Mucoadhesive Drug Delivery Systems: An Overview

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ABSTRACT

Today, a pharmaceutical scientist is well versed with the fact that the overall action of a drug molecule is not merely dependent on its inherent therapeutic activity, rather on the efficiency of its delivery at the site of action. Many drug delivery systems (DDS) are aimed to sustain drug blood concentration and controlling the rate of drug delivery to the target tissue, but mucoadhesion is one of the most prominent and latest systems in the design of gastro retentive drug delivery systems. It prolongs the residence time of the dosage form at the site of application or absorption and facilitates an intimate contact of the dosage form with the underline absorption surface and thus contributes to improved and/or better therapeutic performance of the drug. In recent years many such mucoadhesive drug delivery systems have been developed for oral, buccal, nasal, gastrointestinal, rectal and vaginal routes for both systemic and local effects.

Key words: Therapeutic activity, delivery, target tissue, mucoadhesion, contact.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. An ideal DDS should aid in the optimization of drug therapy by delivering an appropriate amount to the intended site and at a desired rate. By and large, a DDS may be employed for spatial placement (i.e., targeting a drug to a specific organ or tissue) or temporal delivery (i.e., controlling the rate of drug delivery to the target tissue).[1]

An immediate release dosage form is administered using a fixed dosing interval which causes several potential problems as like saw tooth kinetics characterized by large peaks and troughs in the drug concentration-time curve (Fig. 1), frequent dosing for drugs with short biologic half-life, and above all the patient noncompliance. Controlled release (CR) DDS attempt to sustain drug blood concentration at relatively constant and effective levels in the body by spatial placement or temporal delivery. The idea of mucoadhesion stems from the need to localize drugs at a specific region of body (e.g stomach) because many drugs show poor bioavailability (BA) in the presence of intestinal metabolic enzymes like cytochrome P450 (CYP3A), abundantly present in the intestinal epithelium.[2]

Another problem associated with the performance of CR systems is that some drugs are absorbed in a particular portion of the GIT only or are absorbed to a different extent in various segments of the GIT. Such drugs show ‘absorption window’, which signifies the region of GIT from where absorption occurs primarily. Drugs having site-specific absorption are difficult to design as oral CRDDS because only the drug released in the region preceding and in close vicinity to the absorption window is available for absorption. After crossing the absorption window, the released drug goes waste with negligible or no absorption (Fig. 2a). This phenomenon drastically decreases the time available for drug absorption after its release and jeopardize the success of the delivery system. The mucoadhesive drug delivery system can improve the controlled delivery of the drugs which exhibit an absorption window by continuously releasing the drug for a prolonged period before it reaches its absorption site, thus ensuring its optimal bioavailability. (Fig. 2b).[3]

ABIODHESION[4] is defined as the attachment of a synthetic or natural macromolecule to biological surface. When the biological surface is the mucosal tissue it is called ‘mucoadhesive.’

Composition of mucus layer[5];

Mucus is translucent and viscid secretion which forms a thin, continuous gel blanket adherent to the mucosal epithelial surface.

It has the following general composition.

<table>
<thead>
<tr>
<th>Component</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Water</td>
<td>95%</td>
</tr>
<tr>
<td>Glycoproteins and lipids</td>
<td>0.5-5%</td>
</tr>
<tr>
<td>Mineral salts</td>
<td>1%</td>
</tr>
<tr>
<td>Free proteins</td>
<td>0.5-1%</td>
</tr>
</tbody>
</table>

Mucus glycoproteins are high molecular proteins possessing attached oligosaccharide units. They are:

- L-fucose
- D-galactose
- N-acetyl-D-glucosamine
- N-acetyl-D-galactosamine
- Sialic acid

Mucoadhesion stages[6];

I. An intimate contact between a bioadhesive and a membrane
II. Penetration of the bioadhesive into the crevice of the tissue surface
III. Mechanical interlocking between mucin and polymer.

Potential sites for mucosal drug delivery[7];

- Buccal
- Sublingual
- Oral transmucosal
- Nasal
- Gastrointestinal
- Rectal
- Vaginal

From the fig. 3, there are 6 potential sites of mucosal delivery:
1. Ocular
2. Nasal
3. Gastrointestinal
4. Oral transmucosal
5. Rectal
6. Vaginal
Mechanisms of Mucoadhesion:

1. Hydration mediated adhesion: Certain hydrophilic polymers have the tendency to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties.
2. Bonding mediated adhesion:

For adhesion to occur, molecules must bond across the interface. These bonds can arise in the following way.

(a) Ionic bonds
(b) Covalent bonds
(c) Hydrogen bonds
(d) Van-der-waals bonds
(e) Hydrophobic bonds

Theories of bioadhesion:

a). Electronic theory
Because of different electronic properties of the mucoadhesive polymer and the mucus glycoprotein, electron transfer between these two surfaces occurs.

b). Absorption theory
Primary and secondary chemical bonds of the covalent and non-covalent types are formed upon initial contact between the mucus and the mucoadhesive polymer.

c). Wetting theory
It describes the ability of a bioadhesive polymer to spread on biological surfaces.

d). Diffusion theory
Diffusion of the bioadhesive polymer chain into the mucus network creates an entangled network between the two polymers.

e). Fracture theory
It relates the force required for the detachment of polymers from the mucus to the strength of their adhesive bond.

Factors affecting mucoadhesion:

A). Polymer related factors
1. Molecular weight of polymer
2. Concentration of active polymer
4. Spatial conformation
5. Hydration (swelling)
6. Charge

B). Environment related factors
1. pH:
2. Applied strength
3. Contact time:

Classification of Mucoadhesive polymers: They are classified as shown in Table 1.

Evaluation of mucoadhesive dosage forms:

1. Bioadhesion test: By tensile strength, shear strength, Fluorescent probe method, Atomic force microscopy (AFM), falling liquid film method, Adhesion number
2. Permeability study: Using different diffusion cells
2. Release rate study: Using USP dissolution test

OCULAR DRUG DELIVERY

A) Liquid dosage forms:
2. Particulate systems: Liposomes, Microspheres and nanospheres

Polymers used are Acrylates, Poly (epsilon-caprolacton), Poly (D,L-lactic acid) and poly(D,L-lactide-co-glycolide).

B) Semi-solid dosage forms:
1. Hydrogels
Types of hydrogel are:
- Preformed gels: - cellulose, PVA, Hyaluronic acid, Carbomer
- Insitu forming gels: - gellan gum, Poloxamer (Pluronic F-127)
2. Pseudolatex: CAP- cellulose acetate phthalate.
3. Ionically induced gelation: Gellan gum is an anionic exocellular polysaccharide.

C) Solid dosage forms:
1. Inserts:
- a) Soluble inserts: Polymers such as Collagen, PVA, cellulose based polymers.
  - Commercial product: - Lacristat
  - Commercial product: - Bio-cor, medilen
- b) Insoluble inserts: Polymers used are Hyaluronan, Chitosan, Polysaccharides.
  - Commercial product: - Ocusert
- c) Bioerodible inserts: Polymers used are Cellulose derivatives, Acrylates, Poly (ethylene oxide) band Thiomers.

Fig. 1: Plasma level profiles showing conventional and controlled release dosing.

Fig. 2: (a) Conventional dosage forms (b) Mucoadhesive drug delivery system
2. NASAL MUCOADHESIVE DRUG DELIVERY

A) Small organic molecules [24]:
- Gentamycin using HPMC
- Vancomycin and Tobramycin using chitosan.

B) Macromolecules:
- Vaccines and DNA Eg, PEG-coated polylactic nanospheres, chitosan-coated polylactic-glycolic acid nanospheres and chitosan nanospheres [25].
- Proteins Eg, cyanocobalamin is incorporated into microcrystalline cellulose, dextran microspheres [26] and crospovidone.

Also Carbopol gels and chitosan microparticles can be used for protein delivery.

Insulin’s nasal absorption was better with chitosan powder than chitosan nanoparticles and chitosan solution formulations.

C) New generation polymers [27-30]:
- Bioadhesive graft copolymers of polymethacrylic acid and polyethylene glycol as a powder delivery for Budesonide.
- Chitosan-4-thio-butyl-amidine chitosan thioglycolic acid and cysteamine conjugates of carboxymethylcellulose and polycarbophil are some of these new generation polymers that are pH sensitive.
- Delivery of plasmid DNA using the thermoresponsive polymer, poloxamer in combination with bioadhesive polymers polycarbophil or polyethylene oxide.

3. GASTRO RETENTIVE MUCOADHESIVE DRUG DELIVERY SYSTEM

Criteria [31-33]:

- Drugs those are primarily absorbed in the stomach;
- Drugs those are poorly soluble at an alkaline pH;
- Drugs with a narrow window of absorption;
- Drugs absorbed rapidly from the GI tract; and
- Drugs those degrade in the colon.

A). Mucoadhesive dosage forms [34-37]:

- Mucoadhesive microspheres and nanoparticles (amoxicillin),

- Mucoadhesive granules (furosemide),
- Mucoadhesive discs (celecoxib),
- Mucoadhesive tablets (atenolol, metformin, nifedipine, felodipine, glipizide, ciprofloxacin, sotolol, acyclovir, gabapentin, ofloxacin, erythropoietin, rosiglitazone, itraconazole, diltiazem, indomethacin.

B). Mucoadhesive Polymers [38-41]:
- Sodium CMC, HPMC, polyacrylate polymers, Carbopol®, Spheromer® III, sodium alginate, guar gum, polyethylene oxide.

4. ORAL TRANS-MUCOSAL DRUG DELIVERY

It is subdivided into [42, 43]:
I. Sublingual drug delivery: Via the mucosa of the ventral surface of the tongue and floor of the mouth under the tongue;
II. Buccal drug delivery: Via the buccal mucosa – the epithelial lining of the cheek, the gums and also the upper and lower lips.

Transport route and mechanisms [44-46]:
- Paracellular route: Between adjacent epithelial cells
- Transcellular route: Across the epithelial cell

Physiological factors affecting oral transmucosal bioavailability are [47]:

Inherent permeability of epithelium, thickness of the epithelium, blood supply.

Formulation design [48-50]:

1. Bioadhesive agents:
2. Penetration enhancers: 3-lauryl ether, Aprotinin, Azone, Benzalkonium chloride, Cetylpyridinium chloride, Cetyltrimethylamonium bromide, Cyclodextrin, Cod – liver oil extract, Dextran sulfate, Lauric acid, Lauric acid, Propylene glycol, SodiumEDTA, Sodium glycocholate, Sodium glycodeoxycholate
3. Enzyme Inhibitors: aprotinin, bestatin, puromycin and some bile salts.
4. Solubility Modifiers: cyclodextrin

Formulations [51-52]:

A). Buccal delivery:
1. Buccal Tablets:
2. Buccal patch:
3. Buccal film:
4. Buccal gel and ointment:

TABLE 1: CLASSIFICATION OF MUCOADHESIVE POLYMERS:

<table>
<thead>
<tr>
<th>Source</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semi-natural/natural</td>
<td>Agarose, chitosan, gelatin, Hyaluronic acid, Various gums (guar, hakea, xanthan, gellan, carragenan, pectin, and sodium alginate), starch, sulfated polysaccharides.</td>
</tr>
<tr>
<td>Synthetic Cellulose derivatives</td>
<td>Carboxy methyl cellulose(CMC), sodium CMC, Hydroxy ethyl cellulose (HEC), Hydroxy propyl cellulose (HPC), Hydroxy propylmethyl cellulose (HPMC), Methyl cellulose (MC), methylhydroxyethylcellulose</td>
</tr>
<tr>
<td>Synthetic Poly(acrylic acid) based polymers</td>
<td>Carbobol, Polycarbophil, polyacrylates, poly(methylvinylether-co-methacrylic acid), poly(2-hydroxyethyl methacrylate), poly(acrylic acid-co ethylhexylacylate), poly(methacrylate), poly(alkylcyanoacrylate), poly(isohexylcyanoacrylate), poly(isobutylcyanoacrylate), copolymer of acrylic acid and Poly ethylene glycol</td>
</tr>
<tr>
<td>Others</td>
<td>Poly(N-2-hydroxypropyl methacrylamide) (PHPAM), polyoxyethylene, Poly vinyl alcohol, Polyvinyl pyrrolidone, thiolated polymers, Poloxamers</td>
</tr>
</tbody>
</table>
New and emerging technologies (33, 34);

1. Sublingual delivery.
2. Buccal delivery.
   a) Innovative drug delivery systems, such as buccal spray and phospholipid vesicles have been recently proposed to deliver peptides via the buccal route.
   b) A novel liquid aerosol formulation - Oralin, Generex Biotechnology
3. Ocular delivery
   a) Phospholipid vesicles, Transfersomes, have been recently devised for the delivery of insulin in the buccal cavity.
   b) Antiviral liposomal preparation
   a) Antiviral vaginal gel
4. Antiviral vaginal delivery
   a) GnRH analogs
5. Therapeutic peptide delivery
   a) Peptide delivery
   b) Biodegradable/Starch microsphere
   c) Hyaluronan ester microsphere
6. Microparticulate system.
   a) Bioadhesive gel - Here biodhesive polymers used are Pluronic F-127, sodium alginate, poloxamer.
   b) A novel liquid aerosol formulation - Oralin, Generex Biotechnology
   c) Phospholipid deformable vesicles, Transfersomes, have been recently proposed to deliver peptides via the buccal route.
   d) Lectins have been studied as specific bioadhesives for drug delivery in the oral cavity.
   e) Guacumin-like insulinotropic peptide (GLP-1) – The Thera Tech delivery system – bilayers tablet.
   f) Lectins have been studied as specific bioadhesives for drug delivery in the oral cavity.

5. RECTAL MUCOSAL DRUG DELIVERY

Structure of vaginal mucosa: The layers of the colorectal wall, proceeding inward from the exterior, are Perirectal adipose(fatty) tissue supported by pelvic fascia, Muscular propria, Submucosa, Mucosa. The rectum is a reservoir 8-13 cm in length that ends with the voluntary muscles of the sphincter. Rectal absorption involves release of drug in the rectum, diffusion to the rectal mucosa, absorption by tissues and transport into general circulation.

Factors affecting rectal absorption:
- Suppositories include Mucoadhesive suppositories, Mucoadhesive liquid suppositories, and thermo reversible suppositories. Here biodhesive polymers used are sodium alginate, poloxamer.
- E.g. Propanolol, Insulin
- Bioadhesive gel - Here biodhesive polymers used are Pluronic F-127.
- E.g. Insulin
- Hydrogel - Here biodhesive polymers used are Carbophil, Sodium alginate.
- E.g. Propanolol

6. VAGINAL MUCOSAL DRUG DELIVERY

Structure of vaginal mucosa: It consists of the epithelium layer, lamina propria, Tunica propria, Muscularis mucosa, tunica adventitia

Factors affecting vaginal drug delivery:
- Physiological factors:
  a) Cyclic changes in vaginal epithelium, Vaginal fluid, vaginal pH, Enzyme activity
  b) Formulation factors: Drug release, Contact time, Concentration

Current technologies in vaginal drug delivery:

1. Vaginal delivery of estrogen and progestones.
2. Vaginal delivery of prostaglandins
3. Therapeutic peptide delivery
   a) GnRH analogs
   b) Insulin
4. Antiviral vaginal delivery
   a) Antiviral vaginal gel
   b) Antiviral liposomal preparation
   c) Antiviral vaginal devices
5. Vaginal mucusaco vaccine.
6. Microparticulate system.
   a) Biodegradable starch microsphere
   b) Hyaluronan ester microsphere

CONCLUSION

The focus of pharmaceutical research is being steadily shifted from the development of new chemical entities to the development of novel drug delivery system (NDDS) of existing drug molecule to maximize their effective in terms of therapeutic action and patent protection. In the recent years the interest is growing to develop a drug delivery system with the use of a mucoadhesive polymer that will attach to related tissue or to the surface coating of the tissue for the targeting various absorptive mucosa such as ocular, nasal, buccal, vaginal etc. Many drug delivery and pharmaceutical companies are exploiting this technology to reexamine active ingredients that were abandoned from formulation programs because of their poor stability in intestine, etc. Therefore a primary objective of using mucoadhesive systems would be achieved by obtaining a substantial increase in residence time of the drug for local drug effect and to permit once daily dosing. There is no doubt that mucoadhesion has moved into a new area with these new specific targeting compounds with researchers and drug companies looking further into potential involvement of more smaller complex molecules, proteins and peptides, and DNA for future technological advancement in the ever-evolving drug delivery arena. The mucoadhesive system will continue to appeal to both pharmaceutical researchers and the pharmaceutical industry.

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