

LABIAL MUCOSA AS A NOVEL TRANSMUCOSAL DRUG DELIVERY PLATFORM

N. V. SATHEESH MADHAV, ABHIJEET OJHA*

DIT-Faculty of Pharmacy, Mussoorie Diversion Road, Dehradun-248009, Uttarakhand, India. Email: abhi_pharm1@rediffmail.com, abhijeetmkp@rediffmail.com

Received: 17 April 2012, Revised and Accepted: 25 May 2012

ABSTRACT

Mucosal drug delivery technologies are expanding exponentially with applications in every imaginable route of administration because of its indisputable therapeutic benefits like site-specific targeting, less frequent dosing, and maintaining effective plasma concentration without increased consumption. The mucous membranes or mucosa is the lining of mostly endodermal origin, covered in epithelium, which is involved in absorption and secretion. Oral mucosa is composed of labial, buccal, palatal, gingival and lingual mucosae. Labial mucosa is a part of oral mucosa. Due to rich blood supply and good permeability, the labial mucosa is expected to be an attractive route of administration for local as well as systemic drug delivery.

Keywords: Novel drug delivery, Mucosa, Labial route, Mucoadhesion, Mucoadhesive polymers.

INTRODUCTION

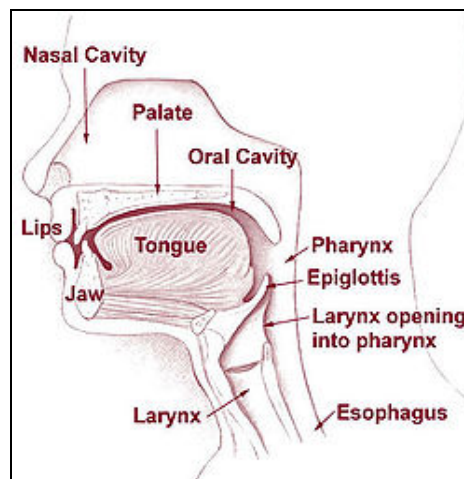
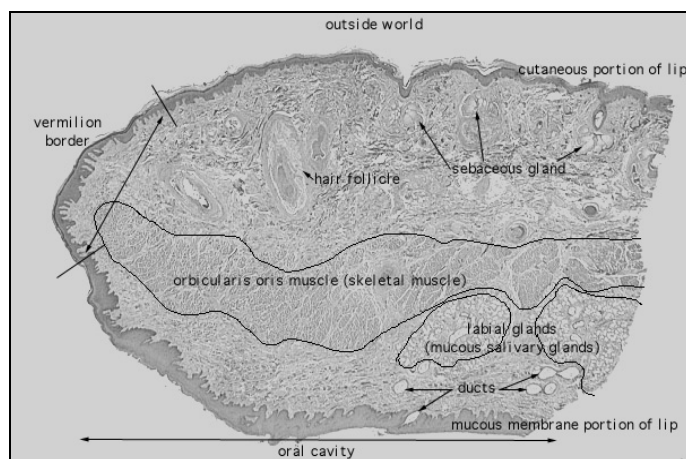
The oral route is the most preferred route of drug delivery to the patient as well as the physician. However, oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs. Consequently, absorptive mucosae are considered as potential sites for drug administration. Transmucosal routes of drug delivery offer distinct advantages over oral administration for systemic drug delivery. These advantages include less dosing frequency, shorter treatment period, improved patient compliance due to less frequent drug administration, reduction in fluctuation in steady-state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects, increased safety margin of high potency drugs and maximum utilization of drug enabling reduction in total amount of drug administered. In near future, drug delivery through labial mucosa can prove to be a promising route of transmucosal delivery.

LABIAL MUCOSA

Superficial anatomy

The oral cavity is formed by a bewildering array of tissues which are associated with the processes that are performed within mouth (Fig. 1). Oral mucosa is composed of labial, buccal, palatal, gingival and lingual mucosae. Labial mucosa is a part of oral mucosa. The lips surround the entrance to the oral cavity. Lips are composed of skin, muscle and mucosa but no bones and no infrastructure, making them unique pliable. The upper lip (Labium superioris) is superior in name only since it is actually somewhat smaller than its partner,

the lower lip (Labium inferioris). The most cosmetically apparent portion of the lip is the vermilion border. This colored border between the lips and the surrounding skin exists only in humans. Rounding out the lip glossary are the philtrum (the vertical groove on the upper lip that forms the so-called "Cupid's bow" and gives the lip its characteristic appearance) and the ergotrid (the stretch of skin between the upper lip and the nose)¹.

Fig. 1: Oral cavity¹Fig. 2: Histology of lip²

Histology

The layers of the upper and lower lips from superficial to deep include the epidermis, subcutaneous tissue, orbicularis oris muscle fibers, and mucosa². In cross-section, the superior and inferior labial arteries can be observed as they course between the orbicularis muscle fibers and the mucosa (Fig. 2). The vermilion is composed of nonkeratinized squamous epithelium that covers numerous capillaries, which give the vermilion its characteristic color. Numerous minor salivary glands can be observed on a histologic section of the lip³.

Blood Supply

Blood supply to both lips stems from the external carotid system. The facial artery ascends from the neck over the midbody of the mandible just anterior to the insertion of the masseter muscle. The facial artery branches into the submental artery that passes under the mandibular body in an anteromedial direction. The facial artery ascends in a plane deep to the platysma, risorius, and zygomaticus major and minor muscles and superficial to the buccinator and levator anguli oris. This artery branches into an inferior and a superior labial artery, which courses beneath the orbicularis oris and anastomose with the contralateral vessel. The superior labial artery usually branches from the facial artery 1.1 cm lateral (SD 0.43) and 0.9 cm (SD 0.20) superior to the oral commissure. The inferior labial artery branches from the facial artery 2.6 cm (SD 0.70) lateral and 1.5 cm (SD 0.45) inferior to the oral commissure^{4,5}.

Lymphatic Drainage

Lymphatic drainage from the upper lip is unilateral except for the midline. The lymphatics coalesce to form 5 primary trunks that mainly lead to the ipsilateral submandibular nodes, with some drainage also going to the periparotid lymph nodes. Occasionally, some drainage may be available to the ipsilateral submental lymph nodes. The lower lip lymphatics also coalesce to form 5 primary trunks that lead to bilateral submental nodes from the central lip and unilateral submandibular lymph nodes from the lateral lip. The submental, submandibular, and parotid lymph nodes are the first echelon nodes for the lips. Submental nodes secondarily drain to ipsilateral submandibular nodes, and both submandibular and parotid nodes secondarily drain to ipsilateral jugulodigastric lymph nodes⁴.

Sensory Innervation

The sensory innervation is from the maxillary and mandibular branches of the fifth cranial nerve. The infraorbital nerve, which is a terminal branch of the maxillary nerve, innervates the upper lip. This nerve exits the infraorbital foramen 4-7 mm below the inferior orbital rim on a vertical line that descends from the medial limbus of the iris. The nerve runs beneath the levator labii superioris and superficial to the levator anguli oris to supply the upper lip. The lower lip and chin receive sensory innervation from branches of the mandibular nerve. The inferior alveolar nerve, a branch of the mandibular nerve, forms the nerve to the mylohyoid just proximal to entering the lingula of the mandible⁶.

LABIAL MUCUS SECRETIONS

Labial mucosa consists of epithelium, lamina propria and muscularis mucosa. The epithelium is very thick and nonkeratinized. The lamina propria has long slender papillae but wide ridges and dense connective tissue with elastic fibers. The submucosa is attached to underlying muscle and contains minor salivary glands. The mucus is a translucent and viscid secretion, secreted by the vesicles within the epithelial cells, which forms a thin, continuous gel blanket adherent to the mucous epithelial surface. The mucus layer contains water - 95%, glycoproteins and lipids - 0.5 to 5%, mineral salts - 0.5 to 1%, free proteins - 0.5 to 1%.

The glycoproteins of mucus are known as mucins that are capable of forming slimy, viscoelastic gels. Mucin is a family of high molecular weight, heavily glycosylated proteins produced by many epithelial tissues⁷. 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. The molecular weight of mucin varies from 2×10^5 daltons to 14×10^6 daltons. Mucins are composed of two regions, the aminoacid and dicarbonyl terminal regions, rich in cysteine and a large central region composed of 10-80 residue sequences made up of serine or threonine. The drug 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. These surface adhesive properties of mucin are being utilized in the development of mucoadhesive drug delivery systems⁸.

FUNCTIONS OF MUCUS LAYER

The functions of mucus layer are as follows^{8,9}:

Protective

Due to its hydrophobicity, mucus protects the mucosa from the diffusion of hydrochloric acid from the lumen to the epithelial surface.

Barrier

The role of the mucus layer as a barrier in tissue absorption of drugs and other substrates influences the bioavailability of drug.

Adhesion

Mucus has strong cohesive properties and firmly binds to the epithelial cell surface as a continuous gel layer.

Lubrication

An important role of the mucus layer is to keep the mucosal membrane moist. Continuous secretion of mucus from the goblet cell is necessary to compensate for the removal of the mucus layer due to digestion, bacterial degradation and volatilization of mucin molecules

There are two major salivary mucin glycoproteins designated MG1 and MG2, which are generally mentioned as typical salivary mucins, as they were first identified in human saliva, and are also known as high and low molecular weight salivary mucins, respectively. They are distinguished by their size, carbohydrate content, sulfation and subunit structure. Simply stated, MG1 is bigger and MG2 is smaller. MG1 has relatively more carbohydrate and sulfation (Table 1). The glycosidic portion of MG1 and MG2 groups binds to specific components of microbial walls, thus mediating the entrapment and clearance of bacteria from the body tracts.

Table 1: Characteristic/Function of MG1 and MG2⁹

Characteristic/Function	MG1	MG2
Molecular weight (dalton)	$>10^6$	$2-2.5 \times 10^5$
Protein	14.9%	30.4%
Carbohydrate	78.1%	68.0%
Size of oligosaccharides	4-16 residues	2-7 residues
Number of oligosaccharides	46	170
Number of sialic acid units	14	67
Sulfate	7.0%	1.6%
Fatty acids	Yes	Negligible

LABIAL MUCOSAL PERMEATION ENHANCERS

Various compounds have been investigated for their use as penetration enhancers in order to increase the flux of drugs through the mucosa (Table 2).

Mechanisms by which penetration enhancers are thought to improve mucosal absorption are as follows^{10, 11}:

Changing mucus rheology

Mucus forms viscoelastic layer of varying thickness that affects drug absorption. Further, saliva covering the mucus layers also hinders

the absorption. The permeation enhancers act by reducing the viscosity of the mucus and saliva.

Table 2: Permeation Enhancers¹⁰

S. No	Permeation Enhancer
1	23-lauryl ether
2	Aprotinin
3	Azone
4	Methoxysalicylate
5	Cyclodextrin
6	Benzalkonium chloride
7	Menthol
8	Lysophosphatidylcholine
9	Dextran sulfate
10	Phosphatidylcholine
11	Polysorbate 80
12	Polyoxyethylene
13	Sodium EDTA
14	Dextran sulfate
15	Lauric acid
16	Sodium glycolate
17	Sodium taurodeoxycholate
18	Sodium taurocholate
19	Sulfoxides
20	Sodium salicylate
21	Sodium lauryl sulfate
22	Sodium glycodeoxycholate

Increasing the fluidity of lipid bilayer membrane

The most accepted mechanism of drug absorption through mucosa is intracellular route. The enhancers disturb the intracellular lipid packing by interaction with either lipid or protein components.

Acting on the components at tight junctions

Some enhancers act on desmosomes, a major component at the tight junctions thereby increasing drug absorption.

By overcoming the enzymatic barrier

Enhancers act by inhibiting the various peptidases and proteases present within mucosa, thereby overcoming the enzymatic barrier. In addition, changes in membrane fluidity also alter the enzymatic activity indirectly.

Increasing the thermodynamic activity of drugs

Some enhancers increase the solubility of drug and thus alter the partition coefficient. This leads to increased thermodynamic activity resulting better absorption.

LABIAL DRUG DELIVERY SYSTEM

The advantages of labial drug delivery system include ¹²:

- Ease of administration and easy removal from the site of application.
- Permits localized and systemic action of the drug to the oral cavity for longer period of time.
- A significant reduction in dose can be achieved, thereby reducing dose dependent side effects.
- Increased bioavailability can be obtained by this route.
- It can be administered even to unconscious patients.
- Offers excellent route for systemic delivery of drugs with high first pass metabolism, thereby offering greater bioavailability.
- Labial mucosa is highly perfused with blood vessels and offers greater permeability than skin.
- Therapeutic serum concentration of the drug can be achieved more significantly due to rich blood supply and non keratinized squamous epithelium.

- Drugs which are degraded in the acidic environment of stomach or destroyed by enzymatic or alkaline environment of the intestine can be administered by this route.
- It can reduce or minimize the side effects associated with systemic toxicity of the drug.
- It can offer improved patient acceptance and compliance.
- This route is more feasible for site specific as well as systemic drug delivery.

The limitations of labial drug delivery system are as follows ¹²:

- Drugs having unpleasant taste or odour, instability at labial pH, irritability to labial mucosa cannot be administered by this route.
- The drug swallowed with saliva is lost.
- Only those drugs with small dose requirements can be administered.
- Only those drugs which are absorbed by passive diffusion can be administered by this route.
- Eating and drinking may become restricted.
- Drugs which irritate the mucosa or having bitter and unpleasant taste or odour cannot be administered by this route.
- There is always a possibility that the patient may swallow the tablet.
- Drugs contained in the swallowed saliva leads to the loss of drug.
- Once placed at the absorption site, the tablet should not be disturbed.
- Drugs should have short biological half-life (2-8 hours) for delivery through labial route.
- Very little quantity of drug may arrive at the site of action.
- For translabial delivery, the maximum daily dose that can permeate the labial skin should be the order of a few µg to mg.
- Elevated drug level can be produced if new formulation is placed immediately at the old site and their will be possibility of enhanced labial skin toxicity.

LABIAL MUCOADHESION

Bioadhesive polymers have extensively been employed in labial drug delivery. The term bioadhesion can be defined as the state in which two materials, at least one biological in nature, are held together for an extended period of time by interfacial forces. The biological surface can be epithelial tissue or the mucus coat on the surface of a tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. The mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage. The first stage is characterized by the contact between the mucoadhesive and the mucous membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer. In the consolidation step, the mucoadhesive materials are activated by the presence of moisture (Fig. 3). Moisture plasticizes the system, allowing the mucoadhesive molecules to break and to link up by weak Van der Waal forces and hydrogen bonds^{13,14}.

There are five theories for labial mucoadhesion:

Wetting theory

The wetting theory is applied to liquid systems which present affinity to the surface in order to spread over it¹⁵. This affinity can be determined by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle, the greater is the affinity. The contact angle should be equal or close to zero to provide adequate spreadability. The spreadability coefficient,

S_{AB} , can be calculated from the difference between the surface energies γ_B and γ_A and the interfacial energy γ_{AB} , as indicated in the equation given below¹⁶:

$$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$$

Diffusion theory

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond. The adhesion force increases with the degree of penetration of the polymer chains. The depth of interpenetration required to produce an efficient bioadhesive bond lies in the range 0.2-0.5 μm . This interpenetration depth of polymer and mucin chains can be estimated by the following equation.

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

In above equation t is the contact time and D_b is the diffusion coefficient of the mucoadhesive material in the mucus. The adhesion strength for a polymer is reached when the depth of penetration is approximately equivalent to the polymer chain size. In order for diffusion to occur, it is important that the components involved have good mutual solubility, that is, both the bioadhesive and the mucus have similarity in chemical structures. The greater the structural similarity, the better is the mucoadhesive bond¹⁷.

Fracture theory

This theory is based on mechanical measurement of mucoadhesion. It analyzes the force required to separate two surfaces after adhesion is established. This force, S_m , is calculated in tests of resistance to rupture by the ratio of the maximal detachment force,

F_m , and the total surface area, A_0 , involved in the adhesive interaction¹⁸.

$$S_m = F_m / A_0$$

Electronic theory

This theory describes adhesion occurring by means of electron transfer between the mucus and the mucoadhesive system, arising through differences in their electronic structures. The electron transfer between the mucus and the mucoadhesive results in the formation of double layer of electrical charges at the mucus and mucoadhesive interface. The net result of such a process is the formation of attractive forces within this double layer¹⁹.

Adsorption theory

Adhesion is the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. Primary bonds due to chemisorptions result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency. Secondary bonds arise mainly due to Van der Waals forces, hydrophobic interactions and hydrogen bonding. Whilst these interactions require less energy to "break", they are the most prominent form of surface interaction in mucoadhesion processes as they have the advantage of being semi-permanent bonds. The theory states that there is initial wetting of the mucin, and then diffusion of the polymer occurs into mucin layer, thus causing the fracture in the layers to effect the adhesion or electronic transfer or simple adsorption phenomenon that finally leads to the perfect mucoadhesion²⁰.

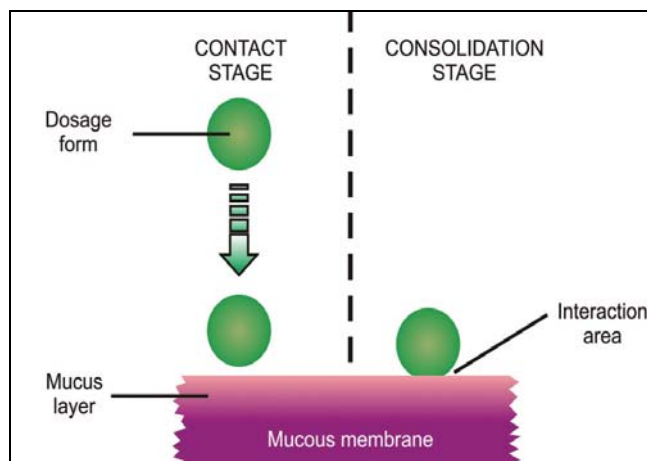


Fig. 3: Mechanism of mucoadhesion¹⁵

There are several factors that affect labial mucoadhesion namely^{18,21}:

Molecular weight

The mucoadhesive strength of a polymer increases with molecular weights above 100,000. Direct correlation between the mucoadhesive strength of polyoxyethylene polymers and their molecular weights lies in the range of 200,000-7,000,000.

Flexibility of polymer chain

Mucoadhesion starts with the diffusion of the polymer chains in the interfacial region. So the polymer chains should have a substantial degree of flexibility in order to achieve the desired entanglement with the mucus.

Cross-linking density

The diffusion of water into the polymer network occurs at a lower rate with the increasing density of cross-linking, which, in turn, causes an insufficient swelling of the polymer and a decreased rate of interpenetration between polymer and mucin.

Hydrogen bonding capacity

Hydrogen bonding is another important factor in mucoadhesion of a polymer. Desired polymers must have functional groups that are able to form hydrogen bonds. Polymers such as poly (vinyl alcohol), hydroxylated methacrylate, and poly (methacrylic acid), as well as all their copolymers, have good hydrogen bonding capacity.

Hydration

Hydration is required to induce mobility in the polymer chains in order to enhance the interpenetration process between polymer and mucin. Polymer swelling permits a mechanical entanglement by exposing the bioadhesive sites for hydrogen bonding and/or electrostatic interaction between the polymer and the mucus network.

Charge

In mucoadhesive polymers, nonionic polymers appear to undergo a smaller degree of adhesion compared to anionic polymers. Strong anionic charge on the polymer is one of the required characteristics

for mucoadhesion. Some cationic polymers are likely to demonstrate superior mucoadhesive properties, especially in a neutral or slightly alkaline medium. Additionally, some cationic high-molecular-weight polymers, such as chitosan, have shown to possess good adhesive properties.

Spatial conformation

Besides high molecular weight or chain length, spatial conformation of a polymer is also important. Polyethylene glycol with a molecular weight of 200,000 has similar adhesive strength like dextran (molecular weight 19,500,000). The reason is that the helical conformation of dextran masks many adhesively active groups, primarily responsible for adhesion.

pH

The pH at the mucoadhesive to substrate interface can influence the adhesion of mucoadhesives possessing ionizable groups. Many mucoadhesives used in drug delivery are polyanions possessing carboxylic acid functionalities. If the local pH is above the pK_a of the polymer, it will be largely ionized; if the pH is below the pK_a of the polymer, it will be largely unionized. The approximate pK_a for the poly (acrylic acid) family of polymers is between 4 and 5. The maximum adhesive strength of these polymers is observed around pH 4–5 and decreases gradually above a pH 6.

Initial contact time

Contact time between the bioadhesive and mucus layer determines the extent of swelling and interpenetration of the bioadhesive polymer chains. Moreover, bioadhesive strength increases as the initial contact time increases.

MUCOADHESIVE POLYMERS

An ideal polymer for a bioadhesive drug delivery system should have the following characteristics⁹:

- The polymer and its degradation products should be nontoxic and nonabsorbable.
- It should be nonirritant.
- It should form a strong noncovalent bond with the mucus or epithelial cell surface.
- It should adhere quickly to moist tissue and possess some site specificity.
- It should allow easy incorporation of the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during the shelf life of the dosage form.
- The cost of the polymer should not be high.

The mucoadhesive polymers have been classified on the following bases^{22, 23, 24}:

1. On the basis of source

Natural

Agarose, chitosan, gelatin, hyaluronic acid, gums (guar, xanthan, gellan, carragenan, pectin and sodium alginate).

Synthetic

Cellulose derivatives [CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methylhydroxyethylcellulose], Poly(acrylic acid)-based polymers [CP, polyacrylates, poly (methylvinylether-comethacrylic acid), poly (2-hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexylacrylate), poly (methacrylate), poly (alkylcyanoacrylate), poly (isohexylcyanoacrylate), poly (isobutylcyanoacrylate), copolymer of acrylic acid and PEG].

Others

Polyoxyethylene, PVA, PVP, thiolated polymers

2. On the basis of aqueous solubility

Water-soluble

CP, HEC, HPC (waterb38 8C), HPMC (cold water), PAA, sodium CMC, sodium alginate.

Water insoluble

Chitosan (soluble in dilute aqueous acids), EC, PC.

3. On the basis of charge

Cationic

Aminodextran, chitosan, (DEAE)-dextran, TMC.

Anionic

Chitosan-EDTA, CP, CMC, pectin, PAA, PC, sodium alginate, sodium CMC, xanthan gum.

Non-ionic

Hydroxyethyl starch, HPC, poly (ethylene oxide), PVA, PVP, scleroglucan.

4. On the basis of potential mucoadhesive forces

Covalent

Cyanoacrylate.

Hydrogen bond

Acrylates [hydroxylated methacrylate, poly (methacrylic acid)], CP, PC, PVA.

Electrostatic interaction

Chitosan

RECENT ADVANCES IN MUCOADHESIVE POLYMERS

The next generation of mucoadhesives functions with greater specificity because they are based on receptor-ligand-like interactions in which the molecules bind strongly and rapidly directly onto the mucosal cell surface rather than the mucus itself. Recently, it has been shown that polymers with thiol groups provide much higher adhesive properties than polymers generally considered to be mucoadhesive. The enhancement of mucoadhesion can be explained by the formation of covalent bonds between the thiolated polymer and the mucus layer which are stronger than non-covalent bonds. The thiolated polymers known as thiomers interact with cysteine rich sub domains of mucus glycoproteins via disulfide exchange reaction or via simple oxidation process²⁵.

A class of compounds that have unique mucoadhesive properties is called lectins. Lectins are proteins or glycoproteins and share the common ability to bind specifically and reversibly to carbohydrates. They exist in either soluble or cell-associated forms and possess carbohydrate-selective recognizing parts. Lectin based drug delivery systems have applicability in targeting epithelial cells, intestinal M cells and enterocytes. One lectin which has been studied to considerable extent *in vitro* binding and uptake is tomato lectin (TL), which has been shown to bind selectively to epithelium²⁶.

Shojaei and Li, 1997 have designed, synthesized and characterized a mucoadhesive copolymer of PAA and PEG monoethylether monomethacrylate (PAA-co-PEG) (PEGMM). By adding PEG to these polymers, many of the shortcomings of PAA for mucoadhesion were eliminated. Hydration studies, glass transition temperature, mucoadhesive force, surface energy analysis and effect of chain length and molecular weight on mucoadhesive force were studied. The resulting polymer has a lower glass transition temperature than PAA and exists as a rubbery polymer at room temperature. Copolymers of 12 and 16-mole% PEGMM showed higher mucoadhesion than PAA. The 16-mole% PEGMM had the most favourable thermodynamic profile and the highest mucoadhesive forces²⁷.

Lele and Hoffman, 2000 investigated novel polymers of PAA complexed with PEGylated drug conjugate. Only a carboxyl group containing drugs such as indomethacin could be loaded into

the devices made from these polymers. An increase in the molecular weight of PEG in these copolymers resulted in a decrease in the release of free indomethacin, indicating that drug release can be manipulated by choosing different molecular weights of PEG²⁸.

A copolymer of oligo (methyl methacrylate) and PAA has been synthesized for prolonged mucosal drug delivery of hydrophobic drug. These copolymers form micelles in an aqueous medium. A model drug, doxorubicin hydrochloride, when incorporated into these micelles, results in its release being prolonged at a slower rate. The results showed that there was considerable improvement in the overall behavior of adhesion and adhesive properties when tested on porcine intestinal mucosa at a pH level above five²⁹.

A novel biomaterial was isolated from the seed coat of *Lallimantia royalena* by the non-solvent addition method. The mucoadhesivity of the biomaterial was determined by the shear stress, Park and Robinson, and rotating cylinder methods, and the results were compared with those of the standard polymers sodium carboxymethyl cellulose and hydroxypropylmethyl cellulose. The research study revealed that the biomaterial from *L. royalena* seed coat exhibits promising inbuilt mucoadhesion and good mucoadhesivity. Hence the isolated biomaterial from the *L. royalena* seed coat can serve as a powerful natural mucoadhesant and may be used to develop mucoadhesive transmucosal drug delivery systems³⁰.

METHODS OF EVALUATION OF MUCOADHESIVE POLYMERS

Mucoadhesive polymers and drug delivery systems can be evaluated by testing their adhesion strength by both in vitro and in vivo tests^{31,32}

Shear stress method

The measurement of the shear stress gives a direct correlation to the adhesion strength. In a simple shear stress measurement based method smooth, polished plexi glass boxes were selected; one block was fixed with adhesive on a glass plate, which was fixed on leveled table. The level was adjusted with the spirit level. To the upper block, a thread was tied and the thread was passed down through a pulley, the length of the thread from the pulley to the pan was 12 cm. At the end of the thread a pan of weight 17 gm was attached into which the weights can be added³³.

Detachment force measurements

The method involves the measurement of the bioadhesive force between the mucosal tissue and the polymer/dosage form attached to a metal wire and suspended into the microtensiometer. The mucosal tissue (usually rat jejunum) is used which is placed in the tissue chamber, this chamber is raised so as to make contact between the tissue and the test material. After a certain period (7 minutes for microspheres) the stage is lowered and the force of

adhesion is measured. This apparatus measures the fracture strength (force per unit area required to break the adhesive bond) and deformation (distance required to move the stage before complete separation occurs)³⁴.

Work of adhesion

This method is used to assess the tendency of mucoadhesive materials to adhere to the oesophagus. In this method, the intestine was removed from the sheep and kept in tyrode solution at 4°C. Segments of 6-7 cm long were cut from the intestine, the lower end tied to the glass tube of diameter 15 mm. The 6 mm paracetamol plane tablets, paracetamol tablets layered on one side with mucoadhesive polymer and the paracetamol in matrix tablets (2:1) ratio were prepared. A fine hole drilled in the tablets to be tested with fine needle in the centre. A thread was passed through it and tied around the tablet. The other end of the thread was tied to the glass rod suspended from the stand. To the other end of the glass rod, a pan was tied in which a beaker was placed. After inserting the tablet into GI segment and lightly pressing the GI segment with tablet by a forcep, the assembly was kept undisturbed for 30 mins to 1 hour. Then water was added to burette slowly drop by drop into the beaker. The amount of water required to pull out the tablet from the intestinal segment represents the force required to pull the tablet against adhesion³⁵.

$$F=0.00981 w/2$$

w= amount of water.

In vitro drug release

These are performed in phosphate buffer pH 6.6, 150 ml at 37°C in a modified dissolution apparatus which consists of a 250 ml beaker and a glass rod attached with a grounded glass disk (2 cm diameter) as a donor tube. An adhesive cyanoacrylate polymer was attached to the glass disk. The donor tube was dipped into the medium and stirred at constant rpm. 5ml aliquots were withdrawn at preset times (0.08, 0.16, 1, 2, 3, 4, 5, 6 hours), filtered through a 0.2 micron filter and absorbance measured at 290 nm³⁶.

Mucoadhesion studies by Novel Madhav-Shankar Muco-retentive Study Apparatus

Novel Madhav-Shankar Muco-retentive Study Apparatus is a novel self designed apparatus by Madhav & Shankar 2008 (Fig. 4). It provides a unique platform for mounting the tissue for the muco-retentive study of the dosage device and it produced reproducible data. The study can be conducted by placing a bioplate of 2 mm diameter, 3 cm away from the narrow open end with the help of a loop. The ringer solution is then allowed to pass at a rate of 5 ml/min. The solution is continuously allowed to flow until dislodgement of bioplate occurs. The time of dislodgement of bioplate is recorded³⁷.

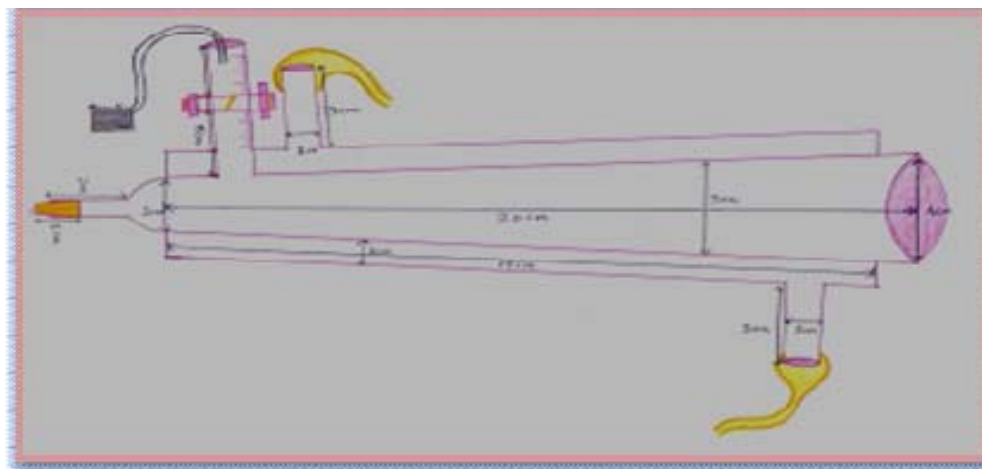


Fig. 4: Madhav-Shankar muco-retentive study apparatus³⁷

GI transit using radio-opaque technique

It involves the use of radio-opaque markers, *e.g.*, barium sulfate, encapsulated in bioadhesive DDS to determine the effects of bioadhesive polymers on GI transit time³⁸. Faeces collection (using an automated faeces collection machine) and x-ray inspection provide a non-invasive method of monitoring total GI residence time without affecting normal GI motility. Mucoadhesives labelled with Cr-⁵¹, Tc-^{99m}, In-^{113m}, or I-¹²³ have been used to study the transit of the DDS in the GI tract^{39,40}.

CONCLUSION

The labial mucosa offers several advantages over controlled drug delivery for extended periods of time. The mucosa is well supplied with both vascular and lymphatic drainage. It also avoids first-pass metabolism in the liver and pre-systemic elimination in the gastrointestinal tract. With the right dosage form design and formulation, the permeability and the local environment of the mucosa can be controlled and manipulated in order to accommodate drug permeation. Current use of mucoadhesive polymers to increase contact time for a wide variety of drugs can show dramatic improvement in labial drug delivery.

FUTURE PROSPECTS

Translabial platform may provide potential benefits for systemic delivery of drugs and this area of research will be more attractive to the pharmaceutical scientist and formulators to design unique viable dosage forms for systemic as well as local delivery of drugs. In near future labial dosage forms like mucoadhesive tablet, mucoadhesive patches and films, mucoadhesive semisolids like ointments and gels, mucoadhesive powders, liposomes, niosomes, nanosomes, emulgels, strips, layers etc loaded with APIs can be formulated for providing a promising significant drug delivery.

REFERENCES

- Sigher H. Oral Anatomy. 4th ed. Mosby: St. Louis; 1965.
- Wheater PR, Burkitt HG, Daniels VG. Functional Histology: A Text and Colour Atlas. Second 2nd ed. New York: Churchill Livingstone; 1987.
- Madhav Satheesh NV, Yadav AP. Lip: An impressive and idealistic platform for drug delivery. J Pharm Res. 2011; 4(4): 1060-1062.
- Pinar YA, Bilge O, Govsa F. Anatomic study of the blood supply of perioral region. Clinical Anatomy. 2005; 18(5): 330-9.
- Calhoun KH, Stiernberg CM. Surgery of the Lip. New York: Thieme Medical Publishers; 1992.
- Nelson DW, Gingrass RP. Anatomy of the mandibular branches of the facial nerve. Plast Reconstr Surg. 1979; 64(4): 479-82.
- Tangri P, Madhav Satheesh NV. Oral mucoadhesive drug delivery systems: A review. International Journal of Biopharmaceutics. 2011; 2(1): 36-46.
- 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.
- Gupta SK, Singhvi IJ, Shirsat M, Karwani G, Agarwal A. Buccal Adhesive Drug Delivery System: A Review. Asian Journal of Biochemical and Pharmaceutical Research. 2011; 1(2): 212-219.
- 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.
- Hill MW, Squier CA. The permeability of oral palatal mucosa maintained in organ culture. J Anat. 1979; 128: 169-178.
- Asane GS. Mucoadhesive gastro intestinal drug delivery system: An overview. 2007; 5(6): <http://www.pharmainfo.net>.
- Flavia C, Marcos LB, Raul C. Mucoadhesive drug delivery systems. Brazilian J Pharm Sci. 2010; 46 (1): 224-230.
- Lee JW, Park JH, Robinson JR. Bioadhesive-based dosage forms: The next generation. J Pharm Sci. 2000; 89(7): 850-866
- Peppas NA, Buri PA. Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissue. J Control Rel. 1985; 2: 257-275.
- Smart JD. The basics and underlying mechanisms of mucoadhesion. Adv Drug Del Rev. 2005; 57 (11): 1556-1568.
- Mikos AG, Peppas NA. Systems for controlled release of drugs. Pharmacol Rev. 1986; 2: 705-716.
- Sachan NK, Bhattacharya A. Basics and therapeutic potential of oral mucoadhesive microparticulate drug delivery systems. Int J Pharm Clin Res. 2009; 1(1): 10-14.
- Huang Y, Leobandung W, Foss A, Peppas NA. Molecular aspects of muco and bioadhesion: Tethers structures and site-specific surfaces. J Control Rel. 2000; 65 (1): 63-71.
- Good RJ. Surface energy of solids and liquids: Thermodynamics, molecular forces, and structure. J Colloid Interface Sci. 1977; 59: 398-419.
- Chang 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.
- Rajput GC, Majmudar FD, Patel JK, Patel KN, Thakor RS, Patel BP. Stomach Specific Mucoadhesive Tablets as Controlled Drug Delivery System – A Review Work. International Journal on Pharmaceutical and Biological Research. 2010; 1(1): 30-41.
- Andrews GP, Laverty TP, Jones DS. Mucoadhesive polymeric platforms for controlled drug delivery. Eur J Pharm Biopharm. 2009; 71: 505-518.
- Yadav VK, Gupta AB, Kumar R, Yadav JS, Kumar B. Mucoadhesive Polymers: Means of Improving the Mucoadhesive Properties of Drug Delivery System. J Chem Pharm Res. 2010; 2(5): 418-432.
- Schnurch BS, Schwarch V, Steininger S. Polymers with thiol groups: A new generation of mucoadhesive polymers. Pharm Res. 1999; 16 (6):876-881.
- Carreno GB, Woodley JF, Florence AT. Studies on the uptake of tomato lectin nanoparticles in everted gut sacs. Int J Pharm. 1999; 183: 7-11.
- Shojaei AM, Li X. Mechanisms of buccal mucoadhesion of novel copolymers of acrylic acid and polyethylene glycol monoethyl ether monomethacrylate. J Control Rel. 1997; 47: 151-161.
- 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 Rel. 2000; 69:237- 248.
- Inoue T, Chen G, Nakamae K, Hoffman AS. An AB copolymer of oligo (methyl methacrylate) and poly (acrylic acid) for micellar delivery of hydrophobic drugs. J Control Rel. 1998; 51 (2-3): 221-229.
- Madhav Satheesh NV, Uma Shankar MS. A novel smart mucoadhesive biomaterial from Lallimantia royalena seed coat. Science Asia. 2011; 37: 69-71.
- Shaikh R, Thakur R, Martin J, David W, Ryan F. Mucoadhesive drug delivery systems. J Pharm Bioallied Sci. 2011; 3(1): 89-100.
- Smart JD. An in vitro assessment of some mucosa-adhesive dosage forms. Int J Pharm. 1991; 73: 69-74.
- Grabovac VD, Guggi A, Bernkop S. Comparison of the mucoadhesive properties of various polymers. Adv Drug Deliv Rev. 2005; 57: 1713-1723.
- Vasir JK, Tambwekar K, Garg S. Bioadhesive microspheres as a controlled drug delivery system. International Journal of Pharmaceutics. 2003; 255: 13-32.
- Seham S, Hady A, Nahed D, Gehanne AS, Ragia A. Development of in situ gelling and mucoadhesive mebeverine hydrochloride solution for rectal administration. Saudi Pharmaceutical Journal. 2003; 11(4): 159-171.
- Batchelor HK, Banning D, Dettmar PW, Hampson FC, Jolliffe IG, Craig DQ. An in vitro mucosal model for prediction of the bioadhesion of alginate solutions to the oesophagus. Int J Pharm. 2002; 238: 123-132.

37. Madhav Satheesh N.V., Uma Shankar M.S. 2008. A smart biopolymeric material from *Arachis hypogea* seeds for formulation of amikacin loaded bioplates. Indian patent application filed. 95.
38. Roy SK, Prabhakar B. Bioadhesive Polymeric Platforms for Transmucosal Drug Delivery Systems – A Review. *Tropical J Pharm Res.* 2010; 9(1): 91-104.
39. Patil SB, Murthy RS, Mahajan HS, Wagh RD, Gattani SG. Mucoadhesive polymers: Means of improving drug delivery. *Pharma Times.* 2006; 38 (4): 256-264.
40. Thornton DJ, Khan N, Mehrotra R, Howard M, Veerman E, Packer NH. Salivary mucin MG1 is comprised almost entirely of different glycosylated forms of the MUC5B gene product. *Glycobiology.* 1999; 9: 293-302.