Volume 3, Issue 1, 2024, Page 716-726

International Journal of Pharma Research and Technology

A Comprehensive Review on Mucoadhesive Drug Delivery System

Patil GC[1]*, Jain AS[2], Patil DR[3], Shaikh AZ[4], Shaikh SR[5], Dr. Pawar SP[6]
P. S. G. V. P. M's College of Pharmacy, Shahada Dist. Nandurbar
ganeshpatil10092002@gmail.com

Abstract

By creating innovative drug delivery methods, like the mucoadhesive system, medication effects can be improved. The mucus layer that covers the mucosal surfaces interacts with mucoadhesive medication delivery methods. Mucin molecules and the epithelium surface, prolonging the duration the dose form spends at the absorption site. Drugs that have a local effect or that are best absorbed in the gastrointestinal tract (GIT) need to stay there for a longer period of time. There are now five theories that explain mucoadhesion: electronic, adsorption, wetting, diffusion, and fracture. The complex process of mucoadhesion involving a polymeric drug delivery system involves interactions between polymer chains through wetting, adsorption, and other mechanisms. Increased medication plasma concentrations and therapeutic activity are benefits of mucoadhesive dosage formulations. The nature of the mucosal tissue and the physicochemical characteristics of the polymeric formulation are just two examples of the many variables that influence a dosage form's propensity to adhere to mucous membranes. As a result, many mucosal-covered organelles utilize mucoadhesive systems extensively for the transfer of active substances for either local or systemic action. Drugs administered buccally have a number of advantages over those administered orally, including faster action and better patient compliance, especially for paediatric and geriatric patients. An overview of the various elements of mucoadhesion, mucoadhesive materials, factors affecting mucoadhesion, and lastly different mucoadhesive drug delivery systems are all part of this review paper.

Keywords: Oral mucosa, mucoadhesive, and bioadhesive.

Introduction

Mucoadhesive Drug Delivery system

The idea of mucoadhesion has drawn a lot of attention in pharmaceutical technology since the early 1980s [1]. Mucoadhesive drug delivery systems are delivery systems which make use of a given polymer's ability to bioadhere, which makes it stickier when hydrated and can be used to target a medicine to a specific area of the body for a long time. Two materials, at least one of which is biological, are held together by interfacial forces in a process known as bioadhesion. The Attachment could take the form of adhesion between a polymer and a biological membrane, for example, or between an artificial substance and a biological substrate. The word "mucoadhesion" refers to the

attachment of a polymer to the mucin layer of a mucosal tissue [2].Several distribution

- Buccal delivery system
- Oral delivery system
- Vaginal delivery system

Mucoadhesive Oral Drug Delivery Systems

The most recommended method of medicine delivery is via the oral route. The following categories of drug administration through oral cavity membranes are possible:-

1. Sublingual delivery: This is the systemic administration of medication via the mucosal lining of the oral cavity.
2. Buccal delivery: This is the administration of medication through the buccal mucosa, the mucosal lining of the cheeks.
3. Local delivery: Oral drug administration using this method.

The buccal area of the oral mucosal cavity provides a desirable route of administration for regulated systemic medication delivery. The delivery of medications through the mucosal lining of the cheeks is known as buccal administration. Although the buccal mucosa is favoured for systemic transmucosal medication administration, the sublingual mucosa is known to be more permeable. This is because the buccal mucosa is a more favourable area for retentive systems due to its expanse of smooth muscle and relatively immobile mucosa. Therefore, the buccal mucosa is more suited for sustained medication administration [3].

Mucoadhesion

The term bioadhesion can be defined as the state in which two materials, at least one methods are available for mucoadhesive drug delivery systems:

- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

biological in nature, are held together for an extended period of time by interfacial forces [4].

Bioadhesion in biological systems can be divided into three categories:

•Type 1 Adhesion, such as that between platelet aggregations and wound healing.

• Type 2, which refer to the attachment of a biological phase to an artificial substrate, such as the adhesion of cells to culture dishes and the creation of biofilms on prosthetic devices and inserts.

• Type 3: Adhesion of an artificial substance to a biological substrate, as in the case of sealants' adhesion to dental enamel and the adhesion of synthetic hydrogels to soft tissues [5].

Mechanisms of mucoadhesion

Thus, the mucoadhesion mechanism typically consists of two stages:

1. The contact stage 2. The stage of consolidation

The mucoadhesive initial contacts with the mucous membrane, along with the formulation's subsequent swelling and spreading, marks the beginning of its deep engagement with the mucus layer [6]. Sometimes the distribution mechanism is mechanically attached over the membrane, as with ocular or vaginal formulations. Other

times, the aerodynamics of the organ to which the system is supplied, such as for the nasal route, enhance deposition. The presence of moisture in the consolidation process activates the mucoadhesive compounds. Moisture acts as a plasticizer in the solution, allowing the mucoadhesive molecules to dissociate and form weak hydrogen and vander Waals bonds [7]. There are essentially two theories that account for the consolidation step: 1. the diffusion theory. 2. The dehydration theory.

Diffusion hypothesis states that the mucoadhesive molecules and the mucus glycoproteins interact with one another by interpenetrating their chains and forming secondary bonds [7]. The mucoadhesive device has properties that encourage both chemical and mechanical interactions for this to happen [8].Dehydration theory states that substances that can easily gel in an aqueous environment, when in touch with mucus, can dehydrate it because of the difference in osmotic pressure [7].

Advantages of Oral Mucoadhesive Drug Delivery Systems [9]

1. Increases the bioavailability by extending the dosage form's period in residence at the absorption site.

2. Great accessibility and quick start-up.

3. Quick absorption due to a large blood supply and healthy blood flow rates.

4. Drugs are guarded against deterioration in the git's acidic environment.

5. Increased adherence by the patient.

Disadvantages of Mucoadhesive Drug Delivery Systems [9]

1. The occurrence of local ulcerous reactions brought on by prolonged contact with a substance with ulcerogenic properties.

2. The lack of an appropriate model for in vitro screening to discover medications suitable for such administration is one of the key obstacles to the development of oral mucosal delivery.

3. Taste and irritability acceptance by the patient.

4. Eating and drinking are not permitted.

Components / Structural Features of Oral Cavity

The area of the mouth called the oral cavity is defined by the lips, cheeks, hard palate, soft palate, and floor of the mouth. There are two areas of the oral cavity.

• The outer oral vestibule, which is enclosed by the gums, teeth, lips, and cheeks.

• The actual oral cavity, which includes the hard and soft palate on the roof and extends from the teeth and gums back to the fauces (way that leads to the pharynx). From the cavity's floor, the tongue protrudes [2].

Anatomy and Nature of Oral Cavity [10]

The hard and soft palates, the floor of the mouth, and the tonsils serve as the borders of the oral cavity, which can be separated into two areas: the outer oral vestibule and the oral cavity itself.

Physical Description of Oral Cavity

According to their purpose, the three types of mucosa that line the oral cavity can be broken down into the following groups:

1. Masticatory mucosa, which includes the mucosa surrounding the teeth and on the hard palate and has keratinized epithelium.

2. Lining mucosa: This layer, which has non-keratinized epithelium, covers the soft palate, lips, cheeks, fornix, base of the oral cavity, lower part of the tongue, and buccal mucosa.

3. Specialised mucosa: a highly keratinized layer on the tongue's dorsum [10].

Overview of Oral Mucosa

Structure

The oral mucosa is primarily made up of three separate layers, with the basement membrane, lamina propria (connective tissue layer), and sub mucosa acting as the innermost layer [11-12]. The epithelium serves as a layer of defence for the tissue below. It is into keratinized and non-keratinized epithelium. The former is present in the alveolar mucosa, vestibule, lips, cheeks, ventral surface of the tongue, and mucosal lining of the soft palate. The sublingual epithelium has slightly less cells than the buccal mucosa's epithelium, which is roughly 40–50 cell layers thick [13].

Permeability

Permeability Buccal mucosa has a 4–4000 times higher permeability than skin. The thickness and level of keratinization of the tissue affect the permeability of the oral mucosa. According to this, buccal permeability is greater than palatal and sublingual permeability is greater than both. The buccal mucosa is thicker and non-keratinized, the palatal mucosa is intermediate in thickness but keratinized, and the sublingual mucosa is comparatively thin and non-keratinized. The epithelium's makeup changes based on the location in the mouth cavity [11-12]

Environment

The oral epithelia cell is covered in mucus and intracellular metabolites which primarily consists of complexes consisting of proteins and carbohydrates. These complexes may be bound to a specific area of the cell surface or may not. The matrix acts as a lubricant and is crucial for cell-cell attachment. Major and minor salivary glands secrete mucus in the oral mucosa, whereas goblet cells of stratified squamous epithelium secrete mucus in the remainder of the body [11-12]

Composition of Mucus Layer:

Mucus is a translucent and viscid secretion which forms a thin, contentious gel, mean thickness of this layer varies from about 50-450 µm in humans secreted by the goblet cells lining the epithelia. It has the following general composition:-Water -95%, Glycoprotein and lipids – 0.5-3.00%, Mineral salts – 1%, free proteins – 0.5-1.0% [2].

Functions of Mucus Layer

1. Protective, especially due to its hydrophobicity.

2. Barrier: The mucus layer functions as a barrier to tissue medication absorption and affects the bioavailability.

3. Adhesive: Mucus exhibits excellent adhesive qualities.

4. Lubrication: In order to make up for the mucus layer being removed as a result of digestion, bacterial breakdown, and mucin molecule solubilization, it is important to retain the mucus from the goblet cell [2].

Salivary Secretion:

The mouth cavity contains three main saliva-secreting glands: the parotid, sublingual, and submandibular. Saliva has several purposes, including lubricating food for chewing and swallowing and moistening the oral cavity. It also protects tissue from abrasion by potentially sharp objects that may enter the mouth. Saliva is a complex fluid that contains both organic and inorganic elements and is 99% water. Researchers have found that although 1-1.5L of saliva is produced every day, this flow is varied. The saliva in the oral cavity has a limited buffering capacity and a pH range of 5.8 to 7.4 [14-15].

Mucoadhesion Theories

The Mucoadhesion phenomena have been explained by six different theories. These ideas outline different steps of the contact between two substrates and define mucoadhesion as the interaction between a mucoadhesive polymer and mucosal layer. The following presents these theories:

- Wetting Theory
- Adsorption Theory
- Electronic Theory
- Mechanical Theory
- Fracture Theory
- Diffusion Theory

Wetting theory: -According to this notion, a mucoadhesive polymer penetrates the absorbent surface's imperfections where it hardens and causes mucoadhesion. The contact angle can be used to calculate the affinity towards the surface [16].

Adsorption Theory: -This hypothesis uses van der Waals forces and hydrogen bonding to explain how adhesives are attached. These forces are thought to be the primary causes of the sticky contact. The chemisorptions hypothesis, a branch of this, postulates that an interaction across the interface happens as a result of strong covalent bonding [7].

Electronic theory: -According to this idea, the electrical structural variations between two surfaces have a significant impact on their interactions. Through the exchange of electrons between the polymer and the mucous membrane, bonds are formed. An electrical double-layer is responsible for the establishment of the attraction force between the polymer and mucosal surface [17].

Mechanical theory:-Adhesion between two surfaces happens because a mucoadhesive fluid is present on the rough surface. Although imperfections enhance the interface's surface area, this step has a significant impact on mucoadhesion processes [18].

Fracture theory:-Is a little different from the other five in that it links the strength of the adhesive to the forces needed to separate the two involved surfaces after adhesion [7].

Diffusion theory: -The diffusion theory is based on the time it takes for a polymer chain to penetrate the mucus' glycoprotein network

as well as its concentration gradient. When the interpenetration layer thickness reaches between 0.2 and 0.5 m, two things happen: one is the production of a layer of interpenetration, and the other is the realization of an efficient adhesion. This layer's creation is influenced by a gradient in concentration, the molecular weight of the adhesion-promoting macromolecules, hydrodynamic size, mobility, flexibility, and the length of the polymer chains, among other variables [19].

Mucoadhesive Polymers Properties

1. The active compound must substantially load it.

2. Swell in the delivery absorption site's aquatic biological environment.

3. Interact with mucus or any of its elements to ensure proper adherence.

4. They enable the regulated release of the active substance when swollen.

5. Be physiologically reduced to inactive, non-toxic oligomers or excreted unmodified.

6. Enough chemical groups capable of forming hydrogen bonds.

7. Have a heavy molecular structure.

8. Have an extremely flexible chain.

9. Surface tension that causes mucous layer spreading [20].

Polymers Used For Mucoadhesive Drug Delivery

These polymers are classified as,

Hydrophilic polymers

Contains carboxylic group and possess excellent mucoadhesive properties. These are,

- PVP (Poly vinyl pyrrolidine)
- MC (Methyl cellulose)
- SCMC (Sodium carboxyl methyl cellulose)
- HPC (Hydroxyl propyl cellulose)

Hydrogels

These swell when in contact with water and adhere to the mucus membrane. These are further

Classified according to their charge

Anionic polymers -carbopol, polyacrylates

Cationic polymers –chitosan,

Neural/ non-ionic polymers - Eudragit analogues [21].

Factor Affecting Mucoadhesion

Molecular weight: -A polymer's mucoadhesive strength increases as its molecular weight rises above 100,000. Between 200,000 and 70,000, the molecular weight of polyoxyethylene polymers directly correlates to their mucoadhesive strength [22].

Flexibility:-The diffusion of polymer chains in the interfacial region is the first step in mucoadhesion. The polymer chains must therefore have a significant amount of flexibility in order to create the appropriate entanglement with the mucus. Due to the addition of polyethylene glycol, the polymer's structural flexibility improved, which was the cause of the enhanced chain interpenetration. In general, viscosities and diffusion

coefficients can be used to link the mobility and flexibility of polymers, as more flexibility of a polymer results in greater diffusion into the mucus network [23].

Cross linking density: -Three significant and interconnected structural factors of a polymer network are the average pore size, the quantity and average molecular weight of the cross-linked polymers, and the density of cross-linking. Therefore, it makes sense that as crosslinking density increases, water diffusion into the polymer network happens at a slower rate, leading to insufficient polymer swelling and a slower rate of interpenetration between the polymer and mucin [24].

Hydrogen bonding capacity:-Another crucial aspect of a polymer's mucoadhesion is hydrogen bonding. Flexible polymers are essential for improving the hydrogen bonding potential of functional groups, which are necessary for the formation of hydrogen bonds in the desired polymers. Poly (vinyl alcohol), for example, All of the copolymers made from poly (methacrylic acid), hydroxylated methacrylated, and these substances have strong hydrogen bonding abilities [25].

Hydration: -In order for a mucoadhesive polymer to grow and form a suitable macromolecular mesh of appropriate size and to increase the interpenetration process between the polymer and mucin, hydration is also necessary. By exposing the bioadhesive sites for hydrogen bonding and/or electrostatic contact between the polymer and the mucus network, polymer swelling enables a mechanical entanglement. However, optimal swelling and mucoadhesion only occur at a specific level of hydration of the mucoadhesive polymer [25].

Charge: -Generalizations about the charge of bioadhesive polymers have been developed in the past, and it seems that non-ionic polymers exhibit less adherence than anionic polymers. Mucoadhesion requires a number of properties, one of which is a strong anionic charge on the polymer. Particularly in a neutral or slightly alkaline media, some cationic polymers are likely to exhibit improved mucoadhesive characteristics. A few cationic high-molecular-weight polymers, including chitosan, have also demonstrated to have effective adhesive capabilities. There isn't much information in the literature about how the charge of the membrane impacts mucoadhesion, however the pH of the membrane has an impact on mucoadhesion since it can change whether polymers are ionized or unionised [26].

Mucoadhesive Polymers [32]

Drugs and carriers that adhere to the mucous membrane are the foundation of mucoadhesive drug delivery systems. An appropriate carrier is necessary to encourage this adherence.

Ideal Characteristics of Mucoadhesive Polymers

The formulation includes a polymer or mucoadhesion promotoing agent that aids in promoting the adherence of the active medicinal component to mouth mucosa. When in contact with saliva, the agent may possess extra qualities such swelling that will hasten decomposition.

1) The polymer must have a molecular weight of at least 100,000. This is required to strengthen the bond between the polymer and mucus.
2) Long chain polymers - The chain length must be sufficient to encourage interpenetration but not so long that it causes a problem with diffusion.
3) High viscosity.
4) Cross-linking strength affects the chain's mobility and resistance to disintegration. In the presence of water, highly cross-linked polymers expand while maintaining their structure. Swelling enhances the polymer/mucus interpenetration and supports regulated drug release.
5) Spatial conformation.
6) Polymer chain flexibility encourages the polymer's interpenetration into the mucus network.
7) Polymer concentration for the mucoadhesive strength to be enhanced, the polymer must be at its ideal concentration. The dosage form, though, makes a difference.
8) Charge and degree of ionisation. Bernkop-Schnurch and Freudl demonstrated unequivocally the impact of polymer charge on mucoadhesion. When compared to the control, cationic chitosan HCl demonstrated a noticeable amount of adhesiveness. The mucoadhesive strength considerably increased with the addition of an anionic group to EDTA. Due to its low charge, the DTPA/chitosan combination had weaker mucoadhesive strength than cationic chitosan and anionic EDTA chitosan complexes. Since anion > cation > non-ionic, the mucoadhesive strength can be attributed to this.
9) Optimal hydration: Due to the production of slick mucilage, excessive hydration reduces the mucoadhesive strength.
10) Optimal pH - Mucoadhesion is best at low pH levels, but at higher pH levels, the conformation changes to a rod-like structure, making the mucoadhesive surfaces more accessible for inter-diffusion and interpenetration. Positively charged polymers, such as chitosan, form polyelectrolyte complexes with mucus at extremely high pH levels and display potent mucoadhesive forces.
11) It should be inexpensive, biocompatible, non-toxic, and preferably biodegradable [27].

Method Used To Study Bioadhesion

It has been observed that various test procedures can be used to evaluate bioadhesion. These tests are crucial for the creation and design of as they ensure compatibility, physical and mechanical stability; surface analysis, and bioadhesion binding strength, bioadhesion controlled released systems. Two major categories can be used to roughly classify the tests:

In-vitro / Ex-vivo methods

Most in-vitro methods were based on either tensile or shear stress.

a. Modified balance or tensile testers.
b. Wilhelm plate method (shear stress).
c. Other in-vitro methods

The measurement of bioadhesion has also been done using different techniques, such as the thumb test, the adhesion weight method,

the flow channel method, the fluorescent probe method, the falling liquid film method, and the colloidal gold staining method.

In-vivo methods

Rathbone et al. Have explored a number of techniques for determining the rate and volume of medication loss from the human oral cavity. These include the perfusion cells, discs, and buccal absorption test. These techniques have revealed details about the mechanism by which medications are carried across the membranes of the mouth cavity [28].

Mucoadhesive Dosage Form

Tablets: Mucoadhesive tablets have the potential to be used for controlled release drug delivery. However, coupling mucoadhesive properties to tablets has additional benefits. For instance, it offers efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio and facilitates a much more intimate contact with the mucus layer. Patients were able to eat and speak without experiencing any pain or discomfort because to this mucoadhesive pill [29].

Patches: Drug delivery systems that attach to the oral mucosa and come in a variety of forms have been created. Oro-adhesive patches come in three main categories: patches that deliver medications to the mouth cavity through a dissolvable matrix. When used to treat oral candidiasis and mucositis, these patches have a longer duration of action than solid dosage forms like pills and lozenges [30].

Films: They are more flexible and comfortable; mucoadhesive films may be preferable to adhesive tablets. Additionally, they can get around the mucosa's very brief length of residence for oral gels, which is readily washed away and eliminated by saliva. Drugs that can cross the blood-brain barrier are delivered directly to the blood supply in thin strips of polymeric films that dissolve on the tongue in less than 30 seconds. This allows for the quick treatment of conditions like impotence, migraines, motion sickness, pain relief, and nausea [31].

Gels and ointments: Gels and ointments are examples of semisolid dose forms that have the benefit of simple dispersion. Throughout the entire oral mucosa. As opposed to tablets, patches, or films, semisolid dosage forms may not provide the most precise drug dosage. Lacklustre gel retention at the application site has used mucoadhesive compounds to overcome. Hyaluronic acid, carbopol, sodium carboxymethylcellulose, and xanthan gum are a few mucoadhesive polymers that go through a phase change from liquid to semisolid. This alteration increases viscosity, which causes medications to release slowly and under control. Another interesting dosage type for buccal medication administration is hydrogel. Gels have been trilled for the topical delivery of antifungal, anti-inflammatory, and mucoprotective medicines to the oral mucosa as well as systemic analgesics, hypertension, and medications for treating cardiovascular disease [32].

Sprays: Spray that can pass the oral mucosa to deliver big molecules like insulin. A spray can quickly transfer the tiny chemical glyceryltrinitrate over the sublingual oral mucosa to relieve angina [33].

Pastes: Pastes have been used to administer controlled release triclosan in oral care formulations and antibacterial agents for enhanced extraction socket healing following tooth extractions in people with HIV illness. Additionally, pastes are employed for local distribution and preservation for the treatment of periodontal disease, slow-release minocycline is placed in the gingival pocket surrounding the teeth. Both as a solution and in a paste formulation, liposomes have been studied as drug delivery vehicles [34].

Conclusion

A drug delivery system that aims to increase patient compliance and convenience is more crucial than simply delivering the medication to the body. The intimate contact that mucoadhesive systems are known to provide between the dosage form and the absorptive mucosa leads to a high drug flow through the absorbing tissue. Numerous topics have been the subject of studies on mucoadhesive systems. It is a field that is expanding with the intention of creating new tools, more "intelligent" polymers, and new approaches to better understand the mucoadhesion phenomena. With the right technologies, delivery methods and the selection of the polymer for the oral mucosa could, in the future, be used for the treatment of many diseases, both mucosal and systemic, and the selection of pharmaceuticals that can be supplied via the mucosa could be significantly expanded.

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