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POLYMERS IN MUCOADHESIVE MICROSPHERE DRUG DELIVERY SYSTEM- A REVIEW

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ABSTRACT

In the development of drug delivery systems, mucoadhesion of the device is a key element. The term 'mucoadhesive' is commonly used for materials that bind to the mucin layer of a biological membrane. Mucoadhesive polymers have been utilised in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosa. These dosage forms include tablets, patches, tapes, films, semisolids and powders. To serve as mucoadhesive polymers, the polymers should possess some general physiochemical features such as predominantly anionic hydrophilicity with numerous hydrogen bond-forming groups, suitable surface property for wetting mucus/mucosal tissue surfaces and sufficient flexibility to penetrate the mucus network.

Key Words: Mucoadhesive, Biodegradable, Drug delivery systems, Target site.

INTRODUCTION

In pharmaceutical research, the focus is steadily shifted from the development of new chemical entities to the development of novel drug delivery system of existing drug molecule to maximize their effectiveness in terms of therapeutic action, patient compliance and reduced adverse effects. 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 targeting various absorptive mucosa such as ocular, nasal, pulmonary, buccal, vaginal, etc. This system of drug delivery is called mucoadhesive drug delivery system[1].

Of the many polymeric drug delivery systems, biodegradable polymers have been used widely as drug delivery systems because of their biocompatibility and biodegradability. The majority of biodegradable polymers have been used in the form of microparticles, from which the incorporated drug is released to the environment in a controlled manner. The factors responsible for controlling the drug release rate are physicochemical properties of drugs, degradation rate of polymers, and the morphology and size of microparticles[2]. Bioadhesion can be defined as the process by which a natural or a synthetic polymer can adhere to a biological substrate. When the biological substrate is a mucosal layer then the phenomena is known as mucoadhesion[3]. According to potential site of application the mucoadhesive drug delivery system can be classified as follows[4],

- Buccal delivery system
- Vaginal delivery system
- Rectal delivery system
- Nasal delivery system
- Ocular delivery system

Controlled and modified release formulations are widely used in the modern era for the delivery of various ingredient including pharmaceutical and biopharmaceuticals. Release of ingredients may be controlled by several mechanisms for the delivery of pharmaceuticals and biopharmaceuticals[5].

In the early 1980s, the concepts of mucoadhesives are introduced into the controlled drug delivery area.

Mucoadhesives are synthetic or natural polymers that interact with the mucus layer covering the mucosal epithelial surface and main molecules constituting a major part of mucus. The concept of mucoadhesives has alerted many

investigators to the possibility that these polymers can be used to overcome physiological barriers in long-term drug delivery. Extensive research efforts throughout the world have resulted in significant advances in understanding the various aspects of mucoadhesion. The research on mucoadhesives, however, is still in its early stage, and further advances need to be made for the successful translation of the concept into practical application in controlled drug delivery[6,7].

CHARACTERISTICS OF AN IDEAL MUCOADHESIVE POLYMER[8, 9]

An ideal mucoadhesive polymer has the following characteristics,

- It should be nonirritant to the mucous membrane.
- It should allow daily incorporation to the drug and offer no hindrance to its release.
- The polymer and its degradation products should be nontoxic and should be nonabsorable from the gastrointestinal tract.
- The cost of polymer should not be high so that the prepared dosage form remains competitive.
- It should preferably form a strong noncovalent bond with the mucin-epithelial cell surfaces.
- It should adhere quickly to most tissue and should possess some site-specificity.
- The polymer must not decompose on storage or during the shelf life of the dosage form.

POLYMERS IN MUCOADHESIVE DRUG DELIVERY

Mucoadhesive delivery systems are being explored for the localization of the active agents to a particular site. Polymers[10,11,12] have played an significant role in designing such systems so as to enhance the residence time of the active agent at the desired location. Polymers used in mucosal delivery system may be of natural or synthetic origin. In this section we will briefly discuss some of the common types of mucoadhesive polymers.

Synthetic polymers

- Poly (acrylic acid) polymers (carbomers,polycarbophil).
- Cellulose derivatives (MC,EC, HPMC, Sodium CMC).
- Poly (hydroxyethyl methylacrylate).
- Poly (ethylene oxide).
- Poly (vinyl pyrrolidone).
- Poly (vinyl alcohol).

Natural polymers

- Guar gum

- Xanthan gum
- Lectin
- Soluble starch
- Tragacanth
- Sodium alginate
- Karaya gum
- Gelatin
- Pectin
- Chitosan

Mucodhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes[13,14].

- Polymers that adhere through nonspecific, noncovalent interactions that is primarily electrostatic in nature.
- Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- Polymers that combine to specific receptor site on tile self surface.

THE MUCUS LAYER[15]

Mucus is a translucent and viscid secretion, which forms a thin, continuous gel blanket adherent to mucosal epithelial surface. The mean thickness of this layer differ from about 50-450 µm in humans. It is secreted by the goblet cells lining the epithelia or by special exocrine glands with mucus cells. The exact composition of the mucus layer varies substantially, depending on the species, the anatomical location and pathological states. However, it has general composition as shown in table 1.

Table No.1: Composition of mucus

Sr. No.	Components	% Amount
1	Water	95
2	Glycoprotein and lipids	0.5-5.0
3	Minerals salts	1
4	Free proteins	0.5-1.0

FUNCTIONS OF MUCUS LAYER

The primary functions of the mucus layer are protective, barrier, adhesion and lubrication.

Protective: Resulting particularly from its hydrophobic.

Barrier: The role mucus layer as barrier in tissue absorption of drugs and other

substances is well known as it influences the bioavailibity of the drugs.

Adhesion: Mucus has strong cohesional properties and firmly binds to the epithelial cells surface as 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 cells is necessary to compensate for the removal of mucus layer due to digestion, bacterial degradation and solubilization of mucin molecules. At physiological pH, the mucus network may carry a significant negative charge due to the presence of salicylic acid and sulphate residues and this high charge density due to negative charge contributes significantly to the bioadhesion.

MECHANISMS OF MUCOADHESION

The mechanism of adhesion of certain macromolecules to the surface of a mucous tissue is not well understood yet. The mucoadhesive must spread over the substrate to initiate close contact and increase surface contact, promoting the diffusion of its chains within the mucus.

Attraction and repulsion forces arise and, for a mucoadhesive to be successful, the attraction forces must dominate. Each step can be facilitated by the nature of the dosage form and how it is administered. For example, a partially hydrated polymer can be adsorbed by the substrate because of the attraction by the surface water[16].

Thus, the mechanism of mucoadhesion is generally divided in two steps, the contact stage and the consolidation stage (Fig.1). 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 (Fig.1), the mucoadhesive materials are activated by the presence of moisture. Moisture plasticizes the system, allowing the mucoadhesive molecules to break free and to link up by weak Van der Waals and hydrogen bonds. Essentially, there are two theories explaining the consolidation steps such as the diffusion theory and the dehydration theory[17].

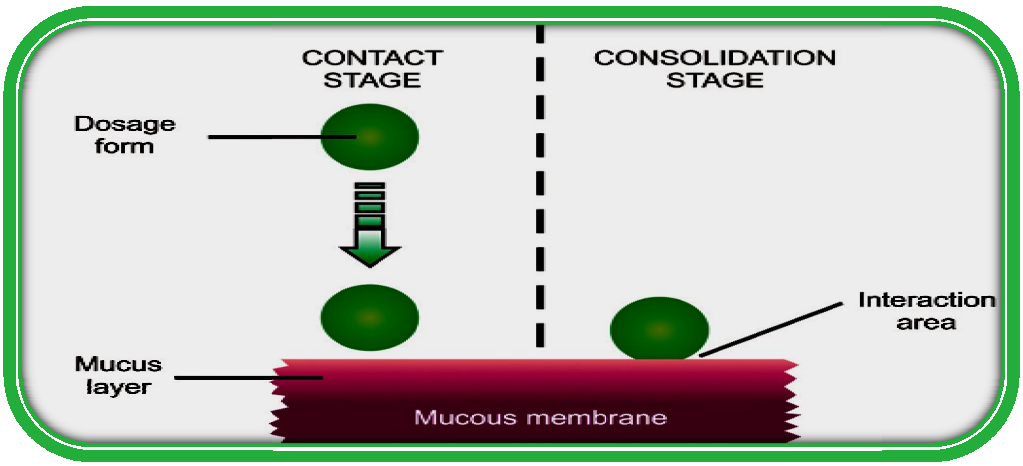

Fig. 1 – The two steps of the mucoadhesion process

According to dehydration theory, materials that are able to readily gelify in an aqueous environment, when placed in contact with the mucus can cause its dehydration due to the difference of osmotic pressure[18]. The difference in concentration gradient draws the water into the formulation until the osmotic balance is reached. This process leads to the mixture of formulation, mucus and thus enhance contact time with the mucous membrane. Therefore, it is the water motion that leads to the consolidation of the adhesive bond, and not the interpenetration of macromolecular chains. However, the dehydration theory is not applicable for solid formulations or highly hydrated form[19].

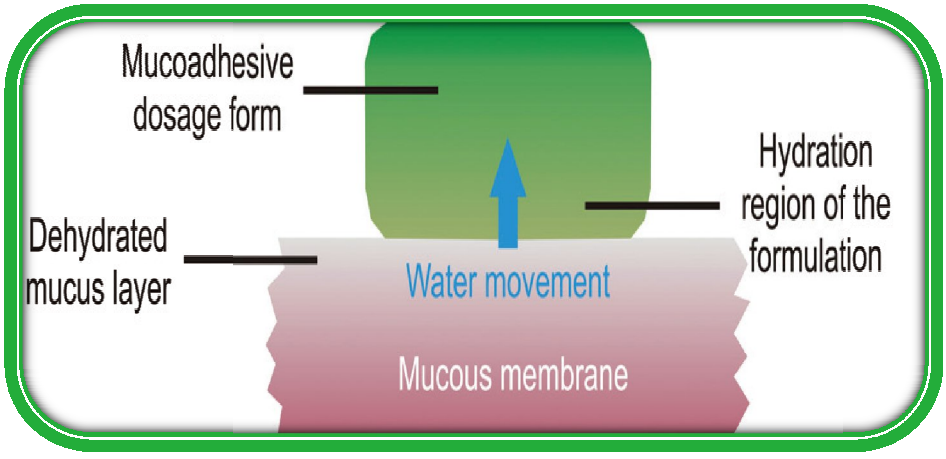

Fig. 2 – Dehydration theory of mucoadhesion

Factors affecting Mucoadhesion

Different factors[20] which affects mucoadhesive property such as follows.

1. **Polymer related factors**
   - Molecular weight
   - Concentration of active polymer
   - Flexibility of polymer chains
   - Spatial confirmation
   - Swelling
2. **Environment related factors**
   - pH of polymer - substrate interface
   - Applied strength
   - Initial contact time
3. **Physiological factors**
   - Mucin turns over
   - Disease state

1. Polymer-Related Factors

Molecular Weight: The optimum molecular weight for maximum bioadhesion depends on the type of bioadhesive polymer at issue. It is generally understood that the threshold required for successful bioadhesion is atleast 100,000 molecular weight. For example, polyethylene glycol (PEG), with a molecular weight of 20,000, has little adhesive character, whereas PEG with 200,000 molecular weight has improved, and a PEG with 400,000 has superior adhesive properties. The fact that bioadhesiveness enhances with increasing molecular weight for linear polymers imply two things:

- Interpretation is more critical for lower molecular weight polymers to be a good bioadhesive,
- Entanglement is important for higher molecular weight polymers.

Adhesiveness of a nonlinear structure follows a quite different trend. The adhesive strength of dextran, with a very high molecular weight of 19,500,000 is similar to that of PEG, with a molecular weight of 200,000. The reason for this similarity may be that the helical conformation of dextran may shield many of the adhesive groups, which are primarily responsible for adhesion, unlike the conformation of PEG.

Concentration of active polymers: There is an optimum concentration of a bioadhesive polymer to produce maximum bioadhesion. In highly concentrated systems, beyond the optimum level, however, the adhesive strength drops significantly because the coiled molecules become separated from the medium so that the chains available for interpenetration become limited.

Flexibility of polymer chains: It is critical for interpenetration and entanglement. As water-soluble polymers become crosslinked,

mobility of individual polymer chains decrease and thus the effective length of the chain that can penetrate into the mucus layer decreases, which reduces bioadhesive strength.

Spatial conformation: Besides molecular weight or chain length, spatial conformation of a molecule is also important. Despite a high molecular weight of 19,500,000 for dextrans, they have similar adhesive strength to the polyethylene glycol with a molecular weight of 200,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers which have a linear conformation.

Swelling: It depends on the polymer concentration, ionic concentration, as well as the presence of water. Over hydration results in the formation of a slippery mucilage without adhesion.

2. Environment Related Factors

pH of polymer - substrate interface:

It can influence the formal charge on the surface of mucus as well as certain ionisable bioadhesive polymers. Mucus will have a different charge density depending on pH due to difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. pH of the medium is important for the degree of hydration of crosslinked polyacrylic acid, showing consistently increased hydration from pH 4 to 7 and then a decrease as alkalinity and ionic strength increases.

Applied strength: To place a solid bioadhesive system, it is necessary to apply a defined strength. Whatever the polymer, poly(acrylic acid / vinyl benzene poly (HEMA) or carbopol 934, the adhesion strength increases with the applied strength or with the duration of its application, upto an optimum. The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interaction with mucin.

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.

3. Physiological Variables

Mucin Turnover: The natural turnover of mucin molecules is important for at least two reasons. First, the mucin turnover is expected to limit the residence time of the

mucoadhesive on the mucus layer. Second, mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with the mucoadhesive before they have a chance to interact with the mucus layer. Mucin turnover may depend on other factors such as presence of food.

Disease States: The physiochemical properties of mucus are known to change during disease conditions such as common cold, gastric ulcers, ulcerative colitis, cystic fibrosis, bacterial and fungal infections of the female reproductive tract.

SITES FOR MUCOADHESIVE DRUG DELIVERY SYSTEMS [21-23]

Buccal cavity: At this site, first-pass metabolism is avoided, and the non-keratinized epithelium is relatively permeable to drugs. Due to flow of saliva and swallowing, materials in the buccal cavity have a short residence time and so it is one of the most suitable areas for the development of bioadhesive devices that adhere to the buccal mucosa and remain in place for a considerable period of time.

Gastrointestinal tract: The gastrointestinal tract has been the subject of intense study for the use of bioadhesive formulations to improve drug bioavailability. The problem associated is that the polymeric bioadhesive formulations bind the intestinal mucus, which is constantly turning over and are transported down the gut by peristalsis. Another problem is that with conventional formulations such as tablets, the active ingredient may diffuse relatively rapidly away from the bioadhesive.

Nasal cavity: Ease of access, avoidance of first-pass metabolism and a relatively permeable and well-vascularised membrane, contribute to make the nasal cavity an attractive site for drug delivery. Although the surface area is not large (between 150-200 cm^2), one major disadvantage of nasal mucosa is the rapid removal of substances by mucociliary action (with a residence time half-life of 15-30 min). This makes it a prime target for bioadhesive formulations to prolong the residence time to allow drug release and absorption

Eye: One major problem for drug administration to the eye is rapid loss of the drug and or vehicle as a result of tear flow, and so it is a target for prolonging the residence time by bioadhesion. The bioadhesive polymers are finding increasing use in ophthalmic formulations, but often as viscosity enhancers rather than as bioadhesives.

Vagina: The vagina is a highly suitable site for bioadhesive formulations and it is here

that the success of the concept can be seen convincingly. The bioadhesion increases the retention time (up to 72 h) and a smaller amount of the active ingredient can be used, reducing any adverse effects.

Oesophagus: Tablets or capsules lodging in the oesophagus leads to delayed absorption and therefore delayed onset of action, as the oesophageal epithelial layer is impermeable to most drugs. Development of a DDS that adheres to the oesophagus has implications in both the protection of the epithelial surface from damage caused by reflux and as a vehicle to deliver drugs for local action within the oesophagus. Bioadhesive dosage forms that adhere to the oesophageal mucosa and prolong contact have been investigated to improve the efficacy of locally acting agents.

MUCOADHESION THEORIES[24, 25]

Although the chemical and physical bases of mucoadhesion are not yet well understood, varies theories adapted from studies on the performance of several materials and polymer-polymer adhesion which explain the phenomenon.

Electronic theory

It defined as the electron transfer from contact of an adhesive polymer with a glycoprotein network, they form an electrical interface at adhesive polymer and glycoprotein network. Adhesion can produce by attractive forces across the double layer.

Absorption theory

Absorption theory are defined as they cause after initial contact between two surfaces that is material surface because a force formed between two surfaces, the force is two types of chemical bond that is,

- Primary chemical bond of covalent bond: they are high strength so they cause permanent bonds.
- Secondary chemical bond has types of force of attraction like electrostatic force, Vander Waals forces, hydrogen and hydrophobic bonds.

Wetting theory

The wetting theory applies to liquid systems which present affinity to the surface in order to spread over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that the lower the contact angle then the greater the affinity (Fig.2). The contact angle should be equal or close to zero to provide adequate spreadability.

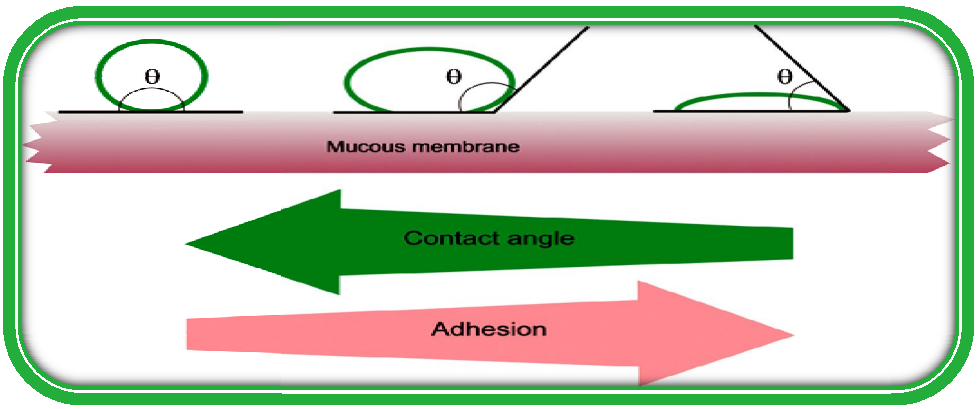

Fig. 3 – Schematic diagram showing influence of contact angle between device and Mucous membrane on bioadhesion

Diffusion theory

Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond (Fig. 4). It is believed that the adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time.

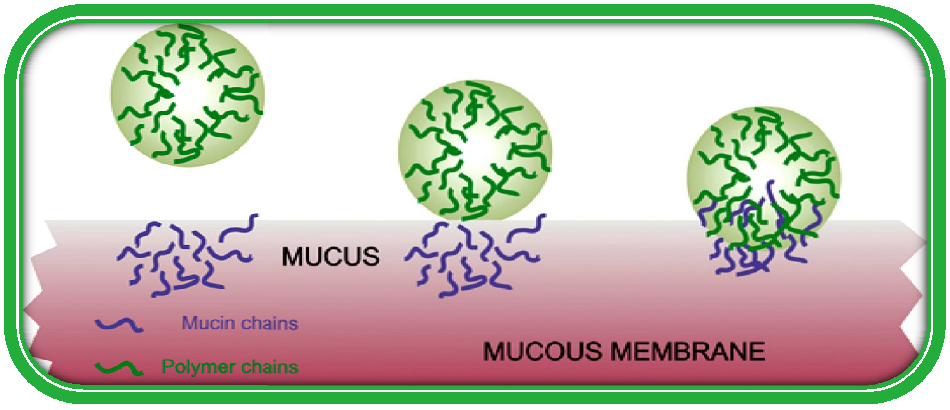

Fig. 4 – Secondary interactions resulting from inter diffusion of polymer chains of bioadhesive device and of mucus

Fracture Theory:

This theory related for difficulty of separation of two surfaces after adhesion, The equation,

G = (E e/L) 1/2

E = Young's formula of elasticity

e = Fracture energy

L= Critical crack length

EVALUATION OF MUCOADHESIVE PROPERTIES[26-28]

Various *in vivo* and *in vitro* methods are used for testing the efficacy of the mucoadhesive nature of a polymer matrix. Commonly used *in vitro*/*ex vivo* methods include tensile strength measurement, shear strength measurement and chip based systems whereas various imaging techniques are used for the evaluation of the delivery systems under *in vivo* conditions. This section will describe various methods used to study the mucoadhesive properties.

In vitro tensile strength measurement is done by dipping a filter paper in 8% mucin dispersion. There after, the mucin coated filter paper is placed in contact with the hydrated polymeric samples (in physiological solutions) for a definite period of time, followed by the determination of the maximum force required to detach the filter-paper and polymer surfaces after the mucoadhesive bonding. Similarly, ex vivo experimentations are also done with the exception that the mucin coated filter-paper is replaced with excised mucosal tissues (e.g. buccal mucosa, intestinal mucosa, vaginal mucosa.

The mucoadhesive properties can also be determined by incubating the hydrated polymer matrix surface kept in contact with a viscoelastic 30 % (w/w) mucin solution in water with the subsequent determination of the maximum detachment force required to separate the polymer matrix and mucin solution surfaces after the adhesion. Wash-off test may also be used to determine the mucoadhesive property of delivery systems. In the test, the mucosal tissue is attached onto a glass slide with the help of a double-sided cyanoacrylate tape. Thereafter, the delivery system is put on the surface of the tissue (exposed mucosal surface) with the subsequent vertical attachment of the system into the USP tablet disintegrator apparatus, which contains 1 L of physiological solution maintained at 37^{o}C. The operation of the equipment gives an up-and-down movement to the tissue-delivery matrix system.

In this study, the time for the complete detachment of the delivery system from the mucosal layer is determined. For the relative measurement of mucoadhesive nature of powder polymer samples modified Du Noiy's tensiometer may be used, while in the shear strength determination method the force required to slide the polymer matrix over the mucus layer is determined. Recently mucoadhesion studies have been reported by using BIACORE® integrated chip (IC) systems. The method involves

immobilization of the polymer (powder) on to the surface of the IC with the subsequent passage of the mucin solution over the same. This results in the interaction of the mucin with that of the polymer surface.

CONCLUSION

Mucoadhesive microsphere drug delivery system have a high potential of being useful means of releasing drugs to the body, perhaps particularly for local administration where the mechanical trauma experienced by the dosage form may be decreased. Current use of mucoadhesive polymers to enhance resident time for a wide variety of drugs and routes of administration has shown dramatic improvement in both specific therapies and more general patient compliance. The general properties of these polymers for purpose of sustained release of chemicals are marginal in being able to accommodate a wide range of physicochemical drug properties. Mucoadhesive polymers may provide an important tool to enhance the bioavailability of the active agent by improving the residence time at the target site.

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