

Oral Mucoadhesive Drug Delivery Systems: A Review

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Abstract - This article focuses on defining the principles of bio adhesive delivery systems based on hydrogels to biological surfaces that are covered by mucus. An overview of the last decade's discoveries on mucoadhesion and applications of mucoadhesive hydrogels as drug carriers is given. Techniques that are frequently used to study the adhesion forces and physicochemical interactions between hydrogel, mucus, and the underlying mucosa are reviewed. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin are held together for extended periods of time by the help of interfacial forces mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. Mucoadhesion is a complex phenomenon which involves wetting, adsorption, and interpenetration of polymer chains. Thereafter, several researchers have focused on the investigations of the interfacial phenomena of mucoadhesion with the mucus. The polymers used for formulation of mucoadhesive drug delivery systems are poly acrylic acid derivatives, chitosan, and newer second-generation polymers. Mucoadhesive drug delivery systems with its various advantages have a lot of potential in formulating dosage forms for various chronic diseases.

Index Terms - Mucoadhesion, Bio adhesion, Oral mucosa, Mucin, Mucus, Hydrogels.

INTRODUCTION

BIOADHESION/MUCOADHESION

The term bio adhesion refers to any bond formed between two biological surfaces or a bond between a biological and a synthetic surface. In case of bio adhesive drug delivery, the term bio adhesion is used to describe the adhesion between polymers, either synthetic or natural and soft tissues or the gastrointestinal mucosa. In cases where the bond is formed with the mucus the term mucoadhesion may be used synonymously with bio adhesion. Mucoadhesion can be defined as a state in which two components, of which one is of biological origin, are held together for

extended periods of time by the help of interfacial forces. Generally speaking, bio adhesion is a term which broadly includes adhesive interactions with any biological or biologically derived substance, and mucoadhesion is used when the bond is formed with a mucosal surface.

MECHANISM OF MUCOADHESION

As stated, mucoadhesion is the attachment of the drug along with a suitable carrier to the mucous membrane. Mucoadhesion is a complex phenomenon which involves wetting, adsorption, and interpenetration of polymer chains. Mucoadhesion has the following mechanism [1],

1. Intimate contact between a bio adhesive and a membrane (wetting or swelling phenomenon) [2][3].
2. Penetration of the bio adhesive into the tissue or into the surface of the mucous membrane (interpenetration) [2][3]. Residence time for most mucosal routes is less than an hour and typically in minutes, it can be increased by the addition of an adhesive agent in the delivery system which is useful to localize the delivery system and increases the contact time at the site of absorption [4]. The exact mechanism of mucoadhesion is not known but an accepted theory states that a close contact between the mucoadhesive polymer and mucin occurs which is followed by the interpenetration of polymer and mucin. The adhesion is prolonged due to the formation of van der Waals forces, hydrogen bonds and electrostatic bonds.

Theories of mucoadhesion [1]

- Wettability theory
- Electronic theory
- Fracture theory
- Adsorption theory
- Diffusion theory
- Wettability theory

The ability of bio adhesive or mucus to spread and develop intimate contact with its corresponding substrate is an important factor in bond formation. The wetting theory was developed predominantly in regard to liquid adhesives, uses interfacial tensions to predict spreading and in turn adhesion [5] [6] [7]. The study of surface energy of polymers and tissues to predict mucoadhesive performance has been given considerable attention [8] [9].

The contact angle (Q) which should ideally be zero for adequate spreading is related to interfacial tensions (g) as per the Youngs equation.

$$g_{tg} = g_{bt} + g_{bg} \cos Q$$

Where the subscripts t, g and b represent tissue, gastrointestinal contents and bioadhesive polymer respectively, for spontaneous wetting to occur [10][11].

$$gtb \geq gbt + gbg$$

the spreading coefficient, $S_{b/t}$ can be given by,

$$S_{b/t} = gtg - gbt - gbg$$

For the bioadhesion to take place the spreading coefficient must be positive, hence it is advantageous to maximize the interfacial tension at the tissue-GI contents interface and minimizing the surface tension at the other two interfaces. The interfacial tension can be measured by methods like the Wilhelmy plate method [12][13]. It has been shown that the BG-tissue interfacial tension can be calculated as,

$$g_{bt} = g_b + g_t - 2F(g_b g_t)^{1/2}$$

Where the values of F (interaction parameter) can be found in published papers [14][15], thus by the wetting theory it is possible to calculate spreading coefficients for various bioadhesives over biological tissues and predict the intensity of the bioadhesive bond.

Adsorption theory

This theory states that the bioadhesive bond formed between an adhesive substrate and the tissue is due to the weak van der waals forces and hydrogen bond formation. It is one of the most widely accepted theories of bioadhesion [18][19].

Diffusion theory

The concept of the interpenetration and entanglement of the bioadhesive polymer chains and mucous polymer chains is supported by the

Electronic theory

The electronic theory depends on the assumption that the bioadhesive material and the target biological material have different electronic surface characteristics. Based on this, when two surfaces come in contact with each other, electron transfer occurs in an attempt to balance the Fermi levels, resulting in the formation of a double layer of electrical charge at the interface of the bioadhesive and the biologic surface. The bioadhesive force is believed to be present due to the attractive forces across this double layer [16].

Fracture theory

This is by-far the most accepted theory on bioadhesion. It explains the forces required to separate the two surfaces after adhesion has taken place. It measures the maximum Tensile stress (s_m) produced during detachment as follows [10].

$$s_m = F_m/A_o$$

Where F_m and A_o represent the maximum force of detachment and the total surface area respectively. In a uniform single-component system, fracture strength (s_f), which is equal to the maximum stress of detachment (s_m), is proportional to the fracture energy (g_c), Youngs modulus of elasticity (E) and the critical crack length (c) of the fracture site as follows [17],

$$s_f = (g_c E/c)^{1/2}$$

fracture energy can be obtained by the sum of the reversible work of adhesion, W_r (work done to produce new fracture surfaces) and the irreversible work of adhesion, W_i (work of plastic deformation),

$$g_c = W_r + W_i$$

diffusion theory. The bond strength increases with the increase in the degree of the penetration. This penetration is dependent on the concentration gradients and the diffusion coefficients. It is believed that interpenetration in the range of 0.2-0.5 μ m is required to produce effective bond strength. The penetration depth (l) can be estimated by [20].

$$l = (tD_b)^{1/2}$$

where t is the time of contact and D_b is the diffusion coefficient of the bio adhesive material in the mucus.

Factors affecting mucoadhesion [21]

The mucoadhesion of a drug carrier system to the mucous membrane depends on the below mentioned factors.

- polymer based factors.

Molecular weight of the polymer
 Concentration of polymer used
 Flexibility of polymer chains
 Swelling factor.

Stereochemistry of polymer

➤ physical factors

pH at polymer substrate interface
 Applied strength.

Contact time.

➤ physiological factors
 Mucin turnover rate
 Diseased state

ADVANTAGES OF ORAL MUCOADHESIVE DRUG DELIVERY

- a. Prolongs the residence time of the dosage form at the site of absorption.
- b. Due to an increased residence time, it enhances absorption and hence the therapeutic efficacy of the drug.
- c. Excellent accessibility
- d. Rapid absorption because of enormous blood supply and good blood flow rates
- e. increase in drug bioavailability due to first pass metabolism avoidance.
- f. Drug is protected from degradation in the acidic environment in the GIT.
- g. Improved patient compliance- ease of drug administration
- h. faster onset of action is achieved due to mucosal surface.

Oral mucosa and mucin Oral mucosa

Within the oral mucosal cavity, the buccal region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply, and it is relatively permeable [3].

Oral histology

The oral mucosa is composed of an outermost layer of stratified squamous epithelium. Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium [22]. The epithelium of the buccal mucosa is about 40-50 cell layers thick, while that of the sublingual epithelium contains somewhat fewer. The

epithelial cells increase in size and become flatter as they travel from the basal layers to the superficial layers. The turnover time for the buccal epithelium has been estimated at 5-6 days [23], and this is probably representative of the oral mucosa as a whole. The oral mucosal thickness varies depending on the site: the buccal mucosa measures at 500-800 μm , while the mucosal thickness of the hard and soft palates, the floor of the mouth, the ventral tongue, and the gingivae measure at about 100-200 μm . The composition of the epithelium also varies depending on the site in the oral cavity. The mucosae of areas subject to mechanical stress (the gingivae and hard palate) are keratinized similar to the epidermis. The mucosae of the soft palate, the sublingual, and the buccal regions, however, are not keratinized [24]. The keratinized epithelia contain neutral lipids like ceramides and acylceramides which have been associated with the barrier function. These epithelia are relatively impermeable to water. In contrast, non-keratinized epithelia, such as the floor of the mouth and the buccal epithelia, do not contain acylceramides and only have small amounts of ceramide [25][26]. They also contain small amounts of neutral but polar lipids, mainly cholesterol sulfate and glucosyl ceramides. These epithelia have been found to be considerably more permeable to water than keratinized epithelia.

Permeability

The oral mucosae in general are somewhat leaky epithelia intermediate between that of the epidermis and intestinal mucosa. It is estimated that the permeability of the buccal mucosa is 4-4000 times greater than that of the skin. As indicative by the wide range in this reported value, there are considerable differences in permeability between different regions of the oral cavity because of the diverse structures and functions of the different oral mucosae. In general, the permeabilities of the oral mucosae decrease in the order of sublingual greater than buccal, and buccal greater than palatal [22]. This rank order is based on the relative thickness and degree of keratinization of these tissues, with the sublingual mucosa being relatively thin and non-keratinized, the buccal thicker and non-keratinized, and the palatal intermediate in thickness but keratinized. It is currently believed that the permeability barrier in the oral mucosa is a result of intercellular material derived from the so-called 'membrane coating granules' (MCG) [26]. This

barrier exists in the outermost 200µm of the superficial layer. Permeation studies have been performed using a number of very large molecular weight tracers, such as horseradish peroxidase [27] and lanthanum nitrate [28]. When applied to the outer surface of the epithelium, these tracers penetrate only through outermost layer or two of cells. When applied to the submucosal surface, they permeate up to, but not into, the outermost cell layers of the epithelium. According to these results, it seems apparent that flattened surface cell layers present the main barrier to permeation, while the more isodiametric cell layers are relatively permeable. Aside from the MCGs, the basement membrane may present some resistance to permeation as well, however the outer epithelium is still considered to be the rate limiting step to mucosal penetration. The structure of the basement membrane is not dense enough to exclude even relatively large molecules.

Table No.1 List of compounds used as oral mucosal permeation enhancers [29]

Permeation Enhancer
23-lauryl ether
Aprotinin
Azone
Benzalkonium chloride
Cetylpyridinium chloride
Cetyltrimethylammonium bromide
Cyclodextrin
Dextran sulfate
Lauric acid
Lauric acid/Propylene glycol
Lysophosphatidylcholine
Menthol
Methoxysalicylate
Methyloleate
Oleic acid
Phosphatidylcholine
Polyoxyethylene
Polysorbate 80
Sodium EDTA
Sodium salicylate
Sodium taurodeoxycholate
Sulfoxides

Environment

The cells of the oral epithelia are surrounded by an intercellular ground substance, mucus, the principal

components of which are complexes made up of proteins and carbohydrates. These complexes may be free of association or some maybe attached to certain regions on the cell surfaces. This matrix may actually play a role in cell-cell adhesion, as well as acting as a lubricant, allowing cells to move relative to one another [30]. Along the same lines, the mucus is also believed to play a role in bioadhesion of mucoadhesive drug delivery systems [5]. In stratified squamous epithelia found elsewhere in the body, mucus is synthesized by specialized mucus secreting cells like the goblet cells, however in the oral mucosa, mucus is secreted by the major and minor salivary glands as part of saliva [31][32]. Up to 70% of the total mucin found in saliva is contributed by the minor salivary glands. At physiological pH the mucus network carries a negative charge (due to the sialic acid and sulfate residues) which may play a role in mucoadhesion. At this pH mucus can form a strongly cohesive gel structure that will bind to the epithelial cell surface as a gelatinous layer. Another feature of the environment of the oral cavity is the presence of saliva produced by the salivary glands. Saliva is the protective fluid for all tissues of the oral cavity. It protects the soft tissues from abrasion by rough materials and from chemicals. It allows for the continuous mineralisation of the tooth enamel after eruption and helps in remineralisation of the enamel in the early stages of dental caries [33]. Saliva is an aqueous fluid with 1% organic and inorganic materials. The major determinant of the salivary composition is the flow rate which in turn depends upon three factors: the time of day, the type of stimulus, and the degree of stimulation [5][32]. The salivary pH ranges from 5.5 to 7 depending on the flow rate. At high flow rates, the sodium and bicarbonate concentrations increase leading to an increase in the pH. The daily salivary volume is between 0.5 to 2 liters and it is this amount of fluid that is available to hydrate oral mucosal dosage forms. A main reason behind the selection of hydrophilic polymeric matrices as vehicles for oral transmucosal drug delivery systems is this water rich environment of the oral cavity.

Buccal Routes of Drug Absorption

There are two permeation pathways for passive drug transport across the oral mucosa: paracellular and transcellular routes. Permeants can use these two routes simultaneously, but one route is usually preferred over the other depending on the

physicochemical properties of the diffusant. Since the intercellular spaces and cytoplasm are hydrophilic in character, lipophilic compounds would have low solubility in this environment. The cell membrane, however, is rather lipophilic in nature and hydrophilic solutes will have difficulty permeating through the cell membrane due to a low partition coefficient. Therefore, the intercellular spaces pose as the major barrier to permeation of lipophilic compounds and the cell membrane acts as the major transport barrier for hydrophilic compounds [34].

Buccal Mucosa as a Site for Drug Delivery

Even though the sublingual mucosa is relatively more permeable than the buccal mucosa, it is not suitable for an oral transmucosal delivery system. The sublingual region lacks an expanse of smooth muscle or immobile mucosa and is constantly washed by a considerable amount of saliva making it difficult for device placement. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action making it appropriate for drugs with short delivery period requirements with infrequent dosing regimen. Due to two important differences between the sublingual mucosa and the buccal mucosa, the latter is a more preferred route for systemic transmucosal drug delivery [22][27]. First difference being in the permeability characteristics of the region, where the buccal mucosa is less permeable and is thus not able to give a rapid onset of absorption (i.e., more suitable for a sustained release formulation). Second being that the buccal mucosa has an expanse of smooth muscle and relatively immobile mucosa which makes it a more desirable region for retentive systems used for oral transmucosal drug delivery. Thus, the buccal mucosa is more fitted for sustained delivery applications, delivery of less permeable molecules, and perhaps peptide drugs.

Similar to any other mucosal membrane, the buccal mucosa as a site for drug delivery has limitations as well. One of the major disadvantages associated with buccal drug delivery is the low flux which results in low drug bioavailability. Various compounds have been investigated for their use as buccal penetration enhancers in order to increase the flux of drugs through the mucosa [34]. Since the buccal epithelium is similar in structure to other stratified epithelia of the body, enhancers used to improve drug permeation in other absorptive mucosae have been shown to work in

improving buccal drug penetration [29]. Drugs investigated for buccal delivery using various permeation/absorption enhancers range in both molecular weight and physicochemical properties. Small molecules such as butyric acid and butanol [35], ionizable low molecular weight drugs such as acyclovir, propranolol, and salicylic acid, large molecular weight hydrophilic polymers such as dextrans, and a variety of peptides including octreotide, leutinizing hormone releasing hormone (LHRH), insulin, and α -interferon have all been studied. A series of studies [36] on buccal permeation of buserelin and fluorescein isothiocyanate (FITC) labelled dextrans reported the enhancing effects of di- and tri-hydroxy bile salts on buccal penetration. Their results showed that in the presence of the bile salts, the permeability of porcine buccal mucosa to FITC increased by a 100-200-fold compared to FITC alone. The mechanism of penetration enhancement of FITC-labelled dextrans by sodium glycocholate (SGC) was shown to be concentration dependent [25]. Below 10 mM SGC, buccal permeation was increased by increasing the intercellular transport and at 10 mM and higher concentrations by opening up a transcellular route. Gandhi and Robinson [29] investigated the mechanisms of penetration enhancement of transbuccal delivery of salicylic acid. They used sodium deoxycholate and sodium lauryl sulfate as penetration enhancers, both of which were found to increase the permeability of salicylic acid across rabbit buccal mucosa. Their results also supported that the superficial layers and protein domain of the epithelium may be responsible for maintaining the barrier function of the buccal mucosa. Table No.1 shows a list of compounds used as oral mucosal permeation enhancers.

Mucin

Mucin is a family of high molecular weight, heavily glycosylated proteins produced by many epithelial tissues. Some mucins remain membrane bound while others are secreted to the mucosal surface or are secreted to be a part of the saliva [37].

Structure

Mucins composed of two regions, the amino acid N-terminal regions, rich in cysteine and a large central region composed of 10-80 residue sequences made up of serine or threonine [29].

Secretion

Mucin is secreted by the stimulation of MARCKS (myristylated alanine rich C kinase substrate) which coordinates the secretion from the vesicles within the epithelial cells. The fusion of the vesicles to the plasma membrane causes release of mucin, this viscoelastic product combined with other secretions is called mucus [29].

Role of mucus

The surface epithelium of the stomach and intestine are exposed to the highly acidic concentration of HCl and proteolytic enzymes like pepsin. But still it retains its integrity due to the mucus secreted by the goblet cells located in the stomach, duodenum, and the transverse colon. This mucus contains mucin, an oligosaccharide with terminal sialic acid (pka= 2.6), which neutralizes the hcl and withstands the effect of pepsin. These surface adhesive properties of mucin are being utilized in the development of mucoadhesive drug delivery systems.

Mechanism

The drugs coated with a mucoadhesive polymer binds to the mucus and hence is retained on the surface epithelium for an extended duration. The drug molecules in turn are constantly released from the polymer over an extended duration of time.

Polymers used for mucoadhesive drug delivery.

[1] The rheology of the mucoadhesion is a typical topic and it deals with a number of forces, factors of the components, state of the material, its derived properties. Based on the rheological aspects, we can categorize the mucoadhesive polymers into two broad categories, materials which undergo matrix formation or hydrogel formation by either a water swellable material or a water-soluble material.

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. These carriers generally polymers are classified as,

Hydrophilic polymers

Contains carboxylic group and possess excellent mucoadhesive properties.

These are pvp (poly vinyl pyrrolidone) Mc (methyl cellulose)

Scmc (sodium carboxy metyhyl cellulose) Hpc (hydroxyl propyl cellulose)

Hydrogels

Hydrophilic polymers

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

Anionic polymers - carbopol, polyacrylates Cationic polymers - chitosan

Neural/ nonionic polymers - eudragit analogues

They can also be classified as, Synthetic polymers.

Natural polymers

Synthetic polymers - cellulose derivatives, carbopols, etc. Natural polymers - tragacanth, pectin, gelatin sodium alginate, acacia.

Ideal muco polymer Characteristics

A mucoadhesion promoting agent or the polymer is added to the formulation which helps to promote the adhering of the active pharmaceutical ingredient to the oral mucosa. The agent can have such additional properties like swelling so as to promote the disintegration when in contact with the saliva.

As understood earlier, that various physical and chemical exchanges can affect the polymer/ mucus adhesion, so as polymer should be carefully selected with the following properties in mind.

1. polymer must have a high molecular weight upto 100,000 or more. This is necessary to promote the adhesiveness between the polymer and mucus [38].
2. Long chain polymers-chain length must be long enough to promote the interpenetration and it should not be too long that diffusion becomes a problem [39].
3. High viscosity.
4. Degree of cross linking- it influences chain mobility and resistance to dissolution. Highly cross-linked polymers swell in presence of water and retain their structure. Swelling favours controlled release of the drug and increases the polymer/mucus interpenetration. But as the cross-linking increases, the chain mobility decreases which reduces the mucoadhesive strength [39].
5. Spatial conformation.

6. Flexibility of polymer chain- this promotes the interpenetration of the polymer within the mucus network [40].
7. Concentration of the polymer- an optimum concentration is required to promote the mucoadhesive strength. It depends however, on the dosage form. For solid dosage form the adhesive strength increases with increase in the polymer concentration. But in case of semi solid dosage forms an optimum concentration is essential beyond which the adhesive strength decreases [41].
8. Charge and degree of ionization- the effect of polymer charge on mucoadhesion was clearly shown by Bernkop-Schnurch and Freudl. In this work, various chemical entities were attached to chitosan and the mucoadhesive strength was evaluated. Cationic chitosan hcl showed marked adhesiveness when compared to the control. The attachment of EDTA an anionic group increased the mucoadhesive strength significantly. DTPA/chitosan system exhibited lower mucoadhesive strength than cationic chitosan and anionic EDTA chitosan complexes because of low charge. Hence the mucoadhesive strength can be attributed as anion>cation>nonionic [42].
9. Optimum hydration- excessive hydration leads to decreased mucoadhesive strength due to formation of a slippery mucilage [43].
10. Optimum Ph – mucoadhesion is optimum at low pH conditions but at higher pH values a change in

the conformation occurs into a rod like structure making those more available for inter diffusion and interpenetration. At very elevated pH values, positively charged polymers like chitosan form polyelectrolyte complexes with mucus and exhibit strong mucoadhesive forces.

11. High applied strength and initial contact time.
12. It should be nontoxic, economic, biocompatible preferably biodegradable.

Table no. 2 shows the relative strength of the various mucoadhesive polymers.

The polymers that are used in mucoadhesive drug delivery were categorised by Park and Robinson as,

- Polymers that become sticky when placed in an aqueous media and owe their bioadhesion to stickiness.
- polymers that adhere through nonspecific, non-covalent electrostatic interactions
- Polymers that bind to specific receptors.

Polymers used for oral mucoadhesive drug delivery PAA derivatives carbomer- carbopol 934.

Novon- polycarbophil

These are polymers of acrylic acid cross linked with polyalkenyl ethers or divinyl glycol. They are produced from primary polymer particles of about 0.2 - 0.6 micron.

Table No. 2 Related research on mucoadhesive polymers and delivery systems [45]-[49].

Bioadhesive Polymer(s) Studied	Investigation Objectives
HPC and CP	Preferred mucoadhesive strength on CP, HPC, and HPC-CP combination
HPC and CP	Measured Bioadhesive property using mouse peritoneal membrane
CP, HPC, PVP, <u>CMC</u>	Studied inter polymer complexation and its effects on bioadhesive strength
CP and HPMC	Formulation and evaluation of buccoadhesive controlled release delivery systems
HPC, HEC, PVP, and PVA	Tested mucosal adhesion on patches with two-ply laminates with an impermeable backing layer and hydrocolloid polymer layer
HPC and CP	Used HPC-CP powder mixture as peripheral base for strong adhesion and HPC-CP freeze dried mixture as core base
CP, PIP, and PIB	Used a two-roll milling method to prepare a new bioadhesive patch formulation
Xanthum gum and Locust bean gum	Hydrogel formation by combination of natural gums
Chitosan, HPC, CMC, Pectin, Xantham gum, and Polycarbophil	Evaluate mucoadhesive properties by routinely measuring the detachment force from pig intestinal mucosa
Hyaluronic acid benzyl esters, Polycarbophil, and HPMC	Evaluate mucoadhesive properties
Hydroxyethylcellulose	Design and synthesis of a bilayer patch (polytef-disk) for thyroid gland diagnosis
Polycarbophil	Design of a unidirectional buccal patch for oral mucosal delivery of peptide Drugs

Poly (acrylic acid) and Poly (methacrylic acid)	Synthesized and evaluated crosslinked polymers differing in charge densities and Hydrophobicity
Number of Polymers including HPC, HPMC, CP, CMC.	Measurement of bioadhesive potential and to derive meaningful information on the structural requirement for bioadhesion
Poly (acrylic acid-co-acrylamide)	Adhesion strength to the gastric mucus layer as a function of crosslinking agent, degree of swelling, and carboxyl group density
Poly (acrylic acid)	Effects of PAA molecular weight and crosslinking concentration on swelling and drug release characteristics
Poly (acrylic acid-co-methylmethacrylate)	Effects of polymer structural features on mucoadhesion
HEMA copolymerized with Polymeg® (polytetramethylene glycol)	Bioadhesive buccal hydrogel for controlled release delivery of buprenorphine
Poly (acrylic acid-co-butylacrylate)	Relationships between structure and adhesion for mucoadhesive polymers
CMC, Carbopol 974P, Carbopol EX-55, Pectin (low viscosity), Chitosan chloride,	Mucoadhesive gels for intraoral delivery
CMC, CP, Polyethylene oxide, Polymethylvinylether/Maleic anhydride (PME/MA), and Tragacanth	Buccal mucoadhesive device for controlled release anticandidal device - CMC tablets yielded the highest adhesive force
HPMC and Polycarbophil (PC)	Buccal mucoadhesive tablets with optimum blend ratio of 80:20 PC to HPMC yielding the highest force of adhesion
PVP, Poly (acrylic acid)	Transmucosal controlled delivery of isosorbide dinitrate
Poly (acrylic acid-co-poly ethyleneglycol) copolymer of acrylic acid and poly ethyleneglycol monomethylether monomethacrylate	To enhance the mucoadhesive properties of PAA for buccal mucoadhesive drug delivery
Poly acrylic acid and polyethylene Glycol	To enhance mucoadhesive properties of PAA by interpolymer complexation through template polymerization
Drum dried waxy maize starch (DDWM), Carbopol 974P, and sodium stearyl fumarate	Bioadhesive erodible buccal tablet for progesterone delivery

Abbreviations: CP = Carbopol 934P, HPC = Hydroxy propyl cellulose, PVP = Poly (vinyl pyrrolidone), CMC = Sodium carboxymethyl cellulose, HPMC = Hydroxy propyl methyl cellulose, HEC = Hydroxy ethyl cellulose, PVA = Poly (vinyl alcohol), PIB = Poly(isobutylene), PIP = Poly(isoprene).

diameter. Each primary particle exists as a network structure of polymer chains interconnected by cross links. Carbopol polymers along with pectin and nonionic polymers are all cross linked. They swell in water upto 1000 times their original volume to form a gel when exposed to a pH of 4.0 to 6.0. The glass transition temperature is about 105°C. Due to presence of carboxylate group and a pKa of 6.0 to 0.5, repulsion between the negative charges occurs leading to increased swelling and hence increased mucoadhesive strength of the polymer.

Today, a large number of companies are using Carbopol polymers because of the following merits.

- Good tableting formulation flowability.
- Long drug release profiles
- Can give drug releases profiles similar to carbopol 974P, with better handling characteristics.
- Are safe and effective for oral administration.
- Are bioadhesive and providing increased bioavailability.

- Are approved by many of the world pharmacopoeias.
- Protect protein and peptides from degradation and hence increase the bioavailability of proteins or peptide-based formulations.

Chitosan [50]

It is a cationic polymer (polysaccharide), it is produced by the deacetylation of chitin. Chitosan is gaining importance in the development of mucoadhesive drug delivery system because of its good biocompatibility, biodegradability, and nontoxic nature. It binds to the mucosa via ionic bonds between the amino group and salicylic acid residues. Chitosan being linear provides greater polymer chain flexibility. Onishi and Machida showed that chitosan and its metabolized derivatives are quickly eliminated by the kidney.

Newer second-generation polymers [1]

They have the following advantages.

- More site specific hence called cytoadhesives.

- Are least effected by mucus turnover rates.,
- Site specific drug delivery is possible.

Lectins [51]

Lectins are naturally occurring proteins that are useful in biological recognition involving cells and proteins. Lectins are a class of structurally diverse proteins and glycoprotein that bind reversibly to specific carbohydrate residues.

After binding to the cell the lectins may either remain on the cell surface or may be taken inside the cell via endocytosis., they hence allow a method for site specific and controlled drug delivery. The lectins have many advantages, but they also have the disadvantage of being immunogenic.

Thiolated polymers [52]

These are thiomers which are derived from hydrophilic polymers such as polyacrylates, chitosan or deacetylated gallan gum. The presence of the thiol group increases the residence time by promoting covalent bonds with the cystiene residues in mucus. The disulphide bonds may also alter the mechanism of drug release from the delivery system due to increased rigidity and cross linking.

e.x. chitosan

- -fluorescent probe method
- flow channel method
- mechanical spectroscopic method
- falling liquid film method
- colloidal gold staining method
- viscometer method
- thumb method
- adhesion number
- electrical conductance
- swelling properties
- in vitro drug release studies
- mucoretentability studies

In vivo methods [55]

- use of radioisotopes
- iminothiolane PAA
- homocystiene Paa
- cysteine
- Alginate cystiene

Polyox WSR [1]

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

- Water soluble hydrophilic nature
- High molecular weight
- Functional group for hydrogen bonding
- Biocompatible and non-toxic
- Can be formulated into tablets, films, gels, microcapsules, syrups.

Novel polymers [53]

- Tomato lectin showed that it has binding selectivity to the small intestine epithelium.
- Shajaei and Li have designed and characterized a co polymer of PAA and PEG monoethylether mono methacrylate (PAA-co-PEG) for exhibiting optimal buccal adhesion.
- Lele et al., investigated novel polymers of PAA complexed with PEGylated drug conjugate.
- A new class of hydrophilic pressure sensitive adhesives (PSA) have been developed by corium technologies. Corplex have been prepared by non-covalent hydrogen bonding crosslinking of a film forming hydrphilic polymer with a short chain plasticizer having reactive OH groups at chain ends.
- Langath N et al., investigated the benefit of thiolated polymers for the development of buccal drug delivery systems.
- Bogataj et al., Al prepared and studied Mucoadhesive microspheres for application in urinary bladder.
- Alur HH et al., studied rthe transmucosal sustained delivery of chlorphenazine maleate in rabbits using a novel natural mucoadhesive gum from hakea as an excipient in buccal tablets. The gum provided sustained releawse and sufficient mucoadhesion.

Methods of evaluation

Mucoadhesive polymers can be evaluated by testing their adhesion strength by both in vitro and in vivo tests.

In vitro tests / exvivo [54]

The importance is layed on the elucidation of the exact mechanisms of bioadhesion. These methods are,

- methods determining tensile strength.

- methods determining shear stress.
- adhesion weight method
- use of pharmacoscintigraphy
- use of electron paramagnetic resonance (EPR) oximetry.
- X ray studies
- Isolated loop technique

RECENT APPLICATIONS IN ORAL MUCOADHESIVE DRUG DELIVERY

Oral mucoadhesive drug delivery has widespread applications for many drugs which on oral administration result in poor bioavailability and are rapidly degraded by the oral mucoadhesive drug delivery provides advantages of high accessibility and low enzymatic activity. Earlier the hydrophilic polymers like SCMC, HPC and polycarbophil were used for the treatment of periodontal diseases, but now the trend is shifting towards the effective utilization of these systems to the delivery of peptides, proteins and polysaccharides [1]

The buccal cavity has additional advantages of high patient compliance. Orabase, a first generation mucoadhesive paste has been used as barrier system for mouth ulcers. Semisolids offer more ease in administration, but tablets have also been formulated. Tablets include matrix devices or multilayered systems containing a mucoadhesive agent. The tablet is kept under the upper lip to avoid clearance mechanism of the salivary gland. Buccostem, an adhesive antiemetic tablet containing prochlorperazine is usually administered in this manner [56].

Buccal mucoadhesive dosage forms may be classified into three types,

- A single layer device with multidirectional drug release.
- A dosage form with impermeable backing layer which is superimposed on top of a drug loaded bioadhesive layer, creating a double layered device and preventing loss from the top surface of the dosage form into the oral cavity.
- Unidirectional release device, the drug is released only from the side adjacent to the buccal mucosa.

CONCLUSION

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

Despite the huge amount of work been done on this drug delivery platform, the focus has been primarily on the formulation of gastroretentive dosage forms, hence, work must be done to exploit this drug delivery system for various other approaches like drug targeting and site-specific drug delivery systems.

REFERENCES

- [1] Andrews GP, Thomas P, Laverty TP, David S, Jones SD. Mucoadhesive polymeric platforms for controlled drug delivery. *Eur. J. Pharm. Biopharm.* 2009; 71: 505-518.
- [2] Chowdary KPR, Srinivas L. Mucoadhesive drug delivery systems: A review of current status. *Indian Drugs.* 2000; 37(9): 400-406.
- [3] Gandhi RE, Robinson JR. Bioadhesion in drug delivery. *Ind. J. Pharm. Sci.* 1988; 50: 145-152.
- [4] Yang X, Robinson JR. In: Okano T, ed. *Biorelated functional polymers and gels: controlled release and applications in biomedical engineering*, San Diego, Academic Press, 1998: 135.
- [5] Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissue. *J. Controlled Release.* 1985; 2: 257-275.

- [6] Mikos AG, Peppas NA. Measurement of the surface tension of mucin solutions. *Int J Pharm.* 1989; 3: 1-5.
- [7] Baszkin A, Proust JE, Monsengo P, Boissonnade MM. Wettability of polymers by mucin aqueous solutions. *Biorheology.* 1990; 27: 503-514.
- [8] Lehr CM, Bodde HE, Bowstra JA, Junginger HE. A surface energy analysis of mucoadhesion. II: Prediction of mucoadhesive performance by spreading coefficients. *Eur J Pharm Sci.* 1993; 1: 19-30.
- [9] Kaelble DH, Moacanin J. A surface energy analysis of bioadhesion. *Polymer.* 1977; 18: 475-482.
- [10] Mathiowitz E, Chickering DE III, Lehr CM. *Bioadhesive Drug Delivery Systems, Fundamentals, Novel Approaches, and Development.* Marcel Dekker, Inc. New York, 2010.
- [11] Ranga Rao KV, Buri P. Bioadhesion and factors affecting the bioadhesion of microparticles. In: M. Szycher, ed. *High Performance Biomaterials.* Lancaster, PA: Technomic Publishing Company, 1988: 259-268.
- [12] Reinhart CT, Peppas NA. Solute diffusion in swollen membranes. Part II. Influence of crosslinking on diffusive properties. *J Membr Sci.* 1984; 18: 227-239.
- [13] Bateup BO. Surface chemistry and adhesion. *Int J Adhes Adhesive.* 1989; 7: 233-239.
- [14] Wu S. Surface and interfacial tensions of polymer melts. II. Poly (methyl methacrylate), poly (n-butyl methacrylate), and polystyrene. *J Phys Chem.* 1970; 74: 632-638.
- [15] Good RJ. Spreading pressure and contact angle. *J Colloid Interface Sci.* 1975; 52: 308-313.
- [16] Derjaguin BV, Toporov YP, Muller VM, Aleinkova IN. On the relationship between the molecular component of the adhesion of elastic particles to a solid surface. *J Colloid Interface Sci.* 1966; 58: 528-533.
- [17] Kammer HW. Adhesion between polymers. *Acta Polym.* 1983; 34: 112.
- [18] Good RJ. Surface energy of solids and liquids. Thermodynamics, molecular forces, and structure. *J Colloid Interface Sci.* 1977; 59: 398-419.
- [19] Tabor D. surface forces and surface interactions. *J Colloid Interface Sci.* 1977; 58: 2-13.
- [20] Mikos AG, Peppas NA. Systems for controlled release of drugs. V. Bioadhesive systems. *STP Pharmacol.* 1986; 2: 705-716.
- [21] Ch'ng HS, Park H Kelly P, Robinson JR. Bioadhesive polymers as platform for oral controlled drug delivery. II: Synthesis and evaluation of some swelling water insoluble bioadhesive polymers. *J. Pharm. Sci.* 1985; 74: 399-405.
- [22] Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity. *J. Pharm. Sci.* 1992; 81: 1-10.
- [23] Wertz PW, Squier CA. Cellular and molecular basis of barrier function in oral epithelium. *Crit. Rev. Ther. Drug Carr. Sys.* 1991; 8: 237-269.
- [24] Squier CA, Cox P, Wertz PW. Lipid content and water permeability of skin and oral mucosa. *The J. Invest. Dermat.* 1991; 96: 123-126.
- [25] Galey WR, Lonsdale HK, Nacht S. The in vitro permeability of skin and buccal mucosa to selected drugs and tritiated water. *J. Invest. Dermat.* 1976; 67: 713-717.
- [26] Gandhi RB, Robinson JR. Oral cavity as a site for bioadhesive drug delivery. *Adv. Drug Del. Rev.* 1994; 13: 43-74.
- [27] Squier CA, Hall BK. The permeability of mammalian non-keratinized oral epithelia to horseradish peroxidase applied in vivo and in vitro. *Arch. Oral Biol.* 1984; 29: 45-50.
- [28] Hill MW, Squier CA. The permeability of oral palatal mucosa maintained in organ culture. *J. Anat.* 128 (1979) 169-178.
- [29] Siegel IA, Gordon HP. Surfactant-induced increase of permeability of rat oral mucosa to non-electrolytes in vivo. *Arch. Oral Biol.* 1985; 30: 43-47.
- [30] Tabak LA, Levine MJ, Mandel ID, Ellison SA. Role of salivary mucins in the protection of the oral cavity. *J. Oral Pathol.* 1982; 11: 1-17.
- [31] Rathbone M, Drummond B, Tucker I. Oral cavity as a site for systemic drug delivery. *Adv. Drug Del. Rev.* 1994; 13: 1-22.
- [32] Edgar WM. Saliva: its secretion, composition, and functions. *Br. Dent. J.* 1992; 172: 305-312.
- [33] Aungst BJ, Rogers NJ. Comparison of the effects of various transmucosal absorption promoters on buccal insulin delivery. *Int. J. Pharm.* 1989; 53: 227-235

- [34] Squier CA, Wertz PW. Structure and Function of the Oral Mucosa and Implications for Drug Delivery, in, M.J. Rathbone, (Eds) Oral Mucosal Drug Delivery, Marcel Dekker, Inc., New York, 1986: 1-26.
- [35] Shojaei AH, Li X. In vitro permeation of acyclovir through porcine buccal mucosa, Proceedings of International Symposium on Controlled Release of Bioactive Materials. 1996; 23: 507-508.
- [36] Oh CK, Ritschel WA. Biopharmaceutic aspects of buccal absorption of insulin, Meth. Find Exp. Clin. Pharmacol. 1990; 12: 205-212.
- [37] Zhang J, Niu S, Ebert C, Stanley TH. An in vivo dog model for studying recovery kinetics of the buccal mucosa permeation barrier after exposure to permeation enhancers: apparent evidence of effective enhancement without tissue damage. Int. J. Pharm. 1994; 101: 15-22.
- [38] Huang Y, Leobandung W, Foss A, Peppas NA. Molecular aspects of mucoadhesion and bioadhesion: tethered structures and site-specific surfaces. J. Control. Release. 2000; 65: 63-71.
- [39] Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery – a promising option for orally less efficient drugs. J. Control. Release. 2006; 114: 15-40.
- [40] Imam ME, Hornof M, Valenta, Reznicek G, Bernkop-Schnurch A. Evidence for the interpretation of mucoadhesive polymers into the mucus gel layer. STP Pharma. Sci. 2003; 13: 171-176
- [41] Ugwoke MI, Agu RU, Verbeke N, Kinget R. Nasal mucoadhesive drug delivery: background, applications, trends and future perspectives. Adv. Drug delivery. Rev. 2005; 57: 1640-1665.
- [42] Bernkop-Schnurch A, Freudl J. Comparative in vitro study of different chitosan-complexing agent conjugates. Pharmazie, 1999; 54: 369-371.
- [43] Mortazavi SA, Smart J. An investigation into the role of water movement and mucus gel dehydration in mucoadhesion. J. Control. Rel. 1993; 25: 197-203.
- [44] Peppas N, Huang Y. Nanoscale technology of mucoadhesive interactions. Adv. Drug Deliv. Rev. 2004; 56: 1675-1687.
- [45] Satoh K, Takayama K, Machida Y, Suzuki Y, Nakagaki M, Nagai T. Factors affecting the bioadhesive property of tablets consisting of hydroxypropyl cellulose and carboxyvinyl polymer. Chem. Pharm. Bull. 1989; 37: 1366-1368.
- [46] Guo JH. Investigating the surface properties and bioadhesion of buccal patches. J. Pharm. Pharmacol. 1994; 46: 647-650.
- [47] Veillard MM, Longer MA, Martens TW, Robinson JR. Preliminary studies of oral mucosal delivery of peptide drugs. J. Control. Release. 1987; 6: 123-131.
- [48] Leung SS, Robinson JR. Polymer structure features contributing to mucoadhesion: II. J. Control. Release. 1990; 12: 187-194.
- [49] Li X, Shojaei AH. Novel copolymers of acrylic acid and polyethylene glycol monomethylether monomethacrylate for buccoadhesion: In vitro assessment of buccoadhesion and analysis of surface free energy. Proceed. Int. Symp. Control. Rel. Bioact. Mater. 1996; 23: 165-166.
- [50] Hassan EE, Gallio JM. A simple rheological method for the in vitro assessment of mucin-polymer bioadhesive bond strength. Pharm, Res. 1990; 7: 491-495.
- [51] Clark MA, Hirst B, Jepson M. Lectin mediated mucosal delivery of drugs and microparticles. Adv. Drug Deliv. Rev. 2000; 43: 207-223.
- [52] Bernkop-Schnurch A. Thiomers: a new generation of mucoadhesive polymers. Adv. Drug deliv. Rev. 2005; 57: 1569-1582
- [53] Shojaei AM, LI X. Mechanism of Buccal Mucoadhesion of Novel Copolymers of Acrylic Acid and Polyethylene Glycol Monomethylether Monomethacrylate. J. Control. Release. 1997; 47: 151-61.
- [54] Gupta A, Garg S, Khar RK. Measurement of bioadhesive strengths of mucoadhesive buccal tablets: Design of in-vitro assembly. Indian Drugs. 1992; 30(4): 152-155.
- [55] Cafaggi S, Leardi R, Parodi B, Caviglioli G, Russo E, Bignardi G. Preparation and evaluation of a chitosan salt-ploxamer 407 based matrix for buccal drug delivery. J. Control. Release. 2005; 102: 159-169.
- [56] Altaf MA, Charyulu N. Ionic gelation-controlled drug delivery systems for gastric-mucoadhesive microcapsules of captopril. Indian J Pharm Sci, 2008; 70: 655-8.
- [57] Gandhi RB, Robinson JR. Bioadhesion in drug delivery. Ind. J. Pharm. Sci. 1988; 50(3): 145-152.

- [58] Lele BS, Hoffman AS. Mucoadhesive Drug Carriers Based on Complexes of poly (acrylic acid) and PEGylated Drugs having Hydrolysable PEG-anhydride-drug Linkages. *J. Control. Release.* 2000; 69: 237-248.
- [59] Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues. *J. Control. Rel.* 1985; 2: 257-275.
- [60] Satheesh Madhav NV, Uma Shankar MS. A smart biopolymeric material from *Arachis hypogea* seeds for formulation of amikacin loaded bioplates. Indian patent application filed. 2008; 95.
- [61] Semalty A, Bhojwani Mona, Bhatt GK, Gupta GD, Shrivastav AK. Design and Evaluation of Mucoadhesive Buccal Films of Diltiazem Hydrochloride. *Indian J. Pharm. Sci.* 2005; 67(5): 548-52.