LABIAL MUCOSA AS A NOVEL TRANSMUCOSAL DRUG DELIVERY PLATFORM

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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).

![Fig. 1: Oral cavity](image1)

![Fig. 2: Histology of lip](image2)
Histology
The layers of the upper and lower lips from superficial to deep include the epithelium, subepithelial tissue, orbicularis oris muscle fibers, and mucosa\(^1\). 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 lip\(^5\).

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 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\(^6\).

Lymphatic Drainage
Lymphatic drainage from the upper lip is unilaterial 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 ipsilumeral 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 nodes\(^6\).

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 mandible\(^6\).

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 viscous 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 tissues\(^7\). 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 x 10\(^6\) daltons to 14 x 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 systems\(^8\).

FUNCTIONS OF MUCUS LAYER
The functions of mucus layer are as follows\(^9\):

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 MG2\(^6\)

<table>
<thead>
<tr>
<th>Characteristic/Function</th>
<th>MG1</th>
<th>MG2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight (dalton)</td>
<td>&gt;10(^6)</td>
<td>2-2.5 x 10(^6)</td>
</tr>
<tr>
<td>Protein</td>
<td>14.9%</td>
<td>30.4%</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>78.1%</td>
<td>68.0%</td>
</tr>
<tr>
<td>Size of oligosaccharides</td>
<td>4-16 residues</td>
<td>2-7 residues</td>
</tr>
<tr>
<td>Number of oligosaccharides</td>
<td>46</td>
<td>170</td>
</tr>
<tr>
<td>Number of sialic acid units</td>
<td>14</td>
<td>67</td>
</tr>
<tr>
<td>Sulfate</td>
<td>7.0%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>Yes</td>
<td>Negligible</td>
</tr>
</tbody>
</table>

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 advantages of labial drug delivery system include:

1. Ease of administration and easy removal from the site of application.
2. Permits localized and systemic action of the drug to the oral cavity for longer period of time.
3. A significant reduction in dose can be achieved, thereby reducing dose dependent side effects.
4. Increased bioavailability can be obtained by this route.
5. It can be administered even to unconscious patients.
6. Offers excellent route for systemic delivery of drugs with high first pass metabolism, thereby offering greater bioavailability.
7. Labial mucosa is highly perfused with blood vessels and offers greater permeability than skin.
8. Therapeutic serum concentration of the drug can be achieved more significantly due to rich blood supply and non keratinized squamous epithelium.
9. 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.
10. It can reduce or minimize the side effects associated with systemic toxicity of the drug.
11. It can offer improved patient acceptance and compliance.
12. This route is more feasible for site specific as well as systemic drug delivery.

The limitations of labial drug delivery system are as follows:

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

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 it. 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,
Flexibility of molecular weights lies in the range of 200,000-7,000,000. The mucoadhesive strength of polyoxyethylene polymers and their weights above 100,000. Direct correlation between the molecular weight and the mucoadhesive 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.

\[ I = \left( \frac{tD_B}{\sqrt{A_B - \gamma_{AB}}} \right)^{16} \]

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 in 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 bond\(^{15}\).

**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 interaction\(^{15}\).

\[ S_m = \frac{F_m}{A_0} \]

**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 layer\(^{19}\).

**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 mucoadhesion\(^{20}\).

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**Fig. 3: Mechanism of mucoadhesion**\(^{15}\)

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 mucin.

**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 mucin 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 polyamions possessing carboxylic acid functionalities. If the local pH is above the pKa of the polymer, it will be largely ionized; if the pH is below the pKa of the polymer, it will be largely unionized. The approximate pKa 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.

MUOADHESIVE POLYMERS

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

- 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:

1. On the basis of source

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

   Synthetic
   Cellulose derivatives [CMC, thiolated CMC, sodium CMC, HEC, HPC, HPMC, MC, methylhydroxylethylcellulose], Poly (acrylic acid)-based polymers [CP, poly(acrylates, poly (methylmethacrylate-co-hydroxymethyl methacrylate), poly (2-hydroxyethyl methacrylate), poly(acrylic acid-co-ethylhexyl acrylate), poly (methacrylate), poly (alkylcyanoacrylate), poly (isoxyethylxynoacrylate), 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 (water b38 °C), 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
   Qyanoacrylate.

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

   Electrostatic interaction
   Chitosan

RECENT ADVANCES IN MUOADHESIVE 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 noncovalent bonds. The thiolated polymers known as thiomers interact with cysteine rich sub domains of mucus glycoproteins via disulfide exchange reaction or via simple oxidation process.

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 epithelium.

Shojaii 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 forces.

Lele and Hoffman, 2000 investigated novel polymers of PAcomplexed 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 PEG.

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 five.

A novel biomaterial was isolated from the seed coat of Lallimanta 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 mucoretentability. 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 systems.

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.

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 added.

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).

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 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 adhesion.

\[ F = 0.00981 \times \frac{w}{2} \]

where \( w \) is 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 nm.

Mucoadhesion studies by Novel Madhav-Shankar Mucoretentive Study Apparatus

Novel Madhav-Shankar Mucoretentive 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 mucoretentive 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 recorded.

Fig. 4: Madhav-Shankar mucoretentive study apparatus
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 time. Faces collection (using an automated faces 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.

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


