Novel Inovation Medication Promots Controlled With Adhesion Mucosal Drug Delivery Systems.

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➢ **Abstract:**

Mucoadhesive drug delivery systems function by establishing interactions with the mucus layer covering mucosal epithelial tissues, primarily through bonding with mucin molecules. This adhesion prolongs the residence time of the dosage form at the absorption site, which is crucial for drugs requiring extended gastrointestinal retention or intended for local therapeutic action. As a result, mucoadhesive formulations significantly enhance plasma drug concentration and overall therapeutic efficacy. This review highlights the underlying mechanisms and theoretical principles of mucoadhesion, the variables influencing mucoadhesive performance, and various dosage forms designed using mucoadhesive polymers. Although several assessment methods have been proposed for evaluating bioadhesion and mucoadhesion, the absence of a standardized testing protocol limits accurate comparison across research studies. Therefore, the aim of this work is to establish a systematic and unified in vitro technique applicable to multiple pharmaceutical dosage forms. To achieve this goal, the peak detachment force and work of adhesion of minitablets, pellets, and bioadhesive emulsions were measured using a texture analyzer, with porcine tissue selected as an experimental model to simulate human stomach and skin conditions. Comparative analysis was conducted between formulations containing bioadhesive components and those without adhesion-enhancing materials.

Mucoadhesive drug delivery systems represent an advanced and innovative approach developed to improve therapeutic efficiency by extending mucosal retention time. These systems employ polymers capable of adhering to buccal, nasal, ocular, rectal, and vaginal membranes to enable controlled and sustained drug release. Prolonged contact at the absorption site enhances bioavailability, reduces dosage frequency, and minimizes systemic adverse effects. Recent advancements in natural, semi-synthetic, and synthetic mucoadhesive polymers have facilitated the development of dosage forms such as tablets, films, gels, nanoparticles, and transdermal patches for precise and targeted drug delivery.

Keywords: Mucoadhesion, Mucoadhesive Drug Delivery Systems, Bioadhesion, Controlled Release, Mucoadhesive Polymers, Dosage Forms, Absorption Enhancement

➢ Introduction:

In recent years, the focus of pharmaceutical research has shifted from the discovery of new drug molecules to the development of novel drug delivery systems (NDDS) for existing therapeutic agents. This approach aims to improve clinical effectiveness, enhance patient outcomes, and extend patent life. The progress of NDDS has been significantly supported by the availability of advanced polymers capable of modifying and controlling drug release patterns.

Among various innovative approaches, mucoadhesive drug delivery systems (MDDS) have gained considerable attention. These systems utilize polymers that can adhere to mucosal surfaces such as the buccal, nasal, ocular, pulmonary, rectal, and vaginal mucosa. By forming close contact with the absorption membrane, MDDS enhances drug retention time and provides improved permeability and therapeutic action.

Dosage forms designed for mucoadhesive delivery must be flexible, comfortable, and patient-friendly, ensuring that they do not cause irritation during application. Ideal characteristics include a high drug-loading capacity, prolonged and preferably unidirectional drug release, strong adhesion capability, smooth texture, and ease of administration. Erodible mucoadhesive systems are particularly advantageous as they eliminate the need for removal after the drug is delivered.

Multiple pharmaceutical formulations have been developed utilizing mucoadhesive principles to improve the bioavailability of drugs, including peptides and proteins that ordinarily show poor absorption due to high molecular weight or enzymatic degradation at mucosal sites. Traditional sustained-release dosage forms release drugs over extended periods but often fail to maintain therapeutic levels if they detach prematurely from the absorption site. In contrast, mucoadhesive systems maintain prolonged residence time, ensuring improved drug utilization and therapeutic effectiveness.

➢ Classification of Polymers (General Classification)

1. **Based on Origin**

Sr no:	Type	Example
1)	Natural polymers:	Starch, Cellulose, Rubber, Gelatin, Proteins
2)	Synthetic polymers:	Nylon, Polyethylene, PVC, Polystyrene, Acrylics
3)	Semi-synthetic polymers:	Cellulose acetate, Nitrocellulose, Rayon

2. Based on Structure

Sr. No:	Type	Characteristics	Examples
1)	Linear polymers	Long straight chains	HDPE, PVC, Nylon
2)	Branched polymers	Side chain branches	LDPE, Glycogen
3)	Cross-linked/Network polymers	3D network, rigid	Bakelite, Melamine, Vulcanized Rubber

3. **Based on Mechanism of Polymerization**

Sr. No:	Type	Example
1)	Addition (chain growth) polymers	Polyethylene,PVC,PTFE, Polystyrene
2)	Condensation (step growth) polymers	Nylon-6,6,Polyester(PET), Bakelite Polyamide

4. Based on Physical Properties

Sr. No:	Type	Example
1)	Elastomers	Rubber, Neoprene, Silicone
2)	Fibers	Nylon Rayon, Polyester
3)	Plastomers	Polyethylene, PVC

➢ **The mucoadhesive drug delivery system includes various routes, one of which is the buccal delivery system**.

he buccal mucosa covers an area of approximately 30 cm^2 and is composed of three main layers—the connective tissue, the basement membrane, and the epithelial layer.

The gingival region and hard palate consist of keratinized mucosa, whereas the buccal and sublingual areas are made up of non-keratinized soft tissue.

The buccal epithelium has a thickness ranging between 500–800 μm and is made up of around 40–50 cell layers.

Saliva, secreted from the salivary glands, contains mucus which forms a protective coating with a thickness of 0.1–0.7 mm. The turnover time of buccal epithelial cells is generally 5–6 days.

The permeability barrier of the oral mucosa is attributed to the intercellular lipid components derived from membrane-coating granules.

- **Vaginal Drug Delivery Systems:**

The vagina is a fibro-vascular tube lined with stratified squamous epithelium and acts as an important route for both local and systemic drug delivery. Conventional vaginal dosage forms such as gels, creams, suppositories, suspensions, tablets, and solutions generally have short residence time, which reduces therapeutic effectiveness.

To overcome this, bioadhesive formulations are developed to control drug release and prolong retention in the vagina, and they may contain active drugs or moisturizers to relieve vaginal dryness.

An acid-buffering bioadhesive vaginal tablet containing clotrimazole and metronidazole was developed for genitourinary infections. Using polycarbophil and sodium carboxymethyl cellulose, the tablet showed over 24-hour retention, controlled drug release comparable to Infa-V®, and better antimicrobial activity than Infa-V®, Candid-V® and Canesten®.

Additionally, clomiphene citrate (CLM) gels prepared with Carbopol polymers, especially C934P-Cys, showed the highest mucoadhesion and slower drug release, making them suitable for prolonged therapy.

- **Rectal Drug Delivery System**:

The rectum is the terminal part of the colon, approximately 10 cm long with a surface area of around 300 cm^2. Its main physiological role is water absorption. Due to the absence of villi, the surface available for drug absorption is limited, and most drugs are absorbed through simple diffusion across lipid membranes.

Rectal administration is especially useful for drugs that undergo extensive first-pass metabolism, as this route can improve bioavailability when targeting conditions near the anal region. The use of bioadhesive polymers in rectal formulations helps to reduce migration within the rectum and enhances the residence time and absorption.

- **Nasal Drug Delivery System:**

The nasal cavity provides a surface area of about 150 cm^2, with a rich blood supply and a permeable mucosal membrane, making it suitable for rapid drug absorption and bypassing first-pass metabolism. However, limitations include mucociliary clearance within 5 minutes, local irritation, the presence of proteolytic enzymes, and reduced effectiveness during cold or allergy conditions.
Bioadhesive liquids, semisolids, and powders can significantly increase retention time and improve drug absorption.

Nasal delivery of proteins and peptides is often limited by short mucosal contact time, but bioadhesive polymers can prolong residence time and enhance uptake. Techniques such as gamma scintigraphy have been used to assess nasal retention and insulin absorption.

Bioadhesive powder formulations containing starch (Amioca®) and poly(acrylic acid) (Carbopol® 974P) were examined for intranasal delivery of influenza vaccine in rabbits. Results showed that these carriers improved systemic immune response by increasing anti-HA antibodies.

- **Ocular Drug Delivery System:**

Drug administration to the eye is challenging due to natural protective mechanisms such as tear production, tear drainage, and blinking, which rapidly wash away conventional formulations. Solutions and suspensions provide very short contact time, while ointments blur vision due to altered tear refractive index. To overcome these limitations, mucoadhesive systems are developed to prolong ocular residence time and improve therapeutic effectiveness.

Bioadhesive sulfacetamide sodium microspheres prepared with pectin, polycarbophil, and HPMC by spray drying showed enhanced treatment of ocular keratitis, with a polymer:drug ratio of 2:1 giving the best results. Bioadhesive HA–chitosan DNA nanocarriers showed potential for ophthalmic gene therapy by successfully entering ocular cells and achieving significant gene expression. Clinical studies on mucoadhesive ocular films demonstrated improved retention and reduced irritation compared to older systems such as Ocusert®.

- **Gastro intestinal Delivery System:**

The oral route is the most preferred method for drug administration; however, challenges such as hepatic first-pass metabolism, enzymatic degradation, mucosal barriers, and rapid mucus turnover limit effective drug absorption. To overcome these issues, bioadhesive gastrointestinal (GI) delivery systems have been developed. These systems use bioadhesive polymers that adhere to the GI epithelial surface, thereby prolonging residence time, enhancing drug absorption, and improving bioavailability.

Ahmed (33) reported the development of gastric-retentive formulations (GRFs) using natural carbohydrate polymers loaded with riboflavin. These GRFs showed rapid swelling in gastric fluid and released the drug in a zero-order manner for 24 hours. In animal and human studies, the GRF remained in the stomach for more than 9 hours and improved riboflavin bioavailability over three times compared to an immediate-release formulation. Additionally, Salman (34) developed thiamine-coated bioadhesive nanoparticles for targeted oral vaccination. Studies in rats showed strong mucosal adhesion and selective targeting of enterocytes and Peyer's patches, indicating their potential use in oral vaccines and immunotherapy.

- **Benefits of Mucoadhesive Drug Delivery System:**

1) Mucoadhesive drug delivery systems offer several advantages.
2) They bypass first-pass metabolism, enhancing drug bioavailability, and allow prolonged drug release, reducing the frequency of dosing and improving patient compliance.

3) Drugs can be administered conveniently, even in emergencies, and unstable drugs in the acidic stomach environment can be delivered via buccal routes.

4) Absorption occurs mainly through passive diffusion, and the system provides flexibility in terms of dosage form, shape, size, and surface characteristics.

➢ **Bioadhesion and Mucoadhesion:**

Bioadhesion is the phenomenon where a material, at least one being biological, adheres to a biological surface for a prolonged period via interfacial forces. It can be classified into three types:

1. Adhesion between two biological phases (e.g., platelet aggregation, wound healing)

2. Adhesion of a biological phase to an artificial substrate (e.g., cell attachment to culture dishes, biofilm formation on implants)

3. Adhesion of an artificial material to a biological substrate (e.g., synthetic hydrogels on soft tissues, dental sealants on enamel).

In drug delivery, bioadhesion refers to the attachment of a drug carrier to a biological site, such as epithelial tissue. Mucoadhesion is a specific type of bioadhesion where the material binds specifically to a mucus layer.

While bioadhesion can occur on any biological surface, mucoadhesion is restricted to mucosal surfaces, involving interactions between polymers (synthetic or natural) and mucin.

➢ Mechanism of Mucoadhesion:

Mucoadhesion is the phenomenon where two substances, typically a synthetic mucoadhesive polymer and the mucin layer of the mucosal tissue, are held together through interfacial attractive forces. A mucoadhesive material is an artificial agent capable of interacting with the mucus membrane and remaining attached to it for an extended period.

1. Contact Stage: In this initial stage, the mucoadhesive comes into contact with the mucus membrane, allowing close wetting between the two surfaces. The presence of mucus in the membrane helps facilitate this wetting, ensuring effective initial adhesion.

2. Consolidation Stage: After contact, various physicochemical forces—such as Van der Waals interactions, electrostatic attractions, and hydrogen bonding—stabilize the bond between the mucoadhesive and the mucus membrane. This reinforcement prolongs the adhesion and is known as the consolidation stage.

➢ THEORIES OF MUCOADHESION:

Mucoadhesion is a complex phenomenon, and several theories have been proposed to explain its underlying mechanisms. The main theories include:

a) Wetting Theory:

This theory explains that when a polymer comes into contact with the mucus layer, the liquid environment facilitates its spreading across the mucosal surface. The degree of wetting depends on the polymer's surface tension. Polymers with better wetting (lower contact angle) form a larger contact area, increasing the likelihood of adhesive interactions. This suggests that using hydrophilic polymers or wetting agents can enhance initial adhesion.

b) Diffusion Theory:

According to this theory, mucoadhesion occurs when the polymer chains interpenetrate the mucus layer to a sufficient depth, forming semi-permanent adhesive bonds. This process is driven by concentration gradients and is influenced by the polymer's molecular chain length, mobility, and the cross-linking density. Greater molecular weight and optimal chain mobility favor stronger adhesion.

c) Fracture Theory:

This theory relates adhesion to the force required to separate two surfaces after bonding. The adhesive strength is considered equivalent to the fracture strength, which can be expressed as:

$$G = \sqrt{\frac{E e}{L}}$$

Where:

= Young's modulus of elasticity

= Fracture energy

= Critical crack length at separation

d) Electronic Theory:

This theory proposes that when a polymer contacts the mucus glycoprotein network, electron transfer occurs due to differences in electronic structure. This creates an electronic double layer at the interface, and adhesion arises from the attractive forces across this double layer.

e) Adsorption Theory:

This theory explains mucoadhesion as the attachment of an adhesive to the mucus layer through hydrogen bonding and Van der Waals forces. The bonding can occur via two types of chemical interactions: primary bonds, which are covalent, and secondary bonds, which include electrostatic interactions, Van der Waals forces, and hydrophobic interactions.

- **Adsorption in Mucoadhesion:**

Adsorption in mucoadhesion describes the attachment of a mucoadhesive polymer to the mucosal surface at the interface. This bonding occurs through relatively weak physical forces, including:

- **Hydrogen bonds**
- **Van der Waals interactions**
- **Electrostatic attractions**
- **Hydrophobic interactions**

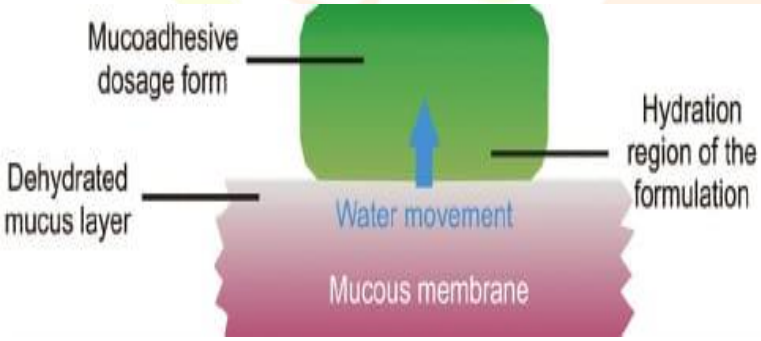

Figure:1 Adsoption theory

➢ **Factors Affecting Mucoadhesion:(9,10,11)**

Mucoadhesion is influenced by several factors, which can be broadly categorized into polymer-related, environment-related, and physiological factors:

1. Polymer-Related Factors:

- Molecular Weight: Higher molecular weight generally enhances adhesion.
- Polymer Concentration: Adequate concentration of the active polymer improves bonding.
- Chain Flexibility: Flexible polymer chains can better interact with the mucosal surface.
- Spatial Conformation: The three-dimensional structure of the polymer affects attachment.
- Swelling (Hydration): Polymers that swell upon hydration create better contact.

2. Environment-Related Factors:

- pH at the Polymer–Substrate Interface: Affects ionization and bonding.
- Swelling Factor & Molecular Weight: Influence the extent of polymer–mucus interpenetration.
- Stereochemistry of Polymer: Spatial arrangement of functional groups affects bonding.
- Applied Strength and Initial Contact Time: Proper pressure and sufficient contact time improve adhesion.
- Moistening: Moist surfaces facilitate better wetting and adhesion.
- Presence of Metal Ions: Can influence polymer–mucus interactions.

3. Physiological Factors:

- Mucin Turnover: Faster mucus replacement can reduce adhesion.
- Rate of Renewal of Mucosal Cells: High turnover may decrease the duration of adhesion.
- Tissue Movement: Movement of the mucosa can disrupt adhesion.
- Disease States or Concomitant Conditions: Certain pathologies can alter mucus properties and affect adhesion.

Figure:2 Facter affecting mucoadhesion

➢ **Mucoadhesive Dosage Form(16)**

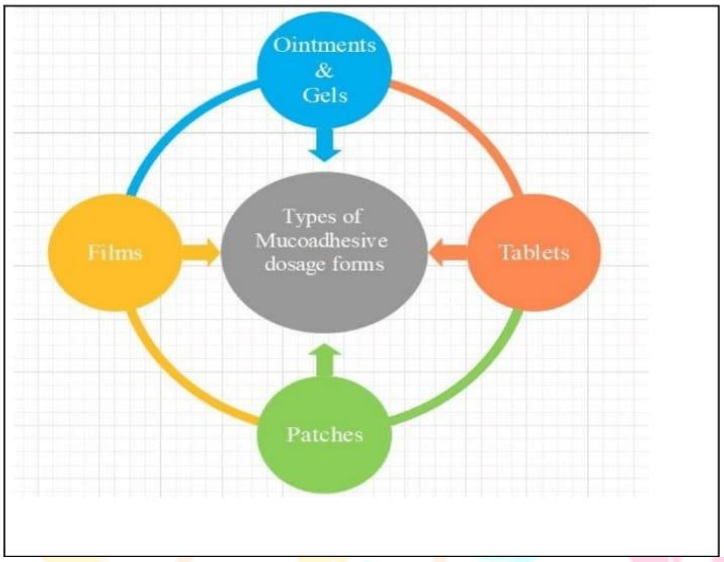

Figure:3 Mucoadhesive Dosage Form

➢ **Method of Preparation:**

a) Tablet:

Mucoadhesive tablets are small, typically flat or oval, measuring around 5–8 mm in diameter. Unlike conventional tablets, they allow activities such as speaking and drinking without causing much discomfort. Once administered, these tablets soften and adhere to the mucosal surface, remaining in place until the drug is fully released or dissolved.

Mucoadhesive tablets are often used for controlled drug release, and their mucoadhesive properties offer additional advantages. By increasing the contact between the drug and the mucus layer, they improve drug absorption and bioavailability due to a favorable surface-to-volume ratio. These tablets can be tailored to stick to various mucosal tissues, including the gastric mucosa, enabling both localized and systemic drug delivery.

They are particularly useful for localized drug action in the stomach and are valued for sustained medication release, reduced dosing frequency, and improved patient compliance. However, one limitation is their limited physical flexibility, which may affect patient comfort and adherence during long-term or repeated use.

b) Film:

Mucoadhesive films are preferred over tablets because of their superior flexibility and comfort. They can overcome the short residence time of oral gels, which are quickly washed away by saliva. For local treatment in the oral cavity, these films protect the wound surface, reduce pain, and enhance therapeutic effectiveness. An ideal mucoadhesive film should be flexible, elastic, and soft, yet strong enough to withstand stresses from mouth movements.

Strong mucoadhesive properties are crucial to keep the film in place for the required duration. Any swelling of the film should be controlled to prevent discomfort.

c) Patches:

Mucoadhesive patches are multilayered systems consisting of an impermeable backing layer, a drug-containing reservoir that enables controlled drug release, and an adhesive surface to attach securely to mucosal tissues. Their design and functioning are similar to transdermal patch delivery systems. Adhesive patches can be fabricated mainly by two techniques: solvent casting and direct milling.

In the solvent casting method, a uniform film is formed by pouring a solution containing the drug and polymer(s) onto the backing membrane and allowing the solvent to evaporate. On the other hand, the direct milling technique involves thoroughly blending all formulation ingredients, after which the mass is compressed to a specific thickness and then cut or punched into required patch sizes and shapes.

An additional impermeable backing layer is often incorporated to control the drug release direction, minimize drug loss, and maintain the structural integrity of the patch by reducing deformation or disintegration during its application period.

d) Gels and Ointments:

Semisolid formulations such as gels and ointments are widely utilized in buccal drug delivery due to their ability to spread easily over the oral mucosal surface. However, compared to solid dosage forms like tablets, films, or patches, dose precision in these semisolid systems may be less accurate. A major limitation associated with gels is their short residence time at the site of application, which has been effectively improved with the incorporation of mucoadhesive polymers.

Certain polymers—such as sodium carboxymethylcellulose and xanthan gum—undergo a sol-to-gel transition, changing from a liquid state to a semi-solid state after application. This increase in viscosity enhances adhesion, prolongs retention, and enables controlled and sustained drug release. Hydrogels are considered especially valuable for buccal delivery due to their strong water-holding capacity and biocompatibility.

A key therapeutic use of mucoadhesive gels is in the treatment of periodontitis, a chronic inflammatory condition that causes pocket formation between the tooth and gingiva and may eventually lead to tooth loss. Incorporating mucoadhesive polymers into antimicrobial gel formulations makes administration into periodontal pockets easier, often through a syringe. Hydroxypropyl methylcellulose (HPMC) has been applied in the development of adhesive ointments for this purpose. Additionally, highly viscous gels prepared using carbopol and hydroxypropylcellulose have demonstrated the ability to remain at the application site for up to 8 hours.

- **Advantages:**

Good adhesion: Ointment bases such as hydrophilic petrolatum, PEG, and lanolin enhance adherence to moist mucosal surfaces.
Enhanced penetration: Ointments maintain hydration and improve permeation through Mucosa.
Longer residence time: Their greasy or semi-solid nature provides prolonged contact.beneficial for controlled release.
Protection of mucosal surface: Acts as a soothing barrier and supports healing Examples:

Mucoadhesive periodontal ointments.
Rectal and vaginal ointments containing antimicrobial or anti-inflammatory drugs
Buccal ointments delivering antifungals (e.g. for oral candidiasis).

➢ Future Scope:

The field of mucoadhesive controlled drug delivery systems continues to offer significant potential for scientific and clinical advancements. Future research is expected to focus on the development of next-generation smart polymers that respond to specific biological or environmental stimuli such as pH, temperature, and enzymes, enabling more precise and personalized drug release. The integration of nanotechnology, particularly mucoadhesive nanoparticles and nano-gels, will further improve drug penetration across mucosal barriers and enhance therapeutic efficiency for drugs with poor solubility or stability.

Another promising direction is the exploration of biologically active polymers, such as lectins, thiomers, and enzyme-responsive materials, which can enhance tissue interaction and prolong residence time. Additionally, advances in 3D printing and bio-fabrication may allow the customization of mucoadhesive dosage forms tailored to individual patient needs and anatomical variations.

Clinical translation will require extensive in-vivo research, toxicity assessments, and regulatory validation to ensure safety and efficacy. Expansion of mucoadhesive delivery systems for the treatment of chronic diseases, peptide- and protein-based drugs, vaccines, and gene therapy offers notable opportunities. With continuous innovation and interdisciplinary collaboration, mucoadhesive drug delivery systems are expected to become an integral part of modern pharmaceuticals, transforming current therapeutic practices and improving patient outcomes.

➢ RESULTS:

The literature reviewed indicates that mucoadhesive drug delivery systems enhance drug absorption, improve therapeutic efficacy, and prolong drug residence at the site of action. The findings demonstrate that polymers such as carbopol, chitosan, sodium alginate, HPMC, and PVA significantly contribute to improved mucoadhesive strength and controlled drug release. Various dosage forms, including tablets, films, patches, buccal gels, microspheres, and nanoparticles, were found to provide better patient compliance and sustained plasma drug concentration.
Research also showed that mucoadhesive patches and films provide more uniform drug distribution and controlled release compared to traditional oral dosage forms. They effectively bypass first-pass metabolism and improve the bioavailability of drugs with short half-lives or poor solubility. Comparative studies revealed that buccal and nasal mucoadhesive systems show the highest absorption due to high vascularization. Overall, results confirm that mucoadhesive drug delivery provides superior outcomes in systemic and local drug delivery.

➢ DISCUSSION:

Mucoadhesive drug delivery systems represent a significant advancement in pharmaceutical technology. Findings suggest that polymer selection and formulation technique play a crucial role in controlling drug release properties, mucoadhesive strength, and mechanical stability of dosage forms. Hydrophilic polymers create strong interactions with mucosal surfaces through hydrogen bonding, van der Waals forces, and ionic interactions, leading to prolonged contact time and improved drug absorption.

The review demonstrated that innovative formulation methods, such as solvent casting, direct compression, and nanoparticle engineering, enhance drug encapsulation efficiency and release kinetics. Mucoadhesive systems were found particularly promising for drugs undergoing extensive first-pass metabolism, peptides, proteins, and drugs used in diabetes, cardiovascular diseases, pain management, and hormone therapy.

Despite numerous advantages, some limitations were identified, including mucosal irritation, variability in physiological conditions such as saliva or mucus turnover, and challenges in patient handling and stability. However, ongoing research focuses on developing second-generation polymers that exhibit responsiveness to temperature, pH, and enzymatic environment, enabling smart and targeted drug release.

➢ CONCLUSION:

Mucoadhesive drug delivery systems play an important role in improving patient compliance, reducing enzymatic degradation, and maintaining prolonged contact at the site of application. The careful selection of polymers with strong adhesion properties and good biocompatibility remains essential in developing effective mucoadhesive formulations. Current research is increasingly focused on replacing conventional polymers with advanced alternatives, including thiolated polymers and lectin-based systems, which provide superior binding efficiency and extended retention. However, considerable research and clinical validation are still required before these novel approaches achieve routine clinical use for systemic as well as local therapeutic applications.

Novel controlled-release mucoadhesive technologies represent a major step forward in pharmaceutical innovation. By exploiting the natural adhesive capacity of mucosal tissues, these systems extend drug residence time, enhance absorption, and offer sustained therapeutic effects. They effectively address limitations associated with traditional dosage forms, such as short residence time, poor bioavailability, rapid drug clearance, and frequent dosing requirements

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