REVIEW ARTICLE

Polymers in designing the mucoadhesive films: A comprehensive review

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Abstract

Considering the compliance of patients and ease of administration, the oral cavity is profoundly chosen to deliver drugs. This article focuses on mucoadhesive buccal drug delivery system providing sustained release of the drug. The drug of choice for buccal delivery is those which undergoes high first-pass metabolism or undergo acid degradation. This review article aims to focus on various aspects of buccal films, factors affecting mucoadhesion and its evaluating parameters. Different theories involved in mucoadhesion process and along with the polymers that are involved in developing different categories of films have been focused. Factors influencing the polymers involved flexibility, molecular weight, charge, etc., are also considered in this review. Most commonly used polymers in the development of mucoadhesive films are lectins, starch, pectins, and cellulose derivatives, etc. Several agents such as penetration enhancers and mucoadhesive agents are employed to develop an ideal film. These dosage forms are formulated using two processes, namely film casting method and hot-melt extrusion method. The developed films are evaluated based on multiple parameters such as surface pH, flatness, tensile strength, and peel strength. This review gives an overall view of different polymers that are used to develop the mucoadhesive films and compare their degree of mucoadhesion along with their parametric tests to evaluate the developed films.

Key words: Film casting method, hot-melt extrusion method, lectins, Mucoadhesive buccal drug delivery system, pectins, penetration enhancers

INTRODUCTION

Mucoadhesive buccal patch has gained attention and development has been skyrocketing over the past few decades. As a dosage form, patches have grabbed the views of pharma sectors as a novel, convenient, and patient-compatible.[1] The oral mucosa has an enriched supply of blood and is relatively permeable. This delivery of the drug through buccal route escapes first-pass metabolism and has a reduced enzymatic activity when compared to gastrointestinal (GI) tract.[2]

Human Oral Cavity

In humans, the approximate surface area of the oral mucosa is100 cm^2. The oral mucosa can be differentiated as the masticatory mucosa which is 25% of total oral mucosa having a thickness of 100–200 µm. The lining mucosa covers 60% of the total area and has a thickness of 500–800 µm. It is present in lips, cheeks, oral cavity floor, etc. [Figure 1].[3]

Mechanisms of Drug Transportation through Buccal Mucosa

Transportation of drugs involves mainly two basic routes [Table 1]: Transcellular or intracellular which demands to cross the cellular membrane with lipid and polar domain, but paracellular or intercellular transport is accomplished through passive diffusion through extracellular lipid domain.[4]

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Theories of Mucoadhesion

Mucoadhesion can be classified broadly into three categories: Type1mucoadhesion includes aggregation of platelets and healing of the wound (biological phases interaction only). Adhesion of Type 2 category involves a biological phase and a simulated substrate. Adhesion of an artificial material to a substrate of biological nature is described as Type 3, for example, synthetic hydrogels adhesion to soft tissues.

Basic mechanism that is involved in mucoadhesion is as follows:

1. Close contact existing between a membrane and bioadhesive.
2. Piercing of bioadhesive into tissue or mucous membrane.[5]

To explain the mechanism of mucoadhesion, multiple theories have been proposed:

Wetting theory

This theory hypothesizes the penetration of adhesives into the irregularities and gets itself anchored on the surface. It is applicable to liquid or mucoadhesive system having low viscosity. This theory explains the ability of spreadability of mucoadhesive polymer on biological surfaces. Measuring the contact angle, the affinity toward the surface can be determined.[6]

Adsorption theory

As per this theory, two different types of chemical bonding, i.e. H-bonding and Van der Waals forces play an important role in adhesive interactions. Chemisorption theory explains the interaction across the interface takes place due to strong covalent bonding.[7]

Electronic theory

Structural properties and electronic structures differ with different surfaces. Electronic differences in the structure are the backbone of this theory. Transfer of electrons between the polymers and epithelium mucous membrane leads to a formation of the bond. Electronic charges are developed in a bilayer fashion between mucoadhesive system and mucus which leads to the development of attractive force between two surfaces through electronic double-layer.[8]

Fracture theory

This theory explains that the existing bonds of adhesion between the systems are related to the force that is needed to detach the two surfaces. This hypothesis correlates the amount of force required to separate polymer from the mucus is related to the strength of their adhesive bonding. Through the following equation, we can determine fracture strength (σ) and establish a relationship between the separations of two surfaces.

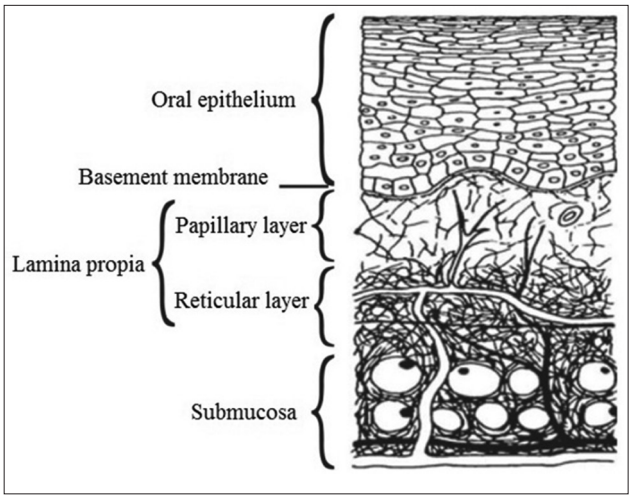


Figure 1: Structure of oral cavity

$$\sigma = \sqrt{(E^*\varepsilon)/L}$$

Where E represents Young's modulus of elasticity, ε represents the energy of fracture, and

L represents the critical length of crack.[9]

Diffusion interlocking theory

According to this theory, the diffusion is dependent on time. In this process, diffusion takes place in two ways where the rate of penetration depends on coefficients of diffusion of both the polymers interacting at the junction. Various factors influencing the process of diffusion are chain flexibility, molecular weight, the density of cross-linking, and temperature [Figure 2]. An interpenetration layer of 0.2–0.5 μm is needed to extend a firm bond. The required time (t) for the highest degree of adhesion during interpenetration among two substrates can be calculated using L (interpenetration depth) and Db (the coefficient of diffusion).[10]

$$t=L^2/Db$$

Mechanical theory

As per this theory, the adhesion takes place due to the rough surface being filled with a mucoadhesive fluid. Although these irregularities increase the area of interface that area is free to interact. But it is considered as the most influential step in the process.[11]

Factors Influencing the Mucoadhesion Action

Mucoadhesion depends not only on the bioadhesive polymer but also the medium as well in which the polymer will adhere to. Factors influencing the polymeric mucoadhesive properties are molecular weight, the capacity of hydrogen bonding, chain flexibility, the density of cross-linking, concentration, hydration, and charge of a polymer, which is described as below:

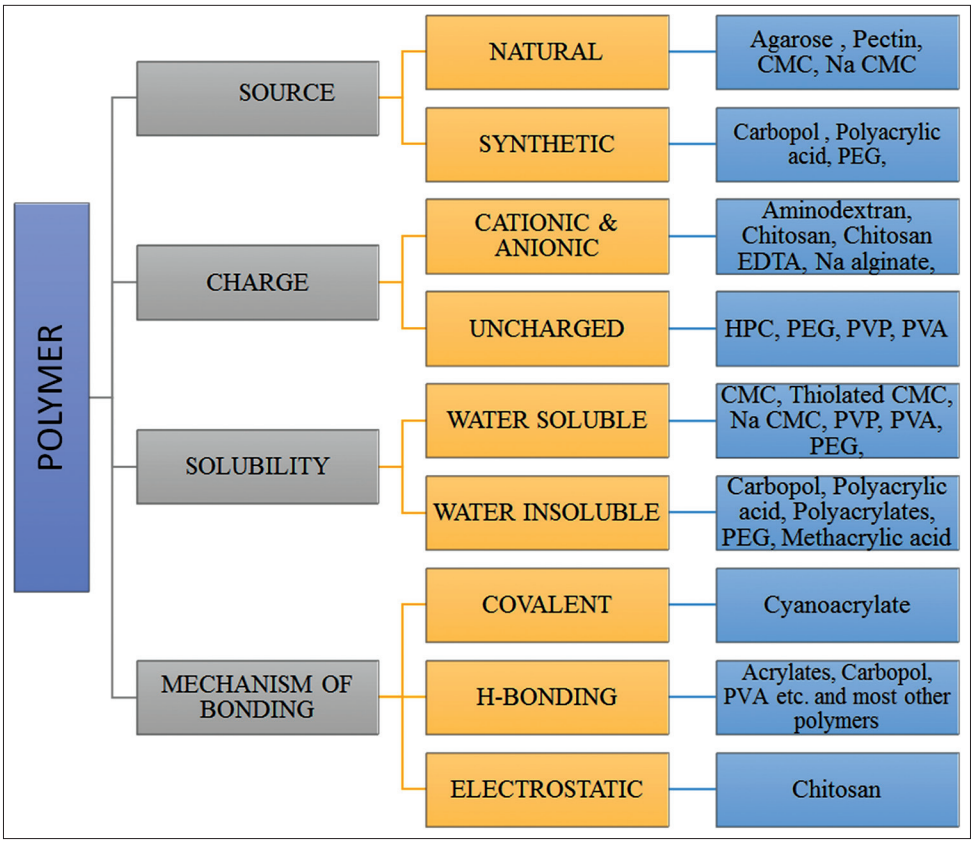


Figure 2: Differentiation of polymers based on several parameters

FACTORS RELATING TO POLYMERS

Molecular Weight

With increments of polymers molecular weight over 100,000 the bioadhesive quality of the polymer increments, therefore. A relationship exists between polyoxyethylene polymer's bioadhesive quality and their resulting atomic weights, varying in the scope of 200,000–7,000,000 and the same has been accounted for by Tiwari *et al*.[12]

Flexibility

Start of bioadhesion takes place when polymer diffuses into the interfacial locale. In this way, it is a need that the chains of the polymer have a significant level of flexibility to accomplish the coveted association with the mucus.[13]

Hydrogen Bonding Capacity

It is an important factor that is involved in the mucoadhesion process of a polymer. Park and Robinson have reported that the polymers of desired quality must possess functional groups that can have the ability to form hydrogen bonds to have desired mucoadhesion.[14] Through further study, it has been revealed that the flexibility of polymer is a crucial aspect that improves the hydrogen bonding potential. A sustainable hydrogen bonding capacity is exhibited by polymers and copolymers such as hydroxylated methacrylate [Figure 3].[15]

Cross-linking Density

The average size of pores in the polymers, the average polymeric molecular weight having cross-link and the cross-linking density are the three most important interrelated structural parameters required for a network of polymer. Thus, it is rational that as the density of cross-linking increases, the diffusion of water into the polymer decreases thus causing the polymer to swell insufficiently. Flory reported that at equilibrium, polymer's limit of the swelling has an inverse relationship with the polymer's extent of cross-linking.[16,17]

Charge

Several rational ideas about the charge that is possessed by the bioadhesive polymers have been previously established, the degree of adhesion to nonionic polymers as compared to anionic polymers is relatively smaller. The anionic charge of the polymer must be strong enough for mucoadhesion to take place. Superior mucoadhesive properties are exhibited by some cationic polymers significantly in a medium which is neutral or slightly alkaline.

Concentration

This is an important factor which is responsible for developing a firm adhesive bond with the mucus. Low polymer concentration lowers the density of penetrating polymer chains in the mucus and there takes place an unstable interaction between polymer and mucus. In general, the highly concentrated polymer would prompt be shaping a more extended infiltrating chain length with higher adhesion. High polymer concentration does not ensure improved properties of mucoadhesion, and in some cases, it actually reverses the action.[18]

Hydration (swelling)

Hydration is necessary to extend mucoadhesive polymers, and a legitimate macromolecular mesh of required size is created which helps in inducing mobility in the chains of polymer which aids in the process of interpenetration existing between mucin and polymer. Swelling of the polymer allows a mechanical inclusion by uncovering the sites of bioadhesion for hydrogen bonding or electrostatic communication among the polymer and the mucous system. Nevertheless, for perfect swelling and bioadhesion to take place, an optimum level of hydration is needed in the mucoadhesive polymer.[19]

Optimum pH

At conditions of low pH, ideal mucoadhesion takes place, but at higher pH range, a conformational change occurs. At a higher pH range, polymers having a positive charge like chitosan form polyelectrolyte complexes with mucus while exhibiting greater forces of mucoadhesion.[20]

Optimum Polymer Chain Length

The polymers should have optimum chain length. The length ought to have the capacity to advance the interpenetration and short to the degree which encourages diffusion.[21]

NATURE OF POLYMERS

Polymers Based on Charge

Numerous polymers possessing charge have proved to be crucial in the development of mucoadhesive formulations with sustained release. Derivatives of polyacrylic acid (PAA) showed enhanced mucoadhesive properties as compared to cellulose derivatives. Ionic complex with the counter-ionic drug molecules may be formed with the ionic polymers to develop mucoadhesive property exhibiting drug delivery matrix. Cationic polysaccharide chitosan has been used in some mucoadhesive formulations for its unique properties such as mucoadhesion, biocompatibility, and non-toxicity.[22,23]

Anionic polymers

Polymers like carboxymethyl cellulose are popularly deployed for developing mucoadhesive drug delivery. Anionic polymers are highly used and are a very popular choice in the pharmaceutical sector. Mucoadhesive polymers of these types exhibit high strength of mucoadhesion and a minimum level of toxicity. As these types of polymers possess functional groups such as carboxyl and sulfate which, in turn, result in general negative charge at pH which is higher than its pKa value. Since strong hydrogen bonds are formed between mucosal mucin layer and these polymers that's responsible for outstanding mucoadhesive properties.

Cationic polymers

Of all the mucoadhesive polymers of cationic nature, chitosan is the most popular and widely studied and are involved in developing several formulations in pure or in derivatized forms. Through deacetylation of chitin, the cationic polysaccharide chitosan is formed. The unique properties of chitosan make it functional in different fields and are also used as an eliciting agent, antipathogenic agent, film-forming agent, as well as in cosmetics.[24,25]

Non-ionic polymers

Mucoadhesives are created utilizing polymers of non-ionic nature such as methylcellulose (MC), hydroxypropyl methylcellulose (HPMC), and poly(vinyl pyrrolidone) (PVP). Out of a few classifications of polymers, non-ionic have demonstrated the best mucoadhesive quality.[26,27] Release profile of HPMC 15cps grade is better compared to HPMC K100LV and HPMC K4M [Figure 2].

Polymers Based on Generation

First generation mucoadhesives

These hydrophilic molecules are natural or synthetic in nature which contains various organic functional groups that can generate bonds of hydrogen such as hydroxyl, amino, and carboxyl groups, which never specifically cohere to different surfaces. Polymers of this class can further be classified into three subcategories: Anionic, cationic, and nonionic. Since cationic molecules are negatively charged at physiological pH, so these molecules can interact the mucous surface. Mucoadhesion occurs in cationic polymers (e.g. chitosan) as the electrostatic interactions that take place between the polymers amino groups and the mucins sialic groups in the mucus layer.

Second-generation mucoadhesive materials

Multifunctional materials are used in novel mucoadhesive systems. An impeccable polymer should display the capacity to fuse with both the water-soluble and lipid soluble drugs, demonstrate mucoadhesive attributes in both of its solid and liquid structures, repress local enzymes or enhance

absorption, be particular for a cell site or region, invigorate endocytosis and in conclusion to have a more extensive safety range (Lee *et al*., 2000). These are multifunctional novel mucoadhesive systems which can be named as second-generation polymers. They act as an alternate option to non-specific bioadhesives as they can cohere to cell or mucous surface having specific chemical structures on them. Molecules similar to invasins, lectins, antibodies, and those acquired by means of adding thiols to know molecules are considered in this group [Figure 4].[28,29]

MUCOADHESIVE POLYMERS

Lectins

From a couple of years back, lectins have gotten tremendous consideration in pharma world for its common potential to tie particularly with moieties of free sugar or with sugar residues of polysaccharides, glycolipids, or glycoproteins which can be either free or bound (as in membranes of cell). Lectins are a decent choice for oral delivery, as they provide moderately great protection from acids and enzymes as well. In any case, binding is possible only just if the comparing sugar moieties are available or accessible on the mucosal epithelium. But there are no homogeneous events of interactions with particular sugar moieties in the GIT.[30]

Acrylates

Mucoadhesive polymers such as hydroxypropyl cellulose (HPC), chitosan, and the derivatives of PAA have picked up prevalence in an extensive variety of formulations. PAA is considered as one of the most efficient mucoadhesive polymers among these mucoadhesives. Its high solubility in water makes it an important carrier for a sustained drug release. Due to the hydrogen bonding being so strong, strong complexation between PVP and PAA could be employed for the preparation of mucoadhesive microspheres. Both the water-soluble polymers PVP and PAA, on coming in contact with each other they precipitate after forming a complex.[31]

Hyaluronic acid

It is anionic in nature and is found all through epithelial, connective, and neural tissues. The size of the polymers can range between 5000 and 20,000,000 Da. It is a significant component present in the synovial fluid and is in charge of increasing the fluid viscosity. With decreasing molecular weight of HA, the performance of mucoadhesion enhances simultaneously.

Gellan gum (GG)

Water-soluble polymers with gel-forming ability when applied to the delivery site are presently the matter of interest. The advantages of these polymers outnumber the other polymers as the liquid form are applied at the delivery site and swelling causes a strong gel to form and thereby increasing the formulation's residence time. GG, a microbial polysaccharide is produced by water-soluble bacterium Sphingomonas elodea. Gums alternate to GG (xanthan gum and karaya gum) have been studied for the controlled delivery of formulations.[32]

Alginate

Alginate belongs to the category of anionic mucoadhesive polymer which through carboxyl hydroxyl interactions with mucin glycoproteins forms strong hydrogen bonds. It's a linear, polysaccharide which is soluble in water has gained attention for applications in different pharmaceutical and biotechnological fields. Mucoadhesive microbeads have been produced from the derivatives of thiolated sodium alginate for the treatment of periodontal pockets locally, and prolonged release has been observed post-application which reflects its potential in the treatment of periodontal disorders.[33]

Poloxamers

Poloxamers like polymers are used on a wide scale in the pharmaceutical sector for their like high viscous nature which also offers for a choice of vehicles for controlled release drug delivery and its high range similarity with a broad-spectrum of drugs and excipients in formulation developments, which makes it a good choice of vehicle for delivery of drug through different administration routes. For its thermoreversible polymeric property, this polymer is useful in mucoadhesive formulations.[34]

Pectin

Pectin is a polysaccharide, anionic in nature is specifically a heteropolysaccharide that is predominantly seen in primary cell walls. Due to the presence of carboxyl groups significantly in the structure, it possesses mucoadhesiveness which causes its interaction with mucus. On hydration, pectin forms hydrogel possessing high viscosity and thereby facilitating mucoadhesion.[35]

Starch

Due to their hydrophilic nature and biocompatibility, polysaccharides, namely starch, alginate, chitosan, and other cellulose derivatives have been generally utilized as

systems to deliver mucoadhesive drugs.[36] Starch (amylum), a polysaccharide formed through glucose units in a large number and connected together through glycosidic bonds. The starch's ability to absorb moisture makes it fit to shape a mucoadhesive gel-like framework. This phenomena of absorption lead to the mucosal membrane dehydration which brings about the drug moiety transportation through paracellular tight intersections.[37] As bioadhesive drug carriers, spray-dried starch or Carbopol 974P showed notable improvement for drug carriers in terms of the mucoadhesive capacity when contrasted with equal physical blends without exhibiting any irritational sign. This further recommended starch as a biocompatible and safe bioadhesive transporter.[38] In addition, with polymer such as Carbopol 974P and HPMC, the matrix of starch indicated an increment in the drug discharge for a model medication of propranolol hydrochloride.[39]

PEG

Another polymer in the mucoadhesive category which is both safe and nonimmunogenic, likewise non-antigenic and has been approved by FDA is PEG. It has high water solubility and has quick *in vivo* clearance and relies on its molecular weight.[40] The hydrogen bond forming capacity with residues of sugar on glycosylated proteins is the reason behind unique mucoadhesive properties of PEG.[41] Incorporation of linear PEG chains to matrices of hydrogel increases the degree of adhesiveness to the mucous membrane because of the interpenetration of chain that occurs at the mucus/hydrogel interface has also been reported.[42]

Sulfated polysaccharide

Sulfated derivatives of polysaccharides have been taken into account, and high focus has been given on both its biological and chemical properties from the past decade.[43] Biological activities have been studied for the sulfated polysaccharides to look for its anticoagulant, antioxidant, and antithrombotic activities.[44] The sulfated polysaccharides show increased water solubility and exhibit changes in the chain conformation, bringing in the modification in their biological properties. Further, the effects of the sulfated polysaccharide and cyclophosphamide in combination were also examined, and the sulfated form of chitosan and chitin were proved to be reliable carriers for delivering several therapeutic agents over a mucosal membrane.[45]

Carrageenan

Carrageenan consists of gelatin quality polysaccharides and is obtained from the extract of the red seaweed plant. Carrageenan is commonly preferred by the vegans and vegetarians when compared to gelatin. It fills various needs in conventional drug, which incorporates security from herpes simplex and personal lubrication and is utilized as a part of the treatment of the HIV. It is likewise a powerful antivirus for treating the common cold. Increment in sulfated ester diminishes the temperature of solvency of the carrageenan and manufactures poor strength gels. In the pharmaceutical industry, it is employed in various medicaments as a mucoadhesive material.[46]

Gelatin

Gelatin, a polyelectrolyte whose net charge relies both on the pH and the sort of gelatin utilized. Type A gelatin is separated through acidic hydrolysis from collagen, with an isoelectric point extending in the vicinity of 7 and 9. However, gelatin of type B is acquired through alkaline hydrolysis having an isoelectric point in the vicinity of 4.7 and 5.3. It has been reported that aminated microspheres of gelatin possess higher ability of gastric mucoadhesion than gelatin microspheres used alone. Higher number of amino group indicates the better flexibility of chain.[47]

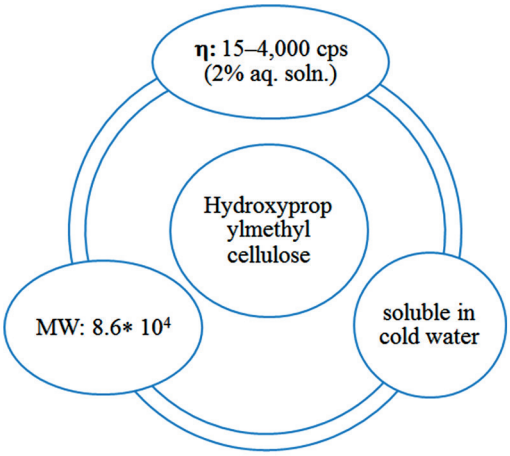
Chitosan

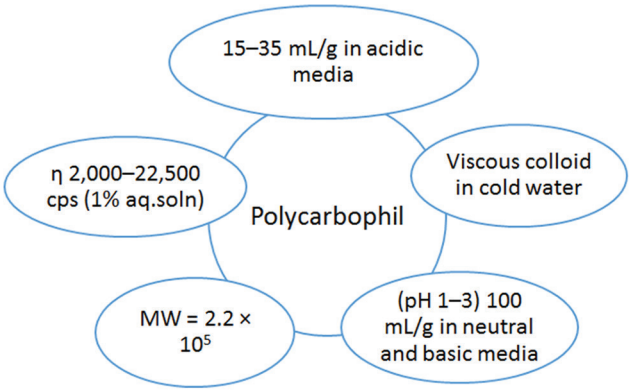
Chitosan is a polysaccharide which is made out of copolymers such as N-acetyl glucosamine and glucosamine. It is insoluble at neutral or higher pH, then again it forms a salt with different organic and inorganic acids. Chitosan is a polymer which is biocompatible and non-toxic in nature. It is having numerous applications in the delivery of drugs and shows enhanced absorption for macromolecular drugs which are hydrophilic in nature. It is also used as an excipient in formulation development. In a swollen state, it serves as an excellent mucoadhesive polymer when studied on mucosa of the porcine intestine. Chitosan is a promising carrier for colon targeted drug delivery because of its insolubility at pH >6.5, a similar condition found in the ileum and jejunum of the GIT on the other hand colonic pH ranges between 5.5 and 6.0. Hence, at colonic pH, chitosan gets solubilized subsequently with the release of the drug moiety (Ludwig, 2005). Chitosan alongside with its metabolized derivatives is promptly disposed of through kidney. The mucoadhesive properties of chitosan are determined by the structure as its degree and sort of interaction with mucin relies on its structure. Electrostatic binding is the primary interaction that takes place among chitosan and mucin. To enhance the chitosan's mucoadhesive properties and to make it appropriate for controlled drug delivery, different adjustments have been done in various ways.[48] The polymeric solution of chitosan is prepared using 1.5% (V/V) acetic acid in distilled water under occasional stirring for 48 h. The final viscous solution of chitosan is filtered through nylon gauze to eliminate suspended particles and debris. The drug release profile is enhanced using a water-soluble hydrophilic polymer PVP K-30 into the chitosan solution under constant stirring.

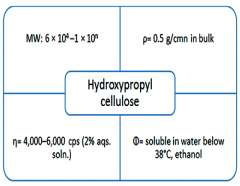
Cellulose derivatives

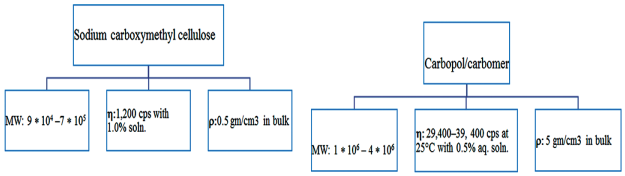
Diverse polysaccharides along with their derivatives, for example, chitosan, hyaluronic acid, guar gum, and so forth have discovered numerous applications in different mucoadhesive delivery systems. Polymers belonging to this category were additionally investigated for mucoadhesive delivery into the eye. NaCMC shows excellent ocular mucoadhesive property among all mucoadhesive cellulose derivates. Many studies uncovers that the surface-dynamic property of the cellulose and its derivatives helps in its film-forming capability.[49,50]

Polymer profile









Formulation design

Conventional dosage forms fail to guarantee the therapeutic drug levels in mucosal and in the circulation when a drug is administered through mucosal and transmucosal route. This happens due to the physiological removal mechanisms that are involved in the oral cavity (mechanical stress and washing impact of salivation), which dislodges the drug away from the active mucosal site, bringing about a shorter time of exposure and unforeseeable drug distribution at the site of action. For having the desired therapeutic action, it is fundamental to expand and enhance the contact between the mucosa and active substance. To fulfil the requirements of therapeutics, designed formulations for administration in the buccal region should have the mentioned functional agents: Agents for mucoadhesion, to keep up a firm and delayed contact of the formulation with the absorption site; penetration enhancers, to upgrade the penetration of medication crosswise over mucosa or into the most profound epithelium layers; and enzyme inhibitors, to finally prevent the degradation of drug through enzymes of mucosa.

Mucoadhesive agents

Depending on the kind of dosage form utilized, buccal mucoadhesion is possible in different situations. Swelling along with polymer hydration play the crucial role in case of partially hydrated or dry formulations. Mucus dehydration and polymer hydration simultaneously could enhance the cohesive properties of mucous that aids in the process of mucoadhesion. Swelling is the driving factor behind chain flexibility of polymer and interpenetration between mucin chains and polymer. The coefficient of spreading and the capacity of forming bonds of physical or chemical nature with mucin elevates when dosage forms of completely hydrated nature are taken into consideration. Henceforth, depending on the formulation type, polymers with varying properties need to be considered.[51]

The polymers that are frequently used in less hydrated buccal dosage forms include polyvinyl alcohol (PVA), HPMC, and HPC. When tested in the total hydrated state, the polymers, for example, PAA, chitosan, and its derivatives, HPC, PVA, and gelatine have shown to interact with buccal mucosa.[52] In recent studies, it has been revealed that cubic and lamellar liquid crystals of glyceryl monooleate have indicated properties of mucoadhesion and it looks to be feasible to use those as carriers to deliver peptides in buccal cavity.[53] In the past few years, as specific bioadhesives lectins have been contemplated for oral drug delivery.[54]

Penetration enhancers

To upgrade the retention of drugs which have poor solubility and especially large molecules which are hydrophilic in nature, permeation enhancers in recent years have become the center of focus.[55] For a drug to enter the systemic

Table 1: Comparison between theories of Mucoadhesion

Theory	Mechanism behind bioadhesion	Comments
Wetting theory	Bioadhesive polymer's ability to develop by spreading close contact with the membrane of mucus	Spreading coefficient of polymer must be positive
Adsorption theory	Chemical bonds are formed due to surface forces	Profound primary forces: Covalent bonding, ionic bonding, hydrogen bonding, and van der Waal's forces.
Electronic theory	Appealing electrostatic forces between mucin system of glycoprotein and the material of bioadhesion	Exchange of electron happens between the development of a two-fold charged electric layer at the interface between two surfaces
Fracture theory	Analysis of the maximum tensile stress that is produced amid separation of the mucosal surfaces	Independent of physical entanglement between mucin strand and bioadhesive polymer chain, hence ideal to study about the bioadhesion of hard polymer, which needs an adaptable chain
Diffusion interlocking theory	Physical entrapment of mucin strands and the flexible chains of polymer	For highest diffusion and higher bioadhesive quality, dissolvability parameters (δ) of both the bioadhesive polymer and the mucus glycoprotein must be comparative

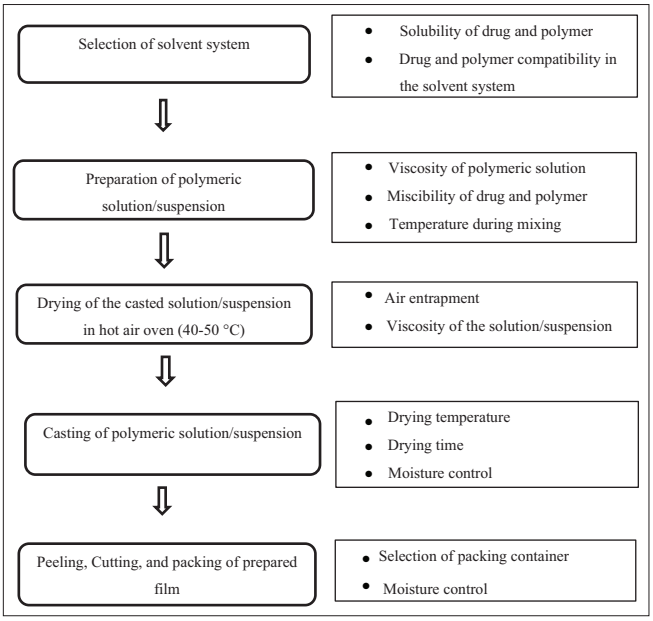


Figure 3: Steps involved in the film casting process and the critical parameters involved

circulation, penetration enhancers are employed to show its therapeutic action. Their nature must be non-irritant and must demonstrate a reversible impact which means that after the drug has been completely absorbed, barrier properties of the epithelium should be able to recover. The common classes included in buccal penetration enhancers are fatty acids (lauric acid, oleic acid, and extract of cod liver oil) which disrupt the packing of intercellular lipids, surfactants and bile salts (by extracting membrane protein or lipids, through fluidizing the membrane, through reverse micellizing the membrane, and making aqueous channels), a zone (through creating a fluid-like region in intercellular lipids), and alcohols (through reorganization of the lipid domains and through changing the conformation in protein).[56,57]

At present, chitosan along with its different derivatives is previously known for their properties of mucoadhesion and has also exhibited to be the potential penetration enhancers for transmucosal absorption of the drug.[58] Due to the brief broadening of the tight junctions existing between the cells, the penetration properties of chitosan through mucosae (intestinal and nasal) are intensified.[59] It must be brought to the attention that different *in vitro* methods and *ex vivo* methods have been carried out to estimate and characterize the penetration enhancement properties of the different materials, but the *in vivo* conditions are not simulated appropriately. The establishment of new standardized biological models that serve as a substitute for animal studies is need of the hour for the evaluation of different materials and compare them [Figure 2].

Absorption enhancement mechanism

In general, permeation enhancers act through the following ways:

1. Elevating the cell membrane's fluidity.
2. Extricating intercellular and intracellular lipids.
3. Disruption of lipid structure.
4. Cellular proteins alteration.
5. Increase the drug's thermodynamic activity.
6. Overcoming barriers of enzymes, especially for protein drugs and peptides.
7. Alteration of the rheology of surface mucin.

Effective in enhancing the absorption of large molecules, some proteins *in vitro* penetration was about 1–3 % but on adding an appropriate enhancer enhanced the value to 10%.

Table 2: List of permeation enhancers

S. No.	Permeation enhancers
1	2,3-Lauryl ether
2	Benzalkonium chloride
3	Aprotinin
4	Dextran sulfate
5	Glycol
6	Sodium EDTA
7	Sodium glycocholate
8	Polysorbate 80
9	Polyoxyethylene

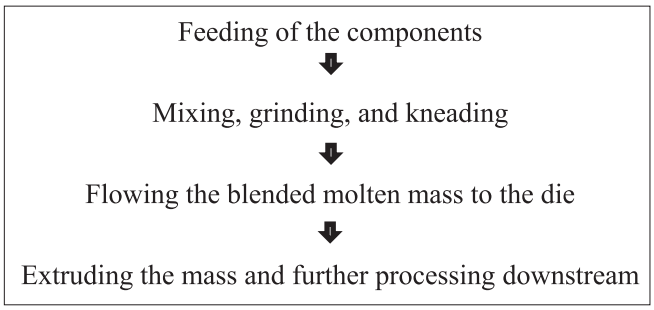


Figure 4: The practical steps involved in hot-melt extrusion technique

Enzyme inhibitors

The simultaneous administration of a drug and enzyme inhibitor is an alternate approach for enhancing the drugs and peptides absorption buccally. Protein containing drugs get stabilized by enzyme inhibitors, such as aprotinin, puromycin, and some bile salts through different mechanisms, which includes alteration of the enzyme activities, changing the peptides or proteins conformation or providing the drug less accessibility to enzymatic degradation.[60] Few mucoadhesive polymers such as poly and chitosan derivatives inhibit the activity of enzymes even if not present in buccal mucosa. Enzyme autolysis with loss of enzyme activity takes place through conformational changes caused when a polyacrylic acid (carbomer) can bind the essential enzyme cofactors calcium and zinc.[61] In the past few years, the derivatives of a polymer having thiol groups on poly(acrylates) or chitosan have been proved to improve inhibitory properties of polymer-enzyme.[62]

Preparation of buccal delivery films

The two major manufacturing processes involved in the development of mucoadhesive buccal films are film casting process and hot-melt extrusion technique.

Film casting

Based on the literature, the method of film casting is surely the most explored and frequently used process for manufacturing films. This is mainly due to the easy steps involved in the process and the inexpensive system setup that incurs at the research on a laboratory scale.

The whole process involves at least six different steps to develop a film:

1. Casting solution preparation.
2. Removal of air from the solution.
3. Transfer of solution into the mold.
4. Drying the casting solution.
5. Cutting the final dosage form containing the required amount of drug.
6. Packaging.

Amid the film manufacturing process, the prime significance is given to the solution or suspension's rheological properties, content uniformity, air bubbles entrapment, and the remaining solvents present in the final form of dose. Air bubbles are acquainted incidentally with the fluid amid the steps of mixing in the manufacturing process and evacuation of air is a crucial step for reasons like homogeneity.[63] Films cast from solutions containing airshow a nonuniform surface and heterogeneous thickness. Presence of organic solvents is a major concern while manufacturing films for buccal delivery. Due to several health problems and undesired hazard exerted by organic solvents on the environment, its used is generally criticized.[64]

Uniformity of content has always been a noteworthy test since the introduction of buccal films. Schmidt in one of his earliest attempts to enhance the drug uniformity in formulated films proposed that the monolayered nature is mainly responsible for the nonuniformity of the films. He further postulated a multi-step technique for manufacturing multi-layered films. On the other hand, Yang *et al*. proposed that self-aggregation is a primary reason for films to show poor uniformity, and the drying process was important in preventing the aggregation of the film formulation ingredients. Adding a viscous agent like gel formers was proposed to avoid non-uniformity of films.[65] The solvent-casting method is used for manufacturing films containing heat-sensitive API's since the required temperatures for the solvent removal are relatively low.

Hot-melt extrusion technique

In this method, a molten blend of required ingredients is forced through an orifice to produce a material of high homogeneity in varying shapes and sizes.[66] This method is used to manufacture the controlled-release formulations such as matrix tablets and pellets[67] and orally disintegrating films as well.[68] However, few articles have reported using this technique to manufacture the mucoadhesive buccal films. Extensive research has been conducted by Repka *et al*.'s on the use of this technique for manufacturing these films and thereby comparing different possible matrix formers and additives for processing the blend.[69,70] In a previous publication, it has been reported that films exclusively

containing HPC could not be produced, however on adding the plasticizers, such as PEG 8000 or triethyl citrate made it possible for manufacturing flexible, thin, and stable HPC films for a longer period of time.[71] Further study revealed that with an increased molecular weight, there was a steep decrease in the release of the films which allows zero-order drug release [Figure 4].

There are several factors influencing the ideal buccal delivery film formulation, yet three critical parameters have been examined broadly in the literature of mucoadhesive buccal films such as properties of mucoadhesion, enhancement of permeation, and controlled release of the drug. The vast majority of the polymers that are utilized in mucoadhesives are essentially water-soluble polymers that swell and permits chain interactions to occur with the buccal mucosa's mucin. Polymers belonging to the poly (acrylic acid) families have been exhaustively used as mucoadhesives, as they belong to the mucoadhesives of first-generation.[72] These polymers must be hydrated so that they can exhibit their mucoadhesive properties; however, the phenomenon is limited by a critical degree of hydration. Overhydration takes place above this critical value which further leads to the slippery mucilage formation lacking mucoadhesive properties. It has been accounted for that the mucoadhesive quality of films got upgraded with an increase in the chitosan part. The authors recommended that with an expansion in the concentration of chitosan, the quantity of amine groups expands that interact with the negatively charged (carboxyl, sulfate, etc.) groups present on the buccal epithelium surface.[73] At present, formulated mucoadhesive films are utilized as platforms to convey nanoparticles through the oral route.[74] A large portion of the polymers for mucoadhesion investigated in the literature are apparently hydrophilic in nature or exhibit some crucial features for mucoadhesion. Although on repeated experiment, it has been found that different insoluble grades of eudragit exhibit some properties of mucoadhesion when used separately or when combined with other water-soluble polymers.[75] It has also been proposed that the plasticizer plays an important role in increasing the mucoadhesion. The study assumed that the best mucoadhesive characteristics are exhibited by the ionizable polymers,[76] which on combination with low-swellable properties would enhance compliance of patients.

Printing technologies

Latest technologies such as 3D printing could be employed to produce mucoadhesive films. It could be used extensively to meet the needs of the individual patient. This will possibly make both ends meet in the pharmaceutical industry to fulfill the future demand of customized medicine. These technologies are gaining popularity for its high flexibility and cost-effectiveness. From the pharmaceutical industry point of view, printing technologies are commonly used for identifying or labeling the pharmaceutical dosage forms, thus optimizing the product to be readily identified and to prevent any counterfeit production. This approach has been recently used for the drug loading of pharmaceutical dosage forms. A combination of both inkjet and flexographic technologies has been practiced as well. The inkjet printing is used for printing of API on a different substrate, and the flexographic printing is employed for coating the drug loaded-substrate with a polymeric thin film. All these techniques contribute to produce the film with high homogeneous distribution and accurate dosage of the drug throughout the films. The accuracy of dose and uniform distribution of the drug substances in the films are responsible for several reasons, such as properties of coating mass, like density or viscosity, which are influenced inherently by the amount and characteristics of the processed drug substances. To summarize, printing a drug on dosage form is the latest breakthrough in film development and proved to be a powerful tool to manufacture dosage form with excellent uniformity, unique speed-ability, and high stability.[77]

EVALUATION PARAMETERS

Surface pH

The developed mucoadhesive film is put on a Petri plate previously containing 4 mL of distilled water then it undergoes swelling at room temperature (25 ± 1°C) for a duration of 1 h. After that, pH of the film is measured by putting the terminal electrode of pH meter on its swelled surface.

Flatness

Mucoadhesive film of distinct size (1 cm^2) is put up against a plane surface, and it is cut vertically in several pieces (strips), and the length is measured subsequently. Percent constriction is calculated using the following formula. A constriction of zero percentage infers 100% flatness.

Constriction (%) = {(L1 −L2)/L1} * 100

Here, L1 represents the initial length of the film and L2 represents the final length of the strip.

Flatness (%)= 100−constriction (%).

Drug content

Small pieces are cut from the mucoadhesive film and are dissolved in 0.1 N NaOH (100 mL) with the assistance of magnetic stirrer. At that point, the solution undergoes filtration through a syringe filter of size 0.45 µm. From the prepared stock solution, a sample of 10 µg/mL concentration is prepared, and scanning is done by ultraviolet (UV)–vis spectrophotometer at 242 nm (λ_{max}). For blank control, placebo mucoadhesive films are used generally. The content of drug is calculated from the absorbance measured.

Swelling study

In the wake of guaranteeing the initial weight and diameter of the film, the samples on the agar plate surface were permitted to swell that was placed in an incubator kept at a temperature of 37°C. The increment in the weight and breadth of the films (n = 3) was measured at pre-set time intervals of (1–5 h). The swelling percent (%S) was determined using the given equation:

$$\%S = \frac{Xt - Xo}{Xo} \times 100$$

where Xt represents the swollen patch's weight or diameter of after a time t, and Xo represents the initial weight or diameter of the film at zero time.

Determination of the *in vitro* residence time

A USP disintegration apparatus is modified to estimate the time for *in vitro* residence. The composition of the disintegration medium is 800 ml of isotonic phosphate buffer (IPB) having pH 6.75 and kept up at37°C. A 3 cm long portion of rabbit intestinal mucosa is stuck to the glass section surface attached to the apparatus in a vertical position. The mucoadhesive film undergoes hydration with IPB of 15 µl with pH 6.75. The slab of glass is settled to the mechanical assembly vertically and permitted to move at the same time up and down to completely immerse the film at the lowest point in the buffer solution and is out again at the highest point. The time needed to completely detach the film from the surface of mucosa is recorded (mean of triplicate trials). Once more, controlling the media composition, pH, temperature, or substrate nature will decide the *in vitro* residence time. Despite the fact that the estimation of the *in vitro* residence time gives information to upgrade the formulation, it does not reveal the actual strength of the mucoadhesive bond. The strength of mucoadhesion is estimated as the highest force needed to withdraw the film from the substrate.

Estimation of mechanical properties of mucoadhesive films

Alongside the imperative parameters such as the strength of mucoadhesion and residence time of buccal films, a critical role is played by the mechanical properties of dosage forms physical integrity. Most pertinent to the study of mucoadhesive buccal films are the tensile strength, elongation at break, and the Young's modulus.

Tensile strength test

Between two discs of polyoxymethylene, an aqueous dispersion sample of a mucoadhesive polymer was placed. The upper disc is movable whereas the disc of the lower end is stationary, settled on a machine frame. The strength needed to perpendicularly detach the mucoadhesive cups from buccal mucosa of freshly removed bovine is termed as tensile strength. The stress is distributed uniformly over the mucoadhesive joint in this test. Mucus membrane the large intestine of a pig is attached to the upper movable disc. After computing the highest force and work for detachment, it is in this way inferred that the tensile strength relies on the concentration used as well as the sort of polymer utilized.

Tensile strength = (Force at failure/Cross-sectional area of the film)

Elongation at Break

(Increase in length at break/Initial film length)*100

In general, elongation is increased with an increase in the quantity of acceptable plasticizing agents in a given formulation.

Young's modulus

The firmness or the deformation process of the film in the region of elasticity is evaluated using this parameter. It is the initial of elastic distortion and is calculated from the proportion of corresponding strain and stress applied. It can also be determined from the slope of the stress-strain curve:

Young's modulus = (Slope of stress-strain curve)/(Film thickness * Cross-head speed)

It is realized that the fragile and slight polymers have a little rigidity, low Young's modulus, and short lengthening at break; however, a sensitive and solid polymer exhibits a direct elasticity, low Young's modulus, and a high extension at break.

Peel strength test

The measure of power or energy needed to separate the mucoadhesive formulation tangentially from the freshly extracted buccal mucosa of bovine. In this test, the edge of the adhesive system is mainly focused on the stress. To estimate the mechanical property of the created mucoadhesive formulations, the tests considered are tensile strength and shear strength. On the other hand, resistance toward the peeling power is determined by the peel strength test. The test for tensile strength is the most normally utilized mucoadhesive assessment strategy as extracted from the literature.

Ex vivo mucoadhesion time

The time for mucoadhesion is studied utilizing a mucoadhesive film. A pH 6.6 phosphate buffer (800 ml) is utilized as a

medium for disintegration kept up at 37°C. Cheek mucosa of porcine, 3 cm in length joined to the glass surface which is vertically connected to the mechanical assembly. The film is then hydrated with 15 µl phosphate buffer from one surface, and it is carried into with the mucosal film's contact. To completely submerge the film in the buffer solution, the apparatus is permitted to climb and down. The time needed to entirely separate the film from the surface of the mucosa is taken in the record.

Mucoadhesive force determination

The mucoadhesive power of the adhesive polymeric systems is tested with a tensile tester utilizing a plastic (PVC) plate. Plastic plates and polymeric films of the predetermined area (1 cm^2 and thickness of 0.8 mm) were cut, and after wetting with water, the film was positioned over the plastic plate surface. Under the force of fingertip, it was put in touch with the plate for 2 min before the measurement. The peak force was measured that is needed to segregate the film from the attached surface of the plastic plate.

In vivo mucoadhesion study

Due to the cost included, time required and other moral worries, there is an acute shortage of *in vivo* study reports in the literature. The mucoadhesive formulation's *in vivo* performance depends on the interfacial mechanisms as well as on the characteristics of the entire mucoadhesive compound such as the mucosa, the dosage form, and the interface connecting them.[78]

CONCLUSION

Mucoadhesive buccal film is a novel and promising drug delivery system which may be mono/multi-layered. The process of mucoadhesion involves various phenomenons such as adsorption, electronic interaction, wetting, fracture, diffusion interlocking, and mechanical. Different kind of polymers used in the preparation of films, such as ionic and non-ionic which are further classified on the generation wise. The selection of the polymers depends on the types of the active pharmaceutical ingredient, method of preparation and also the storage conditions. To design a film, we need certain additives such as mucoadhesive agents, penetration enhancers, and enzyme inhibitors. There are two techniques involved in the manufacturing of a film that is film casting process and hot-melt extrusion process. Due to ease of operation, film casting method is widely used. Nowadays, 3D printing technology is introduced to manufacture a film precisely. The developed films undergo rigorous quality control evaluations tests to check the quality of the films before it could be marketed. Mucoadhesive films possess a great potential to replace the existing formulation in certain disease conditions such as cardiac heart failure (BELBUCA), asthma, gastroesophageal reflux disease, nausea and vomiting caused by cancer chemotherapy, hyperacidity (Gas-X), decongestant (Sudafed PE), opioid dependence (Suboxone), severe pain (Onsolis), migraine (Zolmitriptan Rapidfilm), and constipation (Pedis-Lax).

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