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# REVIEW ON MUCOADHESIVE NANOPARTICLE DRUG DELIVERY SYSTEMS

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**ABSTRACT**

The main goal of pharmaceutical research is to design products with ensured quality to treat diseases effectively. Patient and clinician compliance is crucial to Triple Crown bench-to-bedside translation. Materials of pharmaceutical interest (MPIs) are classified into two main classes: Active pharmaceutical ingredients (API) and nonpharmacological active excipients. The former trigger a pharmacological response, while the latter is incorporated into the formulation to improve its (bio) pharmaceutical properties and performance. One of the challenges in early and late PR and D is the drug's poor aqueous solubility and permeability. This property is common to approximately 50% of the APIs on the market, and it represents a crucial hurdle during the stages of drug product development. Moreover, low solubility in biological fluids ends up into restricted absorption in the gastrointestinal tract (GIT) and restricted bioavailability; the oral route is the most well-known one; in addition, this route is usually associated with hepatic first-pass metabolism, chemical and enzymatic degradation in the GIT medium, basolateral-to-apical efflux by pumps of the ATP-binding cassette super family (ABCs) and reduced bioavailability. The simplest strategy to avoid these disadvantages is the parenteral route. However, it provokes tissue damage, pain, and patient incompliance. Moreover, systemic exposure typically results in adverse effects that cannot be easily controlled. The oral route is also less feasible when more prolonged release kinetics is demanded owing to the short gastric emptying and intestinal transit times. The emergence of micro and nanotechnologies, with the implementation of noninvasive and painless administration routes, has revolutionized the pharmaceutical market and the treatment of disease. The interest in capitalizing the mucus layer that covers the surface of a variety of organs by developing mucoadhesive dosage forms that remain in the administration site for more prolonged times, increasing the local and systemic bioavailability of the administered drug using nanotechnology, is on the rise. Aiming to overcome the mayoral route's main drawbacks and maintain high patient compliance, the engineering of innovative drug delivery systems (DDS) administered by mucosal routes has come to light and gained the scientific community's interest in the possibility of changing drug pharmacokinetics dramatically. In addition, to achieve t, the development of biomaterials has been refined to fit the specific applications to achieve the goal of many drug administration materials having a strong affinity for mucosal surfaces and adhering to the surface of these tissues. Drugs may be physically or chemically bound to these mucoadhesive to increase their residence time at a specific location in the body. Additionally, the mucoadhesive effect allows for site-specific delivery of drugs to the mucosa. In some cases nanoparticles are not able to prolong the drug release for an extended per period to that reason, only mucoadhesive drug delivery systems are developed[3]. The current review presents an updated summary of manyadhesion theories, polymers used for mucoadhesion and their possibilities.

**KEYWORDS**

Bioavailability, Nanoparticles, Mucoadhesion, Prolonged release and Theories of mucoadhesion.

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## INTRODUCTION

A nanoparticle is a small particle ranging between 1 to 100 nanometers. Undetectable by the human eye, nanoparticles can exhibit significantly different physical and chemical properties to their larger material counterparts. The important technological advantages of nanoparticles used as drug carriers

are high stability, high carrier capacity, the feasibility of incorporating both hydrophilic and hydrophobic substances, and the feasibility of variable routes of administration, including oral application and inhalation[1].

Nanoparticles may also be designed to permit controlled (sustained) drug unleash from the matrix. These properties of nanoparticles enable the improvement of drug bioavailability and the reduction of the dosing frequency[2]. Still, the main goal of pharmaceutical research is to design products with ensured quality to treat diseases effectively. Patient and clinician compliance is crucial to productive bench-to-bedside translation. Materials of pharmaceutical interest (MPIs) are classified into two main classes: Active pharmaceutical ingredients (API) and nonpharmacological active excipients[3]. The former trigger a pharmacological response, while the latter is incorporated into the formulation to improve its (bio) pharmaceutical properties and performance. One of the challenges in early and late PR and D is the drug's poor aqueous solubility and permeability. This property is common to approximately 50% of the APIs on the market and it represents a crucial hurdle during the stages of drug product development. Moreover, low solubility in biological fluids leads in restricted absorption in the gastrointestinal tract (GIT) and restricted bioavailability; the oral route is the most known one; in addition, this route is generally associated with hepatic first-pass metabolism, chemical and enzymatic degradation in the GIT medium, basolateral-to-apical efflux by pumps of the ATP-binding cassette super family (ABCs), and reduced bioavailability[4]. The easiest strategy to bypass these disadvantages is the parenteral route. However, it provokes tissue damage, pain, and patient incompliance. Moreover, systemic exposure typically leads to adverse effects that cannot be easily controlled. The oral route is also less feasible when more prolonged release kinetics is demanded owing to the short gastric emptying and intestinal transit times[5]. The emergence of micro and nanotechnologies, with the implementation of noninvasive and painless administration routes, has revolutionized the pharmaceutical market and the treatment of disease. The interest in capitalizing the mucus layer that covers the surface of a variety of organs by developing mucoadhesive dosage forms that remain in the administration site for more prolonged times, increasing the local and systemic bioavailability of the administered drug using nanotechnology, is on the rise. Aiming to overcome the mayoral route's main drawbacks and maintain high patient compliance, the engineering of innovative drug delivery systems (DDS) administered by mucosal routes has come to light and gained the scientific community's interest in the possibility of changing drug pharmacokinetics dramatically[6]. In addition, to achieve t, the development of biomaterials has been refined to fit the specific applications to achieve the goal of many drug administration materials having a strong affinity for mucosal surfaces and adhering to the surface of these tissues. Drugs may be physically or chemically bound to these mucoadhesive to increase their residence time at a specific location in the body[7]. Additionally, the mucoadhesive effect allows for site-specific delivery of drugs to the mucosa. In some cases, particles cannot prolong the drug release for an extended period. For that reason; only mucoadhesive drug delivery systems are developed.

The mucoadhesive drug delivery system interacts with the mucus layer covering the mucosal epithelial surface and nucin molecules. It increases the residence time of the dosage form at the absorption site. A mucoadhesive drug delivery system is a part of a controlled delivery system[8].

**Advantages of mucoadhesion**

MDDS offers several advantages over other controlled oral controlled release systems by prolongation of residence during

Targeting and localization of dosage foam at a specific site

High drug flix at the absorbing tissue

MDDS will serve both the purpose of sustain release and the presence of dosage foam at the site of absorption

Excellent accessibility
Painless administration.
Low enzymatic activity and avoidance first pass metabolism.

## POSSIBILITIES IN MUCOADHESION

**Holds dosage form at the site of action for longer period**

Mucoadhesion allows the formulation of the drug to be applied directly to the target site and remain there longer than can be achieved with the anon mucoadhesive formulation. This enhances drug delivery and prolongs drug action for localized (dosage form at the site of motion) or systemic nine dosage form at absorption site) delivery[9].

**Lubricates the target tissues**

Though beyond any doubt a significant benefit, mucoadhesion can do more than allow longer period localized drug delivery. Mucoadhesive properties can enable a formulation to coat a mucous membrane, providing a lubricating cover for the tissues. This can be beneficial for many products, such as mouthwash for dry mouth or artificial tears for dry eyes.

**Provides a protective covering over the damaged tissue**

On the same note as coating tissues for lubrication, mucoadhesive coatings can shield damaged or sensitive tissues. This isolates the tissues from harsh surroundings that can cause pain or delay healing.

**Enables more convenient, non-invasive products**

Mucoadhesion can benefit a wide variety of dosage forms for use on or in numerous areas of the body, enabling localized, targeting drug delivery; because of this localized delivery, muchadhesion empowers the creation of non-invasive, more convenient dosage forms that would otherwise not be effective[10].

However, if mucoadhesion is effectively formulated into a drug product, patient-preferred dosage forms can be successfully developed, for examples:

Topical gels and emulsion
Patches and films
Oral's solutions and suspensions
Eye drops or contact lenses
Nasal sprays
Lozenges and buccal tablets
Toothpaste and mouth washes

## HISTORY

Since the early years 1980s, mucoadhesion has gained wide interest in pharmaceutical technology. Adhesion can be defined as the bond produced by contact between a pressure-sensitive adhesive and a surface[11]. The American Society of Testing and Materials has described it as the state in which two surfaces are held together by interfacial forces, which may consist of valence forces, interlocking action, or both. Mucoadhesive drug delivery systems prolong the residence time of the dosage form with the underlying absorption surface and thus improve the therapeutic performance of the drug. In recent years, many such mucoadhesive drug delivery systems have been developed for oral, buccal, nasal and vaginal routes for both systemic and local effects[12].

The dosage form designed for mucoadhesive drug delivery should be small and flexible enough to be acceptable for patients and not irritate. Other desired characteristics of mucoadhesion dosage form include high loading capacity and controlled drug release. Good mucoadhesion properties, smooth surface, tasteless and convenient applications. Several peptides, including thyrotropin-releasing hormone, insulin, octreotide, and leuprolide, have been delivered via the mucosal route[13].

Due to their hydrophilicity and large molecular weight, the mucosa's inherent permeation and enzymatic barriers have relatively low availability (0.1-5) owing to their hydrophilicity and large molecular weight.

## THEORIES OF MUCOADHESION

There are six general theories of adhesion, which have been adapted for the investigation of mucoadhesion:

**The electronic theory**

suggests that electron transfer occurs upon contact with adhering surfaces due to differences in their electronic structure; this is proposed to result in the formation of an electrical double layer at the interface, with subsequent adhesion due to attractive forces[14].

**The wetting theory**

This theory is primarily applied to liquid systems. It considers surface and interfacial energies. It involves the ability of a liquid to spread spontaneously onto a surface as a prerequisite for the development of adhesion[15]. The affinity of a drink for a character can be found using techniques such as the contact angle of the liquid on the surface, with the general rule being that the lower the contact angle, the higher the affinity of the liquid to the solid.

**The adsorption theory**

Describes the attachment of adhesives based on hydrogen bonding and van der Waals forces. It has been projected that these forces are the key contributors to the adhesive interaction. A subsection of the chemisorptions theory assumes an interaction across the interface occurs due to strong covalent bonding.

**The diffusion theory**

Describes the inter diffusion of polymer chains across an adhesive interface. This process is defined by concentration gradients and is affected by the available molecular chain lengths and mobilities. The depth of interpenetration semi-permanent adhesive bond[16].

**The mechanical theory**

Assumes that adhesion arises from an interlocking of a liquid adhesive into irregularities on a rough surface. However, uneven surfaces also provide an increased surface area available for interaction and an enhanced viscoelastic and plastic dissipation of energy during joint failure, which is thought to be more important in the adhesion process than mechanical effects.

**The fracture theory**

Differs a little from the other five in that it relates the adhesive strength to the forces required for the detachment of the two involved surfaces after adhesion[17].

## POLYMERS USED IN MUCOADHESIVE DRUG DELIVERY SYSTEMS

Mucoadhesive drug delivery systems are based on the adhesion of a drug carrier to the mucous membrane. To promote this adherence, a suitable page is required.

Ideal Characteristics of mucoadhesive polymers

A Mucoadhesion-promoting agent or polymer is added to the formulation, which helps to promote the active pharmaceutical ingredient's adherence to the oral mucosa. The agent can have additional properties like swelling to promote disintegration when in contact with the saliva[18].

Polymer must have a high molecular weight of up to 100.00 or more. This is important to promote the adhesiveness between the polymer and mucus.

Long-chain polymers' chain length must be long enough to promote interpenetration, and it should not be too long that diffusion becomes a problem[19].

High viscosity

Spatial conformation

Flexibility of the polymer chain promotes the interpenetration of the polymer within the mucus network[20].

Concentration of the polymer an optimum concentration is required to promote the mucoadhesive strength. It depends, however, on the dosage form.

Optimum hydration excessive hydration leads to decreased mucoadhesive strength due to the formation of a slippery mucilage.

It should be non-toxic, economical, biocompatible and preferably biodegradable[21].

**Various mucoadhesive polymers can broadly be categorized as mentioned below**

**Synthetic polymers**

Cellulose derivates (methylcellulose, Ethyl cellulose, Hydroxyethyl cellulose, sodium carboxymethylcellulose)[22].

Poly (Acrylic acid) polymers (carbomers polycarbophil).

Poly hydroxyl ethyl methylacrylate.

Poly ethylene oxide.
Poly vinyl pyrrolidone.
Polyvinyl alcohol.

**Natural polymers**

Tragacanth, sodium alginate, Guar gum, Xanthum gum, soluble starch, Gelatin, Chitosan[23].

## MUCOADHESIVE POLYMERS CAN ALSO BE CLASSIFIED INTO THE FOLLOWING CATEGORIES

**Traditional non-specific first–generation muco adhesive polymers**

First-generation mucoadhesive polymers can be classified into three main subsets[24], these are:
Anionic polymers
Cationic polymers
Non–ionic polymers

Anionic and cationic polymers have been shown to exhibit the greatest mucoadhesive strength among all of the above mentioned polymers. Consequently, such charged polymeric systems will now be examined in more depth[25].

## FACTORS AFFECTING MUCOADHESION

**Polymers-related factors**

Molecular weight
Concentration of polymer
The flexibility of polymer chains
Presence of functional group
Spatial conformation
Cross linking density

**Environment-related factors**

PH of polymer substrate interface
Applied strength

**Physiological factors**

Mucin turn over
Disease state
Molecular weight Mucoadhesive increases with mol wt above 100,000

**Flexibility**

Mucoadhesive starts within the interfacial region with the diffusion of the polymer chains[26].

**Cross-linked density**

Increase the thickness of insufficient cross-linked swelling and decrease the rate of cross-interpenetration between polymer and mucin.

**Hydrogen bonding capacity**

The desired polymer must have functional groups to form hydrogen bonds and flexibility to improve this hydrogen bonding potential.

**Hydration**

Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites or hydrogen bonding, electrostatic interaction between polymer and mucus network, e.g., HMA, PVA.

**Concentration**

When the concentration of the polymer is low, the number of penetrating polymer chains per unit volume of mucus is small and interaction between polymer and mucus unstable[27].

## MUCOADHESIVE DOSAGE FORMS

Liquid
Suspensions
Gel forming liquids

**Solids**

Tablets
Matrix tablet
Bioadhesive
Microparticles

**Semisolid**

Gels and ointment
Films
Patches

**Applications**

Vaccines are delivered to treat diseases like hepatitis, influenza, ricin toxoid and birth control.

Microspheres in vaccine delivery have specific applications like improvement of antigenicity by adjuvant action, and modulation of antigen release stabilization of antigen.

Passive targeting of leaky tumor vessels, active targeting of tumor cells, antigens by intravenous Intra -arterial application.

Chemoembolization involves selective arterial embolization of the tumor along with local delivery of chemotherapeutic agent.

**Imaging**

Various cells, cell lined tissues, and organs can be imaged using radio-labeled microspheres[28].

Targeting of the drug at particular sited of action.

Delivery of insulin and gene therapy with DNA plasmids.

Topical porous microspheres.

Surfaces modified microsphere.

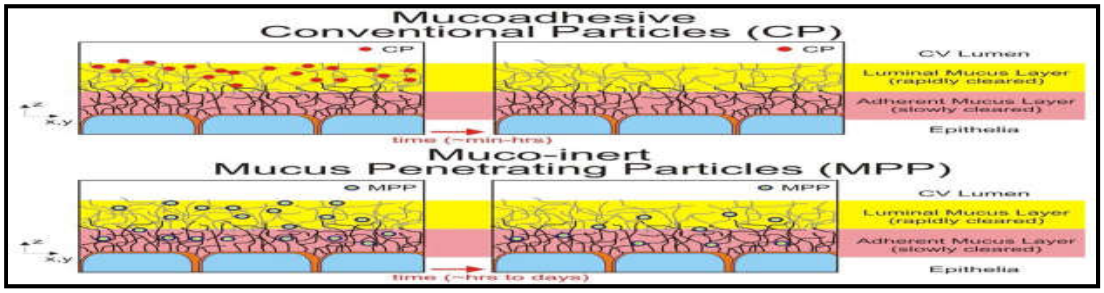


**Figure No.1: Mucoadhesive conventional particles**

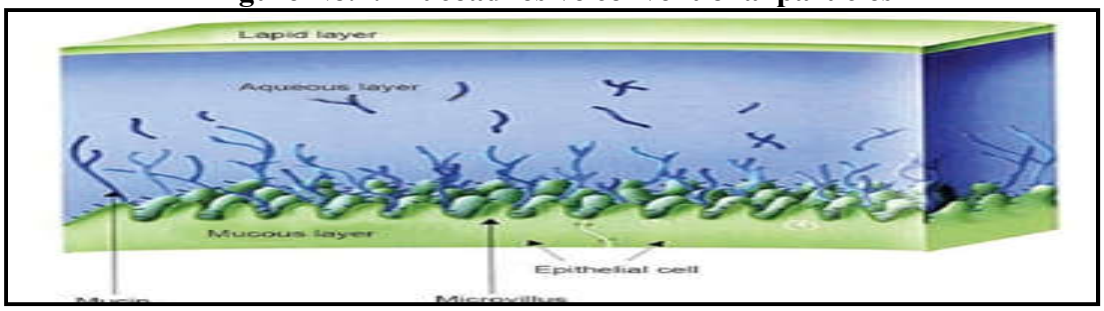


**Figure No.2: Mucoadhesive drug delivery system**

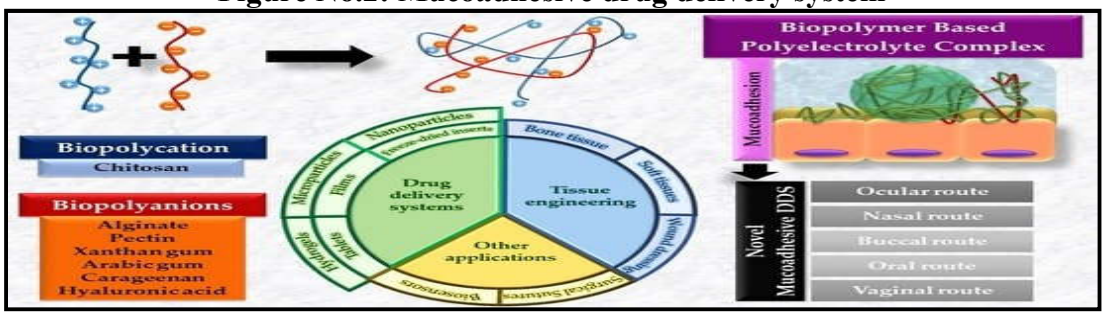


**Figure No.3: Polymers naturally occuring polyelectrolytes and their use for the development of complex-based mucoadhesive drug delivery systems**


**Figure No.4: Factors affecting mucoadhesion**

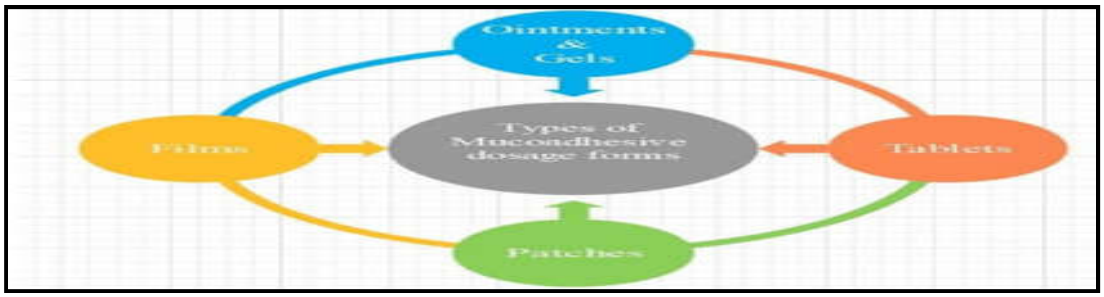


**Figure No.5: Types of mucoadhesive dosage forms**

## CONCLUSION

The phenomenon of mucoadhesion can be used as a model for the controlled drug delivery approaches for several drug candidates. The various benefits of the oral mucoadhesive drug delivery systems, such as prolongation of the residence time of the drug, which in turn increases the absorption of the drug, these are important factors in the oral bioavailability of several drugs. The overall success of the mucoadhesive drug delivery is the polymer physicochemical properties and the *in-vivo* factor such as mucin turnover rate and mucin flow. A number of both *in-vitro* and *in-vivo* techniques have been developed for the analysis of the mucoadhesive drug delivery systems. Mucoadhesive dosage forms extend from the simple oral mucosal delivery to the nasal, vaginal, ocular and rectal drug delivery systems. The most vastly studied and accepted polymers for mucoadhesion are the hydrophilic, high molecular weight, anionic molecules like carbomers. Recently the focus has been shifted on to the novel second-generation polymers like the thiolated polymers.

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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