticipated reduction in formulation development time of up to 40–60%. Natural language processing of scientific literature allowed extracting relationships between structures and properties, and creating knowledge graphs that could be used for generating formulation hypotheses [96].

Generative AI techniques have been employed to develop novel mucoadhesive copolymers' structures with enhanced hydrogen bonding capacity, thiol density, and biodegradation rates confirmed experimentally [97]. An interesting avenue in the future will include integration of AI algorithms with high throughput automated formulation screening technologies that employ robotic dispensing, microassays, and iterations of ML approaches.

9.4 RNA Therapeutics and Gene Delivery via Mucoadhesive Systems

The clinical validation of mRNA vaccines (SARS-CoV-2) and siRNA drugs (patisiran, givosiran) has stimulated research into the design of mucoadhesive drug carriers for the mucosal administration of nucleic acid therapeutics [98]. Mucoadhesive chitosan nanoparticles are able to deliver siRNA that targets TNF-α and IL-17A efficiently in experimental colitis, with improved

mucoadhesion facilitating increased cellular uptake and effective gene silencing within the colon epithelium. The design of mucoadhesive hyaluronic acid-coated lipid nanoparticles for the intranasal delivery of mRNA vaccines is under development, with several candidates undergoing IND-enabling preclinical evaluation. Mucoadhesive nanoparticles that contain CRISPR-Cas9 components have been reported to perform genome editing of specific genes in the colon epithelium in animal models, suggesting potential applications of mucoadhesive genome editing platforms in the management of hereditary colon diseases [99].

9.5 Stimuli-Responsive Smart Mucoadhesive Systems

Mucoadhesive delivery systems responsive to stimuli generated by pathological states in the mucosal milieu have emerged as promising candidates for precision drug delivery [100]. The drug-release mechanism for ROS-responsive mucoadhesive nanoparticles is triggered by the oxidative stress in the mucosal milieu, where the presence of labile groups such as thioketal, diselenide, and phenylboronic ester results in the preferential release of drugs in response to an oxidizing atmosphere without systemic uptake. Nanoparticles made of pH-gradient-responsive Eudragit/Chitosan polyelectrolyte complex undergo surface charge switching from negative to positive and mucoadhesively interact with the near-neutral environment of the intestinal mucosa without degradation in the acidified stomach due to the pH switch.

10. Challenges and Limitations

10.1 Mucus Barrier and Turnover

Mucosal fluid is characterized by constant secretion, renewal, and removal, which creates an intrinsic difficulty to mucoadhesion [101]. Due to the fact that small intestine mucus turns over every 4–5 hours, and nasal mucus is renewed between 1 and 4 hours, even strong mucoadhesive systems are removed together with the mucus matrix. Another factor that can pose an obstacle for nanoparticle delivery through mucus barriers is the diffusional barrier due to the mesh dimensions of the mucus gel (between 100 and 500 nm) and electrostatic, hydrophobic, and hydrogen bonding interactions between carrier surfaces and mucin filaments. Overproduction of mucus in cystic fibrosis, COPD, and IBD significantly changes properties of mucus, thus creating problems in predicting formulations' behavior from healthy tissue studies.

10.2 Inter- and Intra-Subject Variability

Mucoadhesion and rheological properties differ greatly among subjects, as well as within one single subject during different times. Such differences arise due to genetics (MUC polymorphism), pathophysiological conditions, hormonal levels, nutrition, microflora balance, and medications [103]. Consequently, mucoadhesion and absorption properties differ widely from one patient to another. This is especially evident for the vaginal mucosal membrane with pronounced cyclic and post-menopausal changes. Development of new mucoadhesive formulas that will take into account such individual variability (via pH-independent polymeric structures, combined mucoadhesives, or closed-loop dosing) is a key focus of scientific interest.

10.3 Scale-Up and Manufacturing Challenges

Mucoadhesive properties that work well in laboratory settings may not be consistent in pilot or large-scale manufacture due to differences in mixing behavior, uniform hydration of polymers, and film casting conditions [104]. Scaling up

production of mucoadhesive films using roll-to-roll coating technology demands strict control of coating thickness, consistency, and drying conditions for maintaining constant drug load and mucoadhesive activity. Nano-mucoadhesive systems present further difficulties in scaling up due to the need to achieve consistent particle size distributions at large scales, surface modification, and colloidal stability upon storage—difficulties that cannot simply be overcome through increased volume in laboratory techniques.

10.4 Regulatory and Toxicological Considerations

The regulatory path for mucosal drug products is dependent on the mode of administration, the novelty of the polymer, and the therapeutic indication of the drug. Polymers that are known to be Generally Recognized as Safe (GRAS) or have established compendial monographs (e.g., HPMC, Carbomer, Chitosan, Sodium Alginate) have an easier path compared with the development of novel synthetic polymers or novel polymer-drug conjugates which will require the creation of new excipient documentation [106]. Novel materials such as thiomers, receptor-targeted ligands, and stimuli-responsive copolymers that lack established safety data will require thorough testing that will include in vitro cytotoxicity testing (ISO 10993-5) and mucosal irritation testing using in vitro tissue culture models (e.g., Draize test, EpiOral™, EpiGingival™) and genotoxicity and repeat-dose toxicity studies on appropriate animal models.

11. Future Perspectives

The future ten years are likely to witness revolutionary changes in mucoadhesive drug delivery science through the integration of precision medicine, advanced manufacturing, computational biology, and biomaterials. Some areas that have potential are:

Bioinspired mucoadhesive systems based on the adhesive proteins of sea creatures (mussel, sandcastle worm) and mucin-binding glycan biochemistry of commensal bacteria as a new coating strategy for mucoadhesive nanoparticles are investigated, providing covalent binding to mucin under aqueous conditions [108]. Examples of polydopamine, peptide polymers with DOPA residues, and catechol-modified chitosan derivatives provide proof of principle.

Microbiota responsive mucoadhesive systems serve as an emerging approach utilizing the enzymatic action of the gut microbiota as a drug release mechanism. The incorporation of microbiota-degradable linkages (azoreductase-sensitive azo-crosslink, β-glucosidase-sensitive glycosidic bond) releases drug payload in the colonic area rich in microbiota while maintaining mucoadhesive properties during gastrointestinal transit [109].Mucoadhesion organ-on-chip models, microfluidic systems comprising perfused human intestinal, buccal, nasal, or vaginal epithelium with mucus-producing goblet cells under physiological flow rates, are poised to supplant animal models in the investigation of mechanisms of mucoadhesion and formulation screening [110].The combination of wearables and mucoadhesive drug delivery, leading to closed-loop “smart patch” technology that would enable buccal or rectal dosing based on physiological inputs (glucose levels, inflammatory cytokine concentrations, or pH), is at the cutting edge of mucoadhesive personalized pharmacotherapy [111]. Future regulatory science breakthroughs, such as the development of mucoadhesive IVIVC models, physiological mucoadhesive dissolution medium, and mucoadhesive bioequivalence test procedures, will be pivotal to facilitating

translational progress from benchtop innovations to bedside and market success [112].

CONCLUSION

Mucoadhesive delivery platforms have become one of the key paradigms in modern pharmaceutics, providing an elegant and practical approach towards addressing the inherent bottlenecks associated with traditional delivery modalities. Starting from the pioneering bioadhesive polymer tablets in the 1980s to the current stimuli-responsive nanocarriers, AI-formulated platforms, and 3D-printed customized drug delivery formats, the area has experienced significant progress, but at the same time, it has not deviated from its basic principles of polymer-mucin interaction.

The present review has illustrated that the effectiveness of mucoadhesive drug delivery systems relies upon combining the knowledge related to the mechanism of adhesion—ranging from molecular interactions to pharmacokinetics at the tissue level—with advanced design of delivery formulations, which have expanded to numerous mucosal routes. Examples of the clinical applications provided within the review range from pain alleviation, metabolic disorders, central nervous system dysfunction, inflammatory bowel disease, ophthalmic disorders, fertility problems, and infectious diseases.

The discipline is confronted with genuine scientific and technological hurdles that include mucosal shedding, inter-subject variation, scale-up production, and regulation that need to be addressed through intensive multidisciplinary research endeavors. Yet, the combination of nanotechnology, intelligent polymer synthesis, computational formulation development, advanced production, and personalized medicine technologies affords an extraordinary set of tools to overcome these obstacles and unlock the therapeutic capabilities of mucoadhesive drug delivery. The future generation of mucoadhesives will definitely involve bio-inspired designs, computational optimization, continuous production, and personalized clinical application.

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