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ROLE OF MUCOADHESIVE POLYMERS IN FORMULATION OF MUCOADHESIVE MICROSPHERE

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ABSTRACT

The potential of mucoadhesive delivery system for sustained delivery of drug has been established few decades back. Different polymeric systems such as single or combined, substituted, conjugated, pre-activated polymer (s) etc. are used to develop such delivery platform. To explain the mucoadhesion mechanism, several possible theories namely electronic theory, adsorption theory, wetting theory, diffusion theory, fraction theory and mechanical theory have been proposed. But none of these theories alone can explain the mechanism of mucoadhesion. Various mechanisms of mucoadhesion or bioadhesion between polymer and mucin such as H bonding, electrostatic interactions, di-sulfide linkage, van Der Waals attraction etc have been evidenced. Researches are focused to enrich such interaction between the mucous layer and the delivery platform by modifying the system. Wide varieties of polymers such as cationic, anionic, non-ionic, thiolated polymers etc have been used to design and develop mucoadhesive drug delivery system. Therefore reviewing and analyzing the mucoadhesive polymeric system and their mechanism of action is still relevant and necessary. The aim of this current review is to highlight the polymers which are being used under recent scientific researches with emphasis on their mechanism of mucoadhesion. The result of this critique will assist researchers to screen the mucoadhesive polymers for their designated purpose.

KEYWORDS: Mucoadhesive, Polymers, Microsphers, Sustained Release Action.

INTRODUCTION

The mucoadhesion can be defined as the adhesion between the two substances in which one is biological material and other is polymeric materials in order to enhance the retention time of the drug. The binding between the two substances occurs through interfacial forces. The mucoadhesion drug delivery system is better than the traditional drug delivery systems. The mucoadhesive system bypasses the first pass metabolism and is used for localized delivery of biomolecules such as peptides, proteins and oligonucleotides. With the help of mucoadhesion drug delivery, different compounds can be given by different routes of administration like ocular, oral, vaginal, nasal and rectal. The systemic and local delivery of drug is improved in mucoadhesion system as the contact time on the site of application is increased. The mucoadhesive polymers may also act as a therapeutic substance for tissue protection or lubrication.

Microspheres are solid spherical particles ranging in size from 1-1000µm. They are spherical free flowing particles consisting of proteins or synthetic polymers. The microspheres are free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. There are two types of microspheres;

- Micrometrics
- Microcapsules

Microcapsules are those in which entrapped substance is distinctly surrounded by distinct capsule wall and micrometrics in which entrapped substance is dispersing throughout the microsphere's matrix. Solid biodegradable microspheres incorporating a drug dispersed or dissolved through particle matrix have the potential for the controlled release of drug. They are made up of polymeric, waxy, or other protective materials, that is, biodegradable.

Types of Microspheres

- Bio-adhesive microspheres
- Magnetic microspheres
- Floating microsphere

A polymer is a large molecule (macromolecules) composed of repeating structural units. These subunits are typically connected by covalent chemical bonds. Both synthetic and natural polymers are available but the use of natural polymers for pharmaceutical applications is attractive because they are economical, readily available and non-toxic. They are capable of chemical modifications, potentially biodegradable and with few exceptions, also biocompatible. 1 Substances of plant origin pose several potential challenges such as being synthesized in small quantities and in mixtures that are structurally complex, which may differ according to the location of the plants as well as other variables such as the season. This may result in a slow and expensive isolation and purification process. Another issue that has become increasingly important is that of intellectual property rights.

Theories of mucoadhesive

These theories are depending upon the long-established theories of polymer and metallic applicable for.

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, the greater is the affinity. The contact angle should be equal or close to zero to provide adequate spreadability. The spreadability coefficient, *SAB*, can be calculated from the difference between the surface energies γB and γA and the interfacial energy γAB, as indicated in the equation given below.[5] This theory explains the importance of contact angle and reduction of surface and interfacial energies to achieve good amount of mucoadhesion.

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

Diffusion theory: Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond [Figure 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. According to the literature, 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.

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

where *t* is the contact time and *Db* is the diffusion coefficient of the mucoadhesive material in the mucus.

Fracture Theory: This is perhaps the most used theory in studies on the mechanical measurement of mucoadhesion. It analyses the force required to separate two surfaces after adhesion is established. This force, *sm*, is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, *Fm*, and the total surface area, *A0*, involved in the adhesive interaction

$S_m = F_m/A_0$

The 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.

The adsorption theory: In this instance, adhesion is the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. Primary bonds due to chemisorption 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.

Factors affecting mucoadhesion

- Polymer related factors: Several properties or characteristics of the active polymer play a vital role in mucoadhesion. Among them, concentration, swelling, polymer molecular weight, particular confirmation and polymer chains flexibility that may affect the mucoadhesion.
- Environment associated factors: pH of the polymer-substrate interface, functional strength and first contact time is able to influence the mucoadhesion
- Physiological factors: Disease state and mucin turn over are the important physiological factors, which can also affect mucoadhesion.

Mucoadhesive Polymers

Mucoadhesive drug delivery systems are based on the adhesion of a drug/ carrier to the mucous membrane. To promote this adherence a suitable carrier is required.

Ideal Characteristics of Mucoadhesive Polymers

A mucoadhesion promotoing agent or the polymer is added to the formulation which helps to promote the adhering of the active pharmaceutical ingredient to the oral mucosa. The agent can have such additional properties like swelling so as to promote the disintegration when in contact with the saliva.

1) Polymer must have a high molecular weight up to 100.00 or more. This is necessary to promote the adhesiveness between the polymer and mucus.
2) Long chain polymers-chain length must be long enough to promote the interpenetration and it should not be too long that diffusion becomes a problem.
3) High viscosity.

4) Degree of cross linking- it influences chain mobility and resistance to dissolution. Highly crosslinked polymers swell in presence of water and retain their structure. Swelling favours-controlled release of the drug and increases the polymer/mucus interpenetration.
5) Spatial conformation.
6) Flexibility of polymer chain- this promotes the interpenetration of the polymer within the mucus network.
7) Concentration of the polymer- an optimum concentration is required to promote the mucoadhesive strength. It depends however, on the dosage form.
8) Charge and degree of ionization- the effect of polymer charge on mucoadhesion was clearly shown by Bernkop-Schnurch and Freudl. Cationic chitosan HCl showed marked adhesiveness when compared to the control. The attachment of EDTA an anionic group increased the mucoadhesive strength significantly. DTPA/chitosan system exhibited lower mucoadhesive strength than cationic chitosan and anionic EDTA chitosan complexes because of low charge. Hence the mucoadhesive strength can be attributed as anion>cation>non-ionic.
9) Optimum hydration- excessive hydration leads to decreased mucoadhesive strength due to formation of a slippery mucilage.
10) Optimum pH – mucoadhesion is optimum at low pH conditions but at higher pH values a change in the conformation occurs into a rod like structure making those more available for inter diffusion and interpenetration. At very elevated pH values, positively charged polymers like chitosan form polyelectrolyte complexes with mucus and exhibit strong mucoadhesive forces.
11) It should non-toxic, economic, biocompatible preferably biodegradable.

Various mucoadhesive polymers can broadly be categorized as follow.

Synthetic polymers.

1. Cellulose derivatives (Methylcellulose, Ethyl cellulose, Hydroxyl ethyl cellulose, Hydroxyl propyl cellulose, Hydroxy propyl methylcellulose, Sodium carboxy methylcellulose).
2. Poly (Acrylic acid) polymers (Carbomers, Polycarbophil).
3. Poly hydroxyl ethyl methylacrylate.
4. Poly ethylene oxide.
5. Poly vinyl pyrrolidone.
6. Poly vinyl alcohol.

Natural Polymers

Tragacanth, Sodium alginate, Guar gum, Xanthum gum, soluble starch, Gelatin, Chitosan Mucoadhesive polymers can also classify into following categories.

1) Anionic polymers,
2) Cationic polymers,
3) Non-ionic polymers.

Of these, anionic and cationic polymers have been shown to exhibit the greatest mucoadhesive strength. Consequently, such charged polymeric systems will now be examined in more depth. Anionic polymers are the most widely employed mucoadhesive polymers within pharmaceutical formulation due to their high mucoadhesive functionality and low toxicity. Typical examples include poly (acrylic acid) (PAA) and its weakly cross-linked derivatives and sodium carboxymethylcellulose (NaCMC). PAA and NaCMC possess excellent mucoadhesive characteristics due to the formation of strong hydrogen bonding interactions with mucin. Polycarbophil (Noveon) and Carbomers (Carbopol), PAA derivatives have been studied extensively as mucoadhesive platforms for drug delivery to the GI tract.

Cationic Polymers

The cationic polymer systems, undoubtedly chitosan is the most extensively investigated within the current scientific literature. Chitosan is a cationic polysaccharide, produced by the deacetylation of chitin, the most abundant polysaccharide in the world, next to cellulose. The intriguing properties of chitosan have been known for many years with many medicines.

Novel second-generation mucoadhesive: The major disadvantage in using traditional nonspecific mucoadhesive systems (first generation) is that adhesion may occur at sites other than those intended. Unlike first-generation non-specific platforms, certain second-generation polymer platforms are less susceptible to mucus turnover rates, with some species binding directly to mucosal surfaces; more accurately termed ‘‘Cytoadhesives”.

Lecithins: The most widely investigated of such systems in this respect are lectins. Lectins belong to a group of structurally diverse proteins and glycoproteins that can bind reversibly to specific carbohydrate residues. After initial mucosal cell-binding, lectins can either remain on the cell surface or in the case of receptormediated adhesion possibly become internalised via a process of endocytosis.

Thiolated polymers: The presence of free thiol groups in the polymeric skeleton helps in the formation of disulphide bonds with that of the cysteine-rich sub-domains present in mucin which can substantially improve the mucoadhesive properties of the polymers (e.g. poly (acrylic acid) and chitosan).Various thiolated polymers include chitosan–iminothiolane, poly(acrylic acid)– cysteine, poly (acrylic acid)– homocysteine, chitosan–thioglycolic acid, chitosan– thioethylamidine, alginate–cysteine, poly (methacrylic acid)– cysteine and sodium carboxymethylcellulose–cysteine.

Polyox WSR: A class of high molecular weight polyethylene molecular weight polyethylene oxide homopolymers having the following properties.

- Water soluble hydrophilic nature
- Functional group for hydrogen bonding
- Biocompatible and non-toxic
- High molecular weight

CONCLUSION

This review presents the mucoadhesive or bioadhesive polymers, both conventional and substituted or conjugated emphasizing their mechanism of mucoadhesion. It can be concluded from the current study that research with conventional MDDS with conventional polymer is already a past trend. The reason is the maximum mucoadhesion occupancy with a single conventional polymer is already being achieved or studied. It is found from the current study that use of composite material, combined polymer systems, substituted or conjugated polymers are more popular to design a MDDS with desired criteria. Among the substituted polymers, it can be assumed, although not exclusively, that thiolated polymer is more prevalently explored by the researchers than other substituted mucoadhesive polymers. The reason is prolonged mucoadhesion due to the presence of the thiol group.

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