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MUCOSAL DRUG DELIVERY SYSTEM

*Madan Jyotsana, Banode Sagar, Dangi Mahesh

Sinhgad College of Pharmacy, Pune, Maharashtra, India

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ABSTRACT

The process of mucoadhesion involving a polymeric drug delivery system is a complex one that includes processes such as wetting, adsorption and interpenetration of polymer chains. The success and degree of mucoadhesion bonding is influenced by various polymer-based properties such as the degree of cross-linking, chain length and the presence of various functional groupings. The attractiveness of mucosal-targeted controlled drug delivery of active pharmaceutical ingredients, has led formulation scientists to evaluate numerous polymeric systems for such tasks. Formulation scientists have at their disposal a range of in vitro and in vivo mucoadhesion testing setups in order to select candidate adhesive drug delivery system. As such, mucoadhesive systems have found wide use throughout many mucosal covered organelles for active ingredients delivery for local or systemic effect. Evolution of such mucoadhesive formulations has transgressed from first-generation charged hydrophilic polymer networks to more specific second-generation systems based on lectin, thiol and various other adhesive functional groups.

KEYWORDS: Mucoadhesive drugs, mucoadhesive polymers, mucoadhesive routes, Evaluation

*** For Correspondence**
Mrs. Jyotsana Madan.
Asst. Prof: – Dept. of Pharmaceutics.
S. No. 44/1, Vadgaon (Bk), Off. Sinhgad Road,
Pune – 411041, MAHARASHTRA.
Email: jrmadan@hotmail.com
Phone. No.: 9420148817
Telefax: - 020-2435472

INTRODUCTION

The concept of mucoadhesion was introduced in the field of controlled release drug delivery systems in the early 1980s[1,2]. Thereafter, several researchers have focused on the investigations of the interfacial phenomena of mucoadhesive hydro gels with the mucus. For drug delivery purpose, the term bioadhesion implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. Hence a bacterial attachment is to tissue surfaces, and mucoadhesion can be modeled after the adherence of mucus on epithelial tissue. Mucoadhesion is the relatively new and emerging concept in drug delivery. Mucoadhesion keeps the delivery system adhering to the mucus membrane. By this definition, the mucosal routes for drug delivery are:

- Buccal /oral route
- Nasal route
- Ocular route
- Vaginal route
- Gastrointestinal route

NEED OF MUCOADHESIVE DELIVERY

As compared to oral controlled release systems, mucoadhesive delivery system have several advantages by virtue of prolongation of residence time, drug targeting, intimate contact between dosage form and the absorptive mucosa. In addition, mucoadhesive dosage forms have been used to target local disorders at the mucosal surface to reduce dose and to minimize the side effects. Mucoadhesive formulations use polymers as the adhesive component. These polymers are often water soluble and when used in a dry form, they attract water from the mucosal surface and this water transfer leads to a strong interaction further increasing the retention time over the mucosal surfaces and leads to adhesive interactions. Prolonged contact time of a drug with a body tissue through the use of a bioadhesive polymer can significantly improve the performance of many drugs[2].

MECHANISM OF MUCOADHESION

The mechanism of mucoadhesion between hydrogels and mucosa can be described in three steps.

1. Wetting and swelling
2. Interpenetration of the bioadhesive polymer
3. Formation of weak chemical bonds[3].

MUCOADHESIVE POLYMERS

Properties

1. It must be loaded substantially by the active compound.
2. Swell in the aqueous biological environment of the delivery–absorption site.
3. Interact with mucus or its components for adequate adhesion.
4. When swelled they allow, controlled release of the active compound.
5. Be excreted unaltered or biologically degraded to inactive, non-toxic oligomers.
6. Sufficient quantities of hydrogen bonding chemical groups.
7. Possess high molecular weight.
8. Possess high chain flexibility.
9. Surface tension that will induce spreading into mucous layer[2]

Classification

Mucoadhesive polymer are classified as follows:

First generation polymer:

Anionic polymer: poly(-acrylic acid), carbopol, polycarbophil,

Cationic polymer: Chitosan

Second generation polymer: Lecitins, bacterial adhesion

New generation polymer: Thiomers

POLYMER PROPERTIES DESIRABLE FOR MUCOADHESION

Functional group

The mucoadhesive polymer possessing hydrophilic functional group such as COOH, OH, NH_2, and SO_4H may be more favourable in formulating targeted drug delivery system. The functionalized polymer interact with mucus not only through physical entanglement but also through chemical bonds, resulting in formation of cross linked network. Example: Urea is well accepted hydrogen bonding disruptor which decreases mucoadhesiveness of mucin/pectin samples[5,6].

Degree of hydration

Hydration is essential for the relaxation and interpenetration of polymer chains. Excess of hydration could lead to decreased mucoadhesion and/or retention due to the formation of a slippery mucilage. In this situation cross-linked polymers that only permit a certain degree of hydration may be advantageous for providing a prolonged mucoadhesive effect[7,8,9].

Chain length

Chain length and its flexibility is critical for interpenetration and entanglement with the mucus gel. Increased chain mobility leads to increased inter diffusion and interpenetration of the polymer within the mucus network. Long polymer chains lose their ability to diffuse and interpenetrate through mucosal surfaces. Hence as the chain length decreases interpenetration increases[10,11].

Degree of cross linking

The chain mobility and resistance to dissolution is significantly influenced by the degree of cross-linking within a polymer system. Cross-linked hydrophilic polymers swell in the presence of water allowing them to retain their structure. High molecular weight linear hydrophilic polymers are swellable and readily dispersible. Cross-link density increases, chain mobility decreases and hence the effective chain length, decreases, reducing mucoadhesive strength[12].

Polymer concentration

Polymer concentration is dependent on physical state of the delivery system, with differences between semisolid and solid-state dosage form. In the semisolid state, polymer concentration is low which reduces adhesion. Hence lower number of polymer chains are available for interpenetration with mucus. On the other hand, solid dosage forms such as buccal tablets exhibit increased adhesive strength as the mucoadhesive polymer concentration increases[13].

COMMON SITES OF APPLICATION FOR MUCOADHESIVE DRUG DELIVERY PLATFORM

Mucoadhesive formulations have been widely used for their targeted and controlled release delivery to many mucosal membrane-based organelles. Such formulations may deliver active ingredient for local or systemic effect, while bioavailability limiting effects such as enzymatic or hepatic degradation can be avoided or minimised.

Buccal drug delivery

The buccal cavity offers many advantages for drug delivery application. The most significant advantage offered is high accessibility and low enzymatic activity. Additionally, buccal drug delivery can be promptly terminated in cases of toxicity through the removal of dosage form thereby offering a safe and easy method of drug utilisation[19.] Various polymers such as sodium carboxymethylcellulose, hydroxypropylcellulose and polycarbophil are used for delivery of peptides, protein and polysaccharides by this routes have been examined[20,21,22.] Although gel and ointments are the most patient convenient; tablets, patches and films have also been examined. Furthermore buccal drug delivery is associated with high patient compliance, low levels of irritation and offers significant ease of administration[23,24].

Opthalmic drug delivery

The delivery of therapeutic agents to the eye may be achieved using various types of dosage forms including liquid drops, gels, ointments and solid ocular inserts (both degradable and nondegradable)[25,26,].Another interesting delivery system is in situ gelling polymer that undergoes a phase transition after application. Mucoadhesive polymers would be expected only to attach to conjunctival mucus in vivo. Additionally limited bioavailability has been experienced in vivo for carbomer and polycarbophil,[27] as a result of the high swelling capacity of such polymers in the neutral pH environment of the eye. Maintenance of a low viscosity in such systems through pH regulation in the range 4–5 is not acceptable as it may result in patient unease and mild lacrimation, both of which will have an effect on treatment success. User acceptance and compliance may subsequently be limited by physical and psychological barriers surrounding such dosage forms[28].

Vaginal drug delivery systems

Vaginal drug delivery offers many advantages; the avoidance of hepatic first-pass metabolism, a decrease in hepatic side effects and avoidance of pain, tissue damage, and infection commonly observed for parenteral drug delivery routes of administration. While the vagina provides a promising site for systemic drug delivery because of its large surface area, rich blood supply and high permeability, poor retention due to the self-cleansing action of the vaginal tract is often problematic. However, residence times within the vagina tend to be much higher than at other absorption sites such as the rectum or intestinal mucosa. Another important consideration is the change in the vaginal membrane during the menstrual cycle and post-menopausal period. Typical bioadhesive polymers that have been in vaginal formulations include polycarbophil, hydroxypropylcellulose and polyacrylic acid[29-35].

Nasal drug delivery

One of the key advantages provided by intranasal drug delivery is that the nasal cavity provides a large highly vascularised surface area through which first-pass metabolism can be avoided, as blood is drained directly from the nose into the systemic circulation. Successful nasal delivery has been obtained using solutions, powders, gels and microparticles. The most commonly employed intranasal active ingredient are solutions containing sympathomimetic vasoconstrictors for immediate relief of nasal congestion. Local delivery of these alpha adrenergic stimulators is of particular benefit to patients with high blood pressure (or those at heightened risk of cardiovascular incident), as vasoconstriction will occur to the greatest degree within the nose. In addition to local effects, the intranasal route of drug administration has also been used to achieve a distal systemic effect. One such example is the intranasal delivery of the peptide desmopressin that exerts its action on the kidneys, mimicking the action of antidiuretic hormone, used mainly in Diabetes insipidus[36,37].

EVALUATION OF MUCOADHESIVE DRUG DELIVERY SYSTEMS

Measuring the force of attachment

The adhesive strength at bonding interface can be measured by measuring the force required to detach one entity from the other through the application of an external force. Hence the destruction of adhesive bond is usually under the application of either a shearing, tensile or peeling force[38,39]

In vitro residence time study

The mucoadhesive properties of tablets were evaluated by in vivo residence time study as reported by Lehr et al[40]. A 1-cm by 1-cm piece of porcine buccal mucosa was tied onto a glass slide (3-inch by 1-inch) using thread. Tablet was stuck onto the wet, rinsed, tissue specimen, by applying light force with a fingertip for 30 seconds. The prepared slide was hung onto one of the groves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movements in a beaker containing the dissolution medium (0.01 N HCl). At the end of 3 hour, the detachment of tablet from tissue was checked and the time of detachment was recorded as the in vivo residence time.

GI transit study using radio-opaque markers

It is a simple procedure involving the use of radio-opaque markers, e.g. barium sulfate, encapsulated in bioadhesive to determine the effectss of bioadhesive polymers on GI transit time. 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.

Fluorescent probe method

In this method the membrane lipid bilayered and membrane proteins were labeled with pyrene and fluorescein isothiocyanate, respectively. The cells were mixed with the mucoadhesive agents and changes in fluorescence spectra were monitored. This gave a direct indication of polymer binding and its influence on polymer adhesion.

Thumb test

The adhesiveness is measured by the difficulty of pulling the thumb from the adhesive as a function of the pressure and the contact time. Although the thumb test may not be conclusive, it provides useful information on peel strength of the polymer.

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 effect in terms of therapeutic action and patient protection. Mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting thereby in a high drug flux through the absorbing tissue. In addition, mucoadhesive dosage forms have been used to target local disorders at the mucosal surface to reduce the overall dosage required and to minimize the side effects that may be caused by the systemic administration of the drugs.

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Table.1. Theory of Mucoadhesion

SR.NO	Theory[4]	Mechanism of bioadhesion	Comments
1.	Electronic theory	Attractive electrostatic forces between glycoprotein mucin network and the bioadhesive material	Electron transfer occur between the two forming double layer of electric charge at the interface.
2.	Adsorption theory	Surface forces resulting in chemical bonding	*Strong primary forces*: covalent bonds, *weak secondary force:* ionic bonds, hydrogen bonds and Vander Waal's forces.
3.	Wetting theory	Ability of bioadhesive polymer to spread and develop intimate contact with the mucus membrane.	Spreading coefficient of polymer must be positive.
4.	Diffusion theory	Physical entanglement of mucin strands and the flexible polymer chain	For maximum diffusion and best bioadhesive strength and solubility parameters(δ) of the bioadhesive polymer and the mucus glycoprotein must be similar.

Table.2 Various Polymer Used In Drug Delivery System

Polymers[14-18]	Properties	Examples
Poly(cyano acrylate)	Biodegradable depending on the length of the alkyl chain.	• Used as surgical adhesives and glues. • Potentially used in drug delivery.
Polyphosphazenes	Can be tailored with versatile side chain functionality	• Can be made into films and hydrogels. • Applications in drug delivery.
Poly (vinyl alcohol)	Biocompatible	• Gels and blended membranes are used in drug delivery and cell immobilization.
Poly (hydroxytheyl methacrylate)	Biocompatible	• Hydrogels have been used as soft contact lenses, for drug delivery, as skin coatings, and for Immunoisolation membranes.
Poly (ethylene oxide-b-propylene oxide)	Surfactants with amphiphilic properties.	• Used in protein delivery and skin treatments.

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