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Critical review on buccal mucoadhesive drug delivery systems

Ganesh Shanker Pandey
Research Scholar, Department of Pharmacy, Mansarovar Global University, Sehore, Bhopal, Madhya Pradesh, India
Corresponding author email: ganesh_spandey@rediffmail.com

Dr. Aditya Nath Pandey
Professor, Faculty of Pharmacy, Department of Pharmacy, Mansarovar Global University, Sehore, Bhopal, Madhya Pradesh, India

***Abstract*---**Traditional oral dosage forms prone to first pass metabolism and degradation due to enzymes but mucoadhesive dosage form able to bypass first pass metabolism and related degradation. It also offers more patient compliance without risk of chocking in case of paediatric and geriatric patients. Buccal mucosa is considered as a convenient and easily accessible site for the drug administration for both local and systemic delivery. Mucoadhesion is a process involving chemical interactions between mucin and polymers. The use of mucoadhesive polymers in buccal drug delivery has gained a great attention. Various mucoadhesive dosage forms, including tablets, patches, disks, wafers, ointments and gels have recently been developed. Amongst them, buccal patches offer greater flexibility and comfort than the other forms. Smart materials such as stimuli-responsive hydrogels, liposome-based patches, polymeric micelles, etc. play a vital role in the development of these drug delivery systems by their efficient carrier capacity, prolonging the residence time of the drug at the site of absorption, improved drug bioavailability, reduced dosing frequency and improved patience compliance. There are different designs and manufacturing methods such as electrospinning, electrospraying and 3D printing techniques which are considered as novel and efficient methods with some unique characteristics than traditional approaches such as solvent casting. This review provides the brief knowledge about the oral mucosal drug delivery by discussing briefly the structural features of mucosa, mechanisms and theories involved in mucoadhesion, as well as to describe the most-used methodologies, polymers and finally various mucoadhesive drug delivery systems (buccal, nasal, ocular, gastro, vaginal, and rectal).

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Introduction

Today's pharmaceutical industry is facing the challenges to make available efficient treatment options that are readily acceptable to physicians and patients. The contribution of novel drug delivery systems should offer viable alternatives for better therapeutic outcomes in case they intend to equate or supersede oral medication. A variety of approaches have been described for use of delivering medicaments to the body that include intravenous, oral and topical. Several of such approaches involve oral delivery, including delivery to mucosal surfaces by the use of sprays, tablets, devices and the like. Owing to the ease of acceptance and patient compliance, oral route still remains the primary route of drug delivery. However, oral route has its own limitations such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosas are considered as potential sites for drug administration. Transmucosal routes of drug delivery (i.e., the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity) offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for drug absorption. Within the oral mucosal cavity, delivery of drugs is classified into three categories: (i) sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth, (ii) buccal delivery, which is drug administration through the mucosal membranes lining the cheeks (buccal mucosa), and (iii) local delivery, which is drug delivery into the intra-oral cavity [1]. Sobrero first attempted the use of buccal mucosa for drug absorption in 1847, and since then much research has been done to deliver drugs through this route [2]. Through buccal delivery drugs are absorbed rapidly into the reticulated vein, which lies under the oral mucosa and enter the systemic circulation directly, bypassing the liver. Today, research is more focused on the development of suitable delivery devices, permeation enhancement and buccal delivery of drugs that undergo a first-pass effect, such as macromolecules, micromolecules and peptides. In addition, studies have been conducted on the development of controlled or slow release buccal drug delivery systems for systemic and local therapy with the use of mucoadhesive polymers [3].

Overview of oral mucosa

The mouth, also known as the oral or buccal cavity, is placed at the start of the alimentary canal. Gray's Anatomy describes the mouth as consisting of two parts, including an outer, smaller portion, the vestibule (vestibulum oris), and an inner, larger part, the cavity proper (cavum oris proprium). The vestibule is the slit-like aperture bounded in front and laterally by the lips and cheeks, and internally by the gums and teeth. Above and below, the vestibule is limited by the reflection of the mucous membrane from the lips and cheeks, to the gums covering the upper and lower alveolar arch, respectively. The vestibule receives the secretion from the

parotid glands and communicates, when the jaws are closed, with the cavity of the mouth by an aperture on each side behind the wisdom teeth. It is roofed by the hard and soft palate, while the greater part of the floor is formed by the tongue, the remainder being completed by the reflection of the mucous membrane form the sides and under surface of the tongue, to the gum lining the inner aspect of the mandible [4]. The mucous membrane lining the mouth is continuous with the free margin of the lips, and with the mucous lining of the pharynx behind. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. In general, the permeability of the oral mucosa decreases in order of sublingual greater than buccal and buccal greater than palatal. Buccal mucosa is more suited for sustained delivery applications as it is less permeable and has immobile mucosa. The buccal mucosa consists of 20-40 layers of cells with a total thickness of 450-600µm. The main barrier of the buccal mucosa is situated in the outer one third of the epithelium. The submucosa is highly vascularized and rapidly removes any permeated active substances to the systemic circulation thus avoiding first pass metabolism [5].

General concepts of mucoadhesion

Mucus is a viscous and heterogeneous biological product that coats many epithelial surfaces [6]. Mucus-secreting cells are widely spread in different locations in the body, including the nasal, ocular, buccal area and the gastrointestinal, reproductive and respiratory tracts. Mainly, the mucus serves as a lubricant to minimize shear stresses and as a protection barrier against harmful substances. However, mucus can perform other important functions [7-10]. Goblet cells located in the epithelium are unicellular mucus-secreting glands. Mucus is stored in large granules in the goblet cell and can be released by exocytosis or exfoliation of the whole cell [11]. Mucus granules are mainly stored in the apical side of the goblet cell, which results in the characteristic balloon shape of these cells. Although the secretion of mucus can vary depending on age, sex, body location and health condition, the average mucus turnover is approximately 6 h [12]. Goblet cells experience two types of granules exocytosis: basal secretion, which is characterized by a low level, continuous and unregulated secretion and stimulated secretion, which is a regulated exocytosis of granules in response to extracellular stimuli. The stimulated pathway can dramatically increase the mucus secretion [7]. In pathological conditions, secretion of mucus can considerably vary. For example, in ulceration or inflammation, the intestinal mucous layer is thinner [13]. In physiological conditions, it has been observed that the mucous layer on the gastric and duodenal epithelial surfaces has a thickness between 5 and 200 lm in the rat, and twice this variation in the human [14]. Mucus consists mainly of water (up to 95% weight), inorganic salts (about 1% weight), carbohydrates and lipids (less than 1%) and glycoproteins (no more than 5% weight). Mucus glycoproteins are also called mucins and consist of a protein core with branched oligosaccharide chains attached over 63% of its length [7]. Approximately 80% by weight of the glycoprotein consists of oligosaccharides, which make the mucin more hydrosoluble and also protects the protein core from proteolytic degradation. Mucins are responsible for the gel-like properties of the mucus [7]. Glycoprotein concentrations determine the cohesion of the mucus. When a critical mucin concentration is achieved, the hydrodynamic volumes of the molecules start

overlapping and a gel is formed. The main amino acids in the branched protein blocks are serine and threonine, which are linked to the oligosaccharide chains by O-glycosidic bonds. The sugar residues composing the oligosaccharide side chains are galactose, fucose, N-acetylglucosamine, N-acetylgalactosamine and sialic acid. Generally the oligosaccharide chain is linked to the protein core through an ether bond between the a-1 position hydroxyl group from the N-acetylgalactosamine and the hydroxyl group from the serine or threonine amino acids [15]. Oligosaccharide chains are normally 2-19 residues long and often fucose, sialic acid, sulfate esters of galactose and N-acetylglucosamine are the terminal groups [16]. Opposite to the rich serine and threonine branched blocks, the unbranched blocks of the protein core have a normal amino acid composition [15]. Mucin glycoproteins exhibit molecular weights between 0.5 and 40×10^6 Da, although the average MW is 1.8×10^6 Da [7]. They consist of four to six subunits linked together [17]. Mucin subunits are joined together through disulfide bonds between the cysteine residues present in the non-glycosylated areas of the protein core. Intermolecular interactions have also been detected between mucin molecules. They are believed to be noncovalent, being the hydrogen-bonding, hydrophobic interactions and physical entanglement the main intermolecular interactions.

Bioadhesion and mucoadhesion

The term bioadhesion can be defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces [18]. In biological systems, bioadhesion can be classified into 3 types:
Type 1 adhesion between two biological phases, for example, platelet aggregation and wound healing.
Type 2 adhesion of a biological phase to an artificial substrate, for example, cell adhesion to culture dishes and biofilm formation on prosthetic devices and inserts.
Type 3 adhesion of an artificial material to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues [19] and adhesion of sealants to dental enamel.

For drug delivery purposes, the term bioadhesion implies attachment of a drug carrier system to a specified biological location. The biological surface can be epithelial tissue or the mucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. Leung and Robinson [20] described mucoadhesion as the interaction between a mucin surface and a synthetic or natural polymer. Mucoadhesion should not be confused with bioadhesion; in bioadhesion, the polymer is attached to the biological membrane and if the substrate is mucus membrane the term mucoadhesion is used.

Mechanisms of mucoadhesion

The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the

diffusion of its chains within the mucus. Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must dominate. Each step can be facilitated by the nature of the dosage form and how it is administered. For example, a partially hydrated polymer can be absorbed by the substrate because of the attraction by the surface water [21]. Thus, the mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage (Figure 1). The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer [22]. In some cases, such as for ocular or vaginal formulations, the delivery system is mechanically attached over the membrane. In other cases, the deposition is promoted by the aerodynamics of the organ to which the system is administered, such as for the nasal route. On the other hand, in the gastrointestinal tract direct formulation attachment over the mucous membrane is not feasible. Peristaltic motions can contribute to this contact, but there is little evidence in the literature showing appropriate adhesion. Additionally, an undesirable adhesion in the esophagus can occur. In these cases, mucoadhesion can be explained by peristalsis, the motion of organic fluids in the organ cavity, or by Brownian motion. If the particle approaches the mucous surface, it will come into contact with repulsive forces (osmotic pressure, electrostatic repulsion, etc.) and attractive forces (van der Waals forces and electrostatic attraction). Therefore, the particle must overcome this repulsive barrier [23]. In the consolidation step (Figure 1), the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak van der Waals and hydrogen bonds [23]. Essentially, there are two theories explaining the consolidation step: the diffusion theory and the dehydration theory.

According to diffusion theory, the mucoadhesive molecules and the glycoproteins of the mucus mutually interact by means of interpenetration of their chains and the building of secondary bonds [23]. For this to take place the mucoadhesive device has features favoring both chemical and mechanical interactions. For example, molecules with hydrogen bonds building groups (–OH, –COOH), with an anionic surface charge, high molecular weight, flexible chains and surface-active properties, which induct its spreadthroughout the mucus layer, can present mucoadhesive properties [24].

According to dehydration theory, materials that are able to readily gelify in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the difference of osmotic pressure. The difference in concentration gradient draws the water into the formulation until the osmotic balance is reached. This process leads to the mixture of formulation and mucus and can thus increase contact time with the mucous membrane. Therefore, it is the water motion that leads to the consolidation of the adhesive bond, and not the interpenetration of macromolecular chains. However, the dehydration theory is not applicable for solid formulations or highly hydrated forms [23].

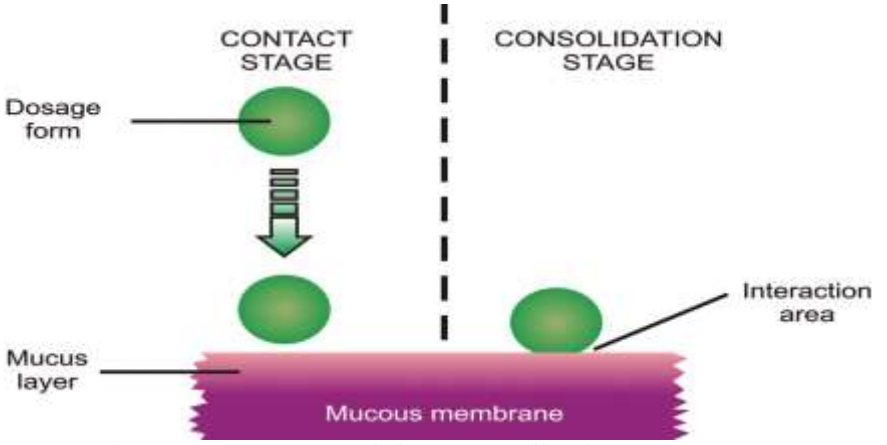

Figure1**:** Two steps of the mucoadhesion process

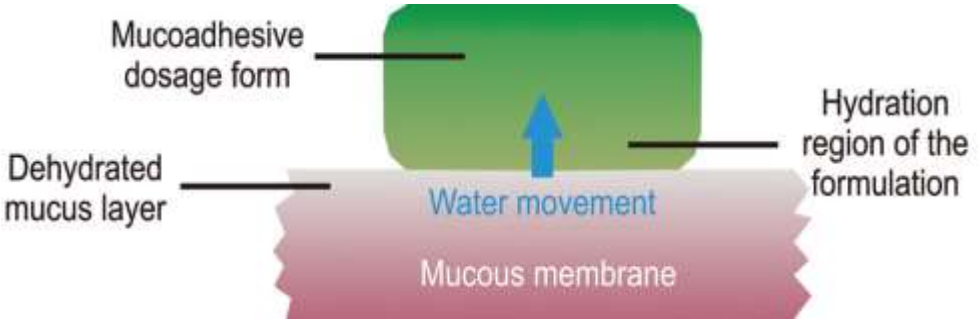

Figure 2: Dehydration theory of mucoadhesion

Theories of mucoadhesion

There are six different theories, which explain phenomenon of mucoadhesion:

Electronic theory

This theory is based on fact that both mucus layer and biological materials have opposing electrical charges that able to create double electronic layer at the edge and thus helps in determination of *mucoadhesive* strength [25].

Wetting theory

Liquid or less viscous molecules enter into mucosal surface and fix themselves by counteracting the surface tension at the interface. This property relates to contact angle, wetting and spread ability capacity of molecule. Contact angle (θ) and interfacial tension (γ) can be determined from following equation [26]:

$$\gamma SG = \gamma SL + \gamma LG\cos S = \gamma SG - (\gamma SL - \gamma LG)$$

Where γLG is liquid-gas surface tension, γSL is solid-liquid surface tension and γSG is solid-gas surface tension.

Diffusion theory

This theory suggests that *mucoadhesive* polymer diffuses into mucus layer by breaking glycoprotein chain network. This diffusion is time dependent and depends on diffusion coefficients and molecular weight of both phases [27].

Adsorption theory

Weak vander waals forces and hydrogen bond mediated adhesion involved in adsoption theory is most accepted theory of mechanism of mucoadhesion. It involves primary and secondary bonding in exhibiting semi permanent surface interactions [28].

Fracture theory

This is the second most accepted theory, which explains the forces required to detach the two surfaces following adhesion. This force is called as tensile stress or fracture strength and can be determined by following equation:

$$Sm = Fm/Ao$$

Where Sm: Tensile stress, Fm: maximum force of detachment and Ao: surface area
OR

$$Sf = (gcE/c)\ ½$$

Where Sf: fracture strength, gc: fracture energy (Wr + Wi = work done to produce new fracture surfaces + irreversible work of adhesion), E: Young's modulus of elasticity and c: critical crack length. Each and every theory is equally important to describe the mucoadhesion process. There is a possibility that there will be initial wetting of the mucin, and then diffusion of the polymer into mucin layer, thus causing the fracture in the layers to effect the adhesion or electronic transfer or simple adsorption phenomenon that finally leads to the perfect mucoadhesion.

Mechanical theory

The mechanical theory considers adhesion due to the filling of irregularities on a rough surface by mucoadhesive liquid. Additionally, such irregularity increases the interfacial area available for interactions and can be considered the most important phenomenon of the process [29].

Factors affecting mucoadhesion

Polymer related factors

Molecular weight: The mucoadhesion strength of a mucoadhesive polymer mainly depends upon its molecular weight and polymeric linearity. Generally, for the linear polymers (e.g., Polyethylene glycol), the bioadhesive property is directly proportional to the molecular weight i.e., PEG-200000 having greater mucoadhesive strength than that of PEG-20000. But in case of nonlinear

polymer, the mucoadhesive strength of polymer may or may not be dependent of its molecular weight. This is mainly because the helical or coiled structures of such polymer may shield some of the adhesive group, which are mainly responsible for the adhesive property.

Concentration of polymer: The concentration of a mucoadhesive polymer is a significant factor of determining its mucoadhesive strength. There is an optimum concentration for a mucoadhesive polymer where it produces the maximum mucoadhesion. For some highly concentrated polymeric systems, beyond the optimum level of polymer, the mucoadhesive strength of polymer starts to fall down significantly because the concentration of polymer molecules starts rising over the molecular concentration of the liquid medium so that there is no further chain formation between liquid medium and polymer. As a result of this, the polymer particles remain separated from liquid medium, due to this the mucoadhesive strength of that polymer starts fallen down. On the other hand, when the concentration of the polymer is too low as compare to the concentration of liquid medium, the number of polymer chains per unit volume of liquid medium is less, the mucoadhesive strength of polymer at that concentration is also very less.

Flexibility of polymer chains: Greater the flexibility of the mucoadhesive chain causes the greater diffusion into the mucus network of buccal cavity. This results in increased mucoadhesion. The flexibility of polymer chain decreases with increase in the concentration of polymer. For an effective bioadhesion, the polymer chain should effectively diffuse into the mucus layer. The flexibility of polymer chain depends on the viscosity and diffusion coefficient of that chain.

Spatial confirmation: The mucoadhesive strength of a polymer is also dependent on the conformation or spatial arrangement of polymers i.e., helical or linear. The polymers showing linear conformation having the greater mucoadhesive strength as compare to the polymers showing helical conformation. Because, the helical conformation of polymer may shield various active groups, that are primarily responsible for mucoadhesion, thus reducing the mucoadhesive strength of the polymer.

Swelling or hydration: The proper hydration of mucoadhesive polymer is essential for the desired mucoadhesive strength. With increase in hydration the pore size of polymer increases which results induced mobility and enhanced interpenetration.

Hydrogen bonding capacity: Hydrogen bonding is another important factor for mucoadhesion of a polymer. For mucoadhesion to occur, desired polymers must have functional groups that are able to form hydrogen bonds. Ability to form hydrogen bonds is due to the presence of (COOH, OH etc.,). Flexibility of the polymer is important to improve its hydrogen bonding potential. Polymers such as polyvinyl alcohol, hydroxylated methacrylate and poly (methacrylic acid) as well as all their co-polymers are having good hydrogen bonding capacity.

Cross linking density: The cross linking density of the polymer determines its higher molecular weight. The cross linking density indicates the number of average molecular weight of the cross linked polymer, which determines the

average pore size. When the cross linking density of polymer is higher, it reduces the pore size of polymer chain which results in reduced diffusion of water into the polymer network. The reduced diffusion results in the decreased penetration of polymer into the mucin and finally decreases the mucoadhesive strength.

Charge: The bioadhesive property of ionic polymer is always higher than that of non-ionic polymer. In neutral or slightly alkaline medium, the cationic polymer shows superior mucoadhesive property. It has been proven that, cationic high molecular weight polymer such as chitosan possess good bioadhesive property [30, 31].

Environment related factors

pH of polymer-substrate interface: The pH of polymer-mucin interface should be same as it is possible, because, the difference in pH amongst the two systems may results in the transfer of charge due to the higher pH gradient. This may affect the mucoadhesion.

Applied strength: While placing a buccal mucoadhesive drug delivery system, sufficient strength should be applied in order to provide a good bioadhesive property. Even though there is no attractive forces between polymer and mucus, then application of high pressure for sufficient long time make the polymer become bioadhesive with mucus.

Initial contact time: Greater the initial contact time between the mucoadhesive polymer and the mucus layer results in the increased swelling as well as interpenetration of the mucoadhesive polymer chain. Hence, increases the mucoadhesion strength of the polymer chain.

Moistening: Moistening is required to allow the mucoadhesive polymer to spread over the surface. It creates a network of polymer chains of sufficient pore size. Through these pores, the interpenetration of polymer and mucin molecules takes place that results in increasing the mobility of polymer chains for the proper diffusion of mucoadhesive polymer in mucin layer [32, 33].

Physiological factors

Mucin turnover: High mucin turnover is not beneficial for the mucoadhesive property because of following reasons: The high mucin turn over limits the residence time of bioadhesive polymer as it detaches from the mucin layer, even though it has a good bioadhesive property. High mucin turn over may produce soluble mucin molecule, thus molecule interact with the polymer before they interact with mucin layer. Hence there will not be sufficient mucoadhesion.

Disease state: In some disease states, the secretion of mucus from the mucus membrane gets decreased (e.g., in Dry Mouth Syndrome and in old age). So that there is not sufficient amount of mucus present at the site of attachment of mucoadhesive dosage form. This may leads to improper moistening and swelling of polymer. Due to which there is decreased mucoadhesive strength of mucoadhesive dosage form.

Rate of renewal of mucosal cells: Rate of renewal of mucosal cells varies extensively from different types of mucosa. It limits the persistence of bioadhesive systems on mucosal surfaces.

Concomitant diseases: Concomitant diseases can alter the physicochemical properties of mucous or its quantity (for example, hypo and hyper secretion of gastric juice), increases in body temperature, ulcer disease, colitis, tissue fibrosis, allergic rhinitis, bacterial or fungal infection and inflammation. Tissue movement: Tissue movement occurs on consumption of liquid and food, speaking, peristalsis in the GIT and it affects the mucoadhesive system especially in case of gastro retentive dosage forms [34].

Buccal mucoadhesive drug delivery system

The mucoadhesive drug delivery system in the mucus membrane of oral cavity can be categorized into three delivery systems:

- Sublingual delivery
- Buccal delivery
- Local delivery

These oral sites provide the high blood supply for the greater absorption of drug with sufficient permeability. From these three sites of oral mucoadhesive drug delivery system, the buccal delivery is the most convenient site. There are many advantages of buccal mucoadhesive drug delivery system over other drug delivery systems are given as follow:

- The buccal mucoadhesive drug delivery system can be used for both local as well as systemic delivery of many drugs.
- Buccal mucoadhesive dosage forms are easy to applicate as compare to other adhesive dosage forms.
- Increased patient compliance over the injectables.
- It is the most preferred delivery system for the local treatment of drugs. So that there are wide range of mucoadhesive formulations has been [35].

Mucoadhesive polymers

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

Various mucoadhesive polymers can broadly be categorized as follow:

Synthetic polymers

1. Cellulose derivatives (Methylcellulose, Ethyl cellulose, Hydroxyl ethyl cellulose, Hydroxyl propyl cellulose, Hydroxy propyl methylcellulose, Sodium carboxy methylcellulose).
2. Poly (Acrylic acid) polymers (Carbomers, Polycarbophil).
3. Poly hydroxyl ethyl methylacrylate.

4. Poly ethylene oxide.
5. Poly vinyl pyrrolidone.
6. Poly vinyl alcohol.

Natural polymers

Tragacanth, Sodium alginate, Guar gum, Xanthum gum, soluble starch, Gelatin, Chitosan
Mucoadhesive polymers can also classify into following categories:

Traditional non-specific first-generation mucoadhesive polymers

First-generation mucoadhesive polymers may be divided into three main subsets, namely:

1) Anionic polymers,
2) Cationic polymers,
3) Non-ionic polymers.

Anionic and cationic polymers have been shown to exhibit the greatest mucoadhesive strength. Consequently, such charged polymeric systems will now be examined in more depth. Anionic polymers are the most widely employed mucoadhesive polymers within pharmaceutical formulation due to their high mucoadhesive functionality and low toxicity. Typical examples include poly (acrylic acid) (PAA) and its weakly cross-linked derivatives and sodium carboxy methyl cellulose (NaCMC). PAA and NaCMC possess excellent mucoadhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin. Polycarbophil (Noveon) and Carbomers (Carbopol), PAA derivatives have been studied extensively as mucoadhesive platforms for drug delivery to the GI tract.

Cationic Polymers

Of the cationic polymer systems, undoubtedly chitosan is the most extensively investigated within the current scientific literature. Chitosan is a cationic polysaccharide, produced by the deacetylation of chitin, the most abundant polysaccharide in the world, next to cellulose. The intriguing properties of chitosan have been known for many years with much medicine.

Novel second-generation mucoadhesive

The major disadvantage in using traditional nonspecific mucoadhesive systems (first generation) is that adhesion may occur at sites other than those intended. Unlike first-generation non-specific platforms, certain second-generation polymer platforms are less susceptible to mucus turnover rates, with some species binding directly to mucosal surfaces; more accurately termed Cytoadhesives.

Lectins

The most widely investigated of such systems in this respect are lectins. Lectins belong to a group of structurally diverse proteins and glycoproteins that can bind reversibly to specific carbohydrate residues. After initial mucosal cell-binding, lectins can either remain on the cell surface or in the case of receptor mediated adhesion possibly become internalized via a process of endocytosis.

Thiolated polymers

The presence of free thiol groups in the polymeric skeleton helps in the formation of disulphide bonds with that of the cysteine-rich sub-domains present in mucin which can substantially improve the mucoadhesive properties of the polymers (e.g. poly (acrylic acid) and chitosan).Various thiolated polymers include chitosan-iminothiolane, poly(acrylic acid)-cysteine, poly (acrylic acid)-homocysteine, chitosan-thioglycolic acid, chitosan-thioethylamidine, alginate-cysteine, poly (methacrylic acid)-cysteine and sodium carboxymethylcellulose-cysteine.

Polyox WSR

A class of high molecular weight polyethylene molecular weight polyethylene oxide homopolymers having the following properties,

- Water soluble hydrophilic nature
- Functional group for hydrogen bonding
- Biocompatible and non toxic
- High molecular weight

Novel polymers

Tomato lectin showed that it has binding selectivity to the small intestine epithelium. A new class of hydrophilic pressure sensitive adhesives (PSA) has been developed by corium technologies. Complex have been prepared by non covalent hydrogen bonding crosslinking of a film forming hydrophilic polymer with a short chain plasticizer having reactive OH groups at chain ends [36, 37].

Buccal permeation-enhancing strategies

The use of permeation (or penetration) enhancers (PE) to improve buccal bioavailability has been studied extensively due to both the barrier feature of the buccal epithelium and its capacity to tolerate permeation enhancers. While mucoadhesive systems have been described as a method for permeation enhancement, functional excipients that modify the physicochemical properties of the barrier are normally assigned the term permeation enhancers, also described as chemical enhancers. Surfactants, bile salts, and fatty acids have been used as PEs in buccal dosage form development with permeability increases seen both small drug molecules and biologics in a variety of bioassays [38, 39]. More recently, amino acids have been studied as PEs for buccally administered insulin. The cationic amino acids lysine and histidine, and the anionic amino acids glutamic acid and aspartic acid enhanced insulin permeation across human filter-

grown TR146 buccal monolayers to different degrees, but without damaging the cell barrier or the insulin [40]. It was hypothesized that due to the ionic state of the amino acids and insulin, ion-pairing resulted in non-covalent complexes that could exploit the amino acid-mediated transport for enhanced insulin permeation through the epithelial model, while being non-cytotoxic at effective concentrations compared to the narrow window of permeability/cytotoxic concentrations seen with the bile salt, sodium deoxycholate [40]. It is important to note that comparison of permeability between the human TR146 model and isolated porcine buccal tissue mucosae using PEs is somewhat problematic, as the monolayers are less resilient and have higher basal permeability com-pared to the tissue mucosae. Iontophoresis is a method to enhance the permeation of molecules through biological barriers by applying an external electric potential and thus generating a flow of ionic hydrophilic molecules. This method has been successfully used in enhancing the permeation of small molecules and biologics through porcine model buccal and oesophageal epithelia as well as in vivo [41-43]. Ren et al. have shown that iontopho- resis can enable drug transport even in keratinized palate regions of the oral cavity mucosa, highlighting its potential for permeation enhancement in periodontal disease [44].

Evaluation of buccal mucoadhesive dosage forms

Experimental methodologies for buccal absorption/permeability study

In-vitro and ex-vivo methods of evaluation: The in-vitro studies are used to determine the release, solubility and dissolution of dosage forms. The ex-vivo studies conducted on the animal tissues and membranes by preparing animal models. The tissues are taken from the freshly died animals and are been used within 2 hrs after their separation. The membranes are then placed and stored in ice-cold (4°C) Kreb's buffer upto the time before they are mounted between diffusion cells for the ex-vivo permeation experiments [46].

In-vivo methods: It is also called as buccal absorption test. For kinetic drug absorption measurement this method can be used. The procedure involves the swirling of a 25 ml sample of the test solution for up to 15 min by human volunteers in their buccal cavity. After 15 min the solution expelled out. In order to calculate the amount of drug absorbed, the amount of drug present in expelled volume can be calculated. The main disadvantages including salivary dilution of drug and accidental swallowing of sample solution may arise. *Experimental animal species:* Choice of animal for the experimental study is very important factor. To perform in-vivo study researchers can prefer the animals depending on test to be perform. Most of animals having the keratinized buccal mucosa, but the rabbit and pig are the only animals which having non-keratinized mucosa as like humans. To study permeation of drug monkey, dog, pig animals are mostly used.
In-vitro release study: For simulating in-vivo conditions, researchers have developed different apparatus like:

- Beaker method
- Dissolution apparatus
- Interface diffusion system
- Modified Keshary Chien cell

Methods to study mucoadhesive strength

Polymer characterization can be done by evaluating their mucoadhesive strength both in-vivo and in-vitro technique.

In-vitro evaluation techniques

Measurement of tensile strength: In this method, the force required for breaking the bioadhesive bond between mucus membrane and bioadhesive polymer is calculated. The following formula can be used for determining the tensile strength of buccal mucoadhesive device.
Force of adhesion (N) =Mucoadhesive strength × 9.81/1000
Bond strength (N/m2) = Force of adhesion (N)/Surface area of tablet (m2)
For the measurement of tensile strength, various instruments are used that are as follows [45].
Modified physical balance or tensile tester.
Wilhelmy plate technique

Measurement of shear strength: In this technique the mucoadhesive strength is determined means of measurement of shear stress applied to the adhesive device. In this technique, firstly select two smooth polished glass box, sand fix one box on a glass plate with adhesive, on a leveled table. To the upper block, tied a thread and then pass down the block through a pulley. The length of the thread from the pulley should be 12 cm. At the bottom side of the thread, attach a 17 g pan along with weights. And hence the shear strength was determined using an appropriate method by correlating the weight required to break the adhesion [46].

Other in-vitro methods

Rheological study: The rheological information of polymer–mucus mixtures can offer an acceptable in-vitro model which can correlate with in-vivo performance of a mucoadhesive polymer. It is best method for determination of mucoadhesive potential of polymer by comparing binary mucus/polymer blends to the equally concentrated monocomponent mucus/polymer system. The rheological behaviour of two macromolecular species can by changed by techniques such as chain interlocking, and chemical interaction that occur between the bioadhesive polymer and mucin chains.

Colloidal gold staining method: This is a new in-vitro method which was described for comparison of mucoadhesive property of various hydrogels. In this technique, there is a use of red colloidal gold particles which are stabilized by the partially or fully adsorbed mucingold. Because of interaction mucoadhesive develops red colour on its surface. The mucoadhesive properties of the mucoadhesive device can be compared by measuring the intensity of red colour.

Fluorescent probe method: In this method lipid bilayer of cultured human conjunctiva cells is labelled with pyrine which is used as a fluorescent probe. If the polymer can adhere to this cell, it can caused change in fluorescence due to chance in surface compression when compared with control cell. This change in degree of fluorescence is directly proportional to amount of polymer binding. To

determine density on adhesion, polymer charge, and charge sign another probe can also be used. It states that determination of bioadhesive bond is based on molecular interaction of polymer with mucus [46].

In-vivo methods of evaluation

Gamma scintigraphy techniques: It is a non destructive method for the evaluation of pharmaceutical dosage forms. This technique is used to get the different information of the different areas of GI tract, the site of drug absorption, the time and site of disintegration of dosage forms. This instrument also used to check the effect of disease and food size on the biopharmaceutical characteristics of the dosage forms. Generally this method is used to study the distribution and the retention time of mucoadhesive tablets.

GIT transit using the radio-opaque technique: In this technique radio opaque markers are used to determine effect of polymer in GI transit time. Non invasive method such as faeces examination and xray evaluation can provide sufficient data to study GI residence time. Cr 51, Tc99 m, In113 m or I123 these are some examples of marker which are used for mucoadhesive drug delivery.

Moisture absorption studies for buccal patches: The determination of moisture absorption by the buccal films or patches is necessary for evaluation of the drug absorption and drug release parameters. Moisture absorption studies can be performed in 5% w/v agar in distilled water. Heat the solution and then transferred to petri plates and allowed to solidify. Then select the six buccal patches from each batch weigh properly. After solidification of agar positioned them on the surface of agar plate and incubate at 37°C in incubator. Weigh all the patches again, and calculate the percentage of the absorbed moisture by using the following formula-

% Moisture absorbed=Initial weight–Final weight/Initial weight×100

Thickness: Select randomly five different patches and with the help of screw gauge measure the thickness.

Folding endurance: Select a patch and fold it repeatedly at the same point until it ruptures. The total number of folding required for cracking or breaking a patch is called as its folding endurance. The folding endurance of the buccal patch should be greater than 150 times. *Swelling study for tablet:* Weigh the mucoadhesive dosage form accurately and place in a beaker containing 200 ml of buffer media. Remove the dosage form after each interval and weigh it again. Follow this process up to 8 hours. The following formula can be used for calculating the swelling index:

Swelling Index (S.I.)=(Wt-Wo)/Wo

Where, S.I.=Swelling index, Wt=Weight of the dosage form at time t, Wo=Initial weight of dry dosage form.

Surface pH study: The surface pH of the buccal dosage form is calculated in order to examine the possibility of any side effects that may be arise in-vivo because of acidic or basic pH. In this method a glass electrode is used for determining pH. Allow the dosage form to swell by keeping it in contact with distilled water at room temperature for 2 hrs. Then measure the pH by taking the electrode in contact with the surface of the dosage form [46]. *Residence time:* For determining the residence time of the buccal dosage forms the modified disintegration apparatus. 800 ml isotonic buffer pH 6.75 solution can be used as disintegration medium 3 cm long rabbit mucosa was attached to glass slide and it was vertically attached to side arm. One surface of mucoadhesive tablet was hydrated with 15 ml of isotonic phosphate buffer solution then it was taken in mucosal contact. The movement of glass slide was allowed to up and down for complete immersion. Then time for detachment of tablet from mucosal surface can be noted [47].

Current & future developments

Challenges offered by drugs which are susceptible to high first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract have led the pharmaceutical researchers into a pursuit of designing and commercializing alternative drug delivery systems. Buccal delivery with its amenability to both systemic and local actions has given new dimensions to drug delivery research. The concerted and resolute efforts by scientist's world over have resulted in many commercial products including Zilactin, Pilobuc, BEMA system etc. The buccal mucosa offers several advantages for controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage. The area is well suited for a retentive device and appears to be acceptable to the patient. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation or local delivery. Buccal drug delivery thus proffers to be a promising area for continued research with the aim of systemic delivery of orally inefficient drugs as well as a feasible and attractive alternative for non-invasive delivery of potent peptide and protein drug molecules. Novel approaches of drug delivery including nanoparticles, microspheres are also using for their potential through buccoadhesion. However, the need for safe and effective buccal permeation/absorption enhancers is a crucial component for a prospective future in the area of systemic buccal drug delivery while an acceptable organoleptic profile of the product remains a caveat for both local and systemically effective systems (48, 49).

Conclusion

Today, drug delivery systems designed with the aim to improve patient compliance and convenience is more important than ever. Therefore huge work is going on to develop novel dosage forms to satisfy increased patient demands of more convenient dosage forms. Oral mucosal delivery offers a convenient way of dosing medication, not only to special populations with swallowing difficulties, but also to the general population. Mucoadhesive dosage forms provide prolonged contact time at the site of attachment, having high patient compliance and are economic as compare to other dosage forms. The use of mucoadhesive polymers has made this delivery system of controlled release application. There are

significant advancements have been achieved in the field of mucoadhesives, but there are still many challenges are not been sought out in this field. However, a lot of research has been done of this drug delivery system. But, these novel mucoadhesive formulations require much more research work to understand how to deliver drug clinically for the treatment of both systemic and topical diseases.

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