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Formulation of Mucoadhesive Microspheres: A Quick Review

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Abstract – Carrier technology provides an interesting as well as an intelligent approach for the delivery of drug. It offers delivery of drug by coupling the drug to a carrier particle such as microspheres, mucoadhesive microspheres, nanoparticles, liposomes, etc. Mucoadhesive microspheres constitute an important part of this particulate drug delivery system because of their small size and other efficient properties. Mucoadhesive microspheres play a vital role in the novel drug delivery system. Some drug delivery problems are overcome by producing controlled drug delivery system which enhances the therapeutic efficacy of a drug. From various approaches one approach is to using mucoadhesive microsphere as a carrier system for drug delivery. Mucoadhesive microspheres exhibit a prolonged residence time at the site of application or absorption and facilitate an intimate contact with the underlying absorption surface and thus contribute to improved and better therapeutic performance of drugs and also mucoadhesive microspheres have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, controlled and sustained release of drug from dosage form and specific targeting of drugs to the absorption site. Mucoadhesive microspheres have been developed for oral, buccal, nasal, ocular, rectal and vaginal for either systemic or local effects. It is an ideal targeting system with high safty profile. This review article gives the information about mucoadhesion and theories of mucoadhesion. It also contains a number of available methods of preparation of mucoadhesive microspheres.

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INTRODUCTION

Recently the novel dosage forms which can control the release rate and target the active drug molecule to a particular site have attained a great formulation interest. Microspheres are one of the novel drug delivery system which possess several applications and are made up of assorted polymers.

Microspheres are small spherical particles (typically 1 µm to 1000 µm), sometimes referred to as micro particles. The microspheres can be made up of either natural or synthetic polymers. Generally microspheres posses' potentiality to be employed for targeted and controlled/extended release of drug, but incorporating mucoadhesive properties to microspheres will furthermore improve absorption and bioavailability of the drugs3-6. Mucoadhesive microspheres enhance the intimate contact with the mucus layer, and drug targeting to the absorption site by anchoring bacterial adhesions , plant lectins8, antibodies9 etc. Tailored mucoadhesive microspheres offers the possibilities of localized as well as controlled release of drugs by adherence to any mucosal tissue present in eye, nasal cavity, urinary, and GI tract.

The oral route of drug administration constitutes the most convenient and preferred means of drug delivery to systemic circulation of body. However oral administration of most of the drugs in conventional dosage forms has short-term limitations due to their inability to restrain and localize the system at gastro-intestinal tract. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity.

Microspheres are the carrier linked drug delivery system in which particle size is ranges from (1-1000 µm) range in diameter having a core of drug and entirely outer layers of polymers as coating material. However, the success of these microspheres is limited due to their short residence time at site of absorption. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membrane (K. Ikeda, et.al., 1992). This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres. Bioadhesive microspheres have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site.

Some of the problems are overcome by producing control drug delivery -system which enhance the

therapeutic efficacy of a given drug for obtain maximum therapeutic efficacy and minimum side effects it necessary to deliver the agent to the target tissue in the optimal amount. In a sustained controlled release fashion, there are various approaches in delivering a therapeutic substance to the target site.

Drug action can be improved by developing new drug delivery system, such as the mucoadhesive microsphere drug delivery system. These systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the action site leading to a bioavailability increase and both local and systemic effects . The oral route of drug administration constitutes the most convenient and preferred means of drug delivery to systemic circulation of body. However oral administration of most of the drugs in conventional dosage forms has short-term limitations due to their inability to restrain and localize the system at gastro-intestinal tract. Microspheres are the carrier linked drug delivery system in which particle size is ranges from 1-1000 µm range in diameter having a core of drug and outer layers of polymer as coating material. The success of these microspheres is limited due to their short residence time at site of absorption. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membrane. This can be achieved by coupling bioadhesion characteristics to microspheres and developing “mucoadhesive microspheres”. Mucoadhesive microspheres have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site.

MICROSPHERES

Microspheres, as carrier for drug is one such approach which can be used in a sustained controlled release fashion 3. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 µm to 1000 µm). Microspheres are sometimes referred to as microparticles.

Dosage forms that can precisely control the release rate sand target drugs to a specific body site have created enormous impact on the formulation and development of novel drug delivery system. The objective of controlled release drug delivery includes two important aspects namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to controlling the rate of drug delivery to the target tissue. Variety of devices have been used for controlled release drug delivery, biodegradable polymer microspheres are one of the most common types and hold several advantages. Microspheres can encapsulate many types of drugs including small molecules, proteins, and nucleic acids and are easily administered through a syringe needle. They are generally biocompatible, can provide high bioavailability, and are capable of sustained release for long periods of time.

MUCOADHESION

Various mucoadhesive dosage forms such as discs, microspheres, and tablets have been prepared and reported by several research groups. mucoadhesive drug delivery systems are used to enhance drug absorption in a site-specific manner . mucoadhesion is defined as the interaction between a mucin surface and a syntheticor natural polymer. Mucoadhesion is defined as the interaction between a mucin surface and a synthetic or natural polymer .Mucoadhesion has been widely promoted as a way of achieving site-specific drug delivery through the incorporation of mucoadhesive hydrophilic polymers with in pharmaceutical formulations such as “microspheres” along with the active pharmaceutical ingredient (API). It is the reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untoward effects. Microspheres received much attention not only for prolonged release, but also for targeting of anticancer drugs to the tumour. In future by combining various other strategies, microspheres will find the central place in novel drug delivery, particularly in diseased cell sorting, diagnostics, gene & genetic materials, safe, targeted and effective *in vivo* delivery and supplements as miniature versions of diseased organ and tissues in the body.

MUCOADHESIVE MICROSPHERES

Recent advances in polymer science and drug carrier technologies have promulgated the development of novel drug carriers such as mucoadhesive microspheres that have boosted the use of bioadhesion in the drug delivery. Mucoadhesive microspheres include microparticles and microcapsules of 1 to 1000 µ*m* in diameter consisting either entirely of mucoadhesive polymer or having an outer coating with adhesive property. Microspheres have the potential to be used for controlled as well as spatial drug delivery. Incorporating mucoadhesivenes to microspheres leads to efficient absorption and enhanced bioavailability of drug. Specific targeting of drug to the absorption site is achieved by using homing devices (ligand) like plant lactin, bacterial adhesion etc. on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to mucosal linings of GIT, thus offering the possibilities of localized as well as systemic absorption of drug in controlled manner.

MECHANISM OF MUCOADHESION

A complete understanding of how and why certain macromolecules attach to a mucus surface is not yet available, but a few steps involved in the process are generally accepted, at least for solid systems. Several theories have been proposed to explain the

fundamental mechanism of adhesion (N.K. Jain, et.al., 1997). A General Mechanism of Mucoadhesion Drug Delivery system is show in Figure 1.

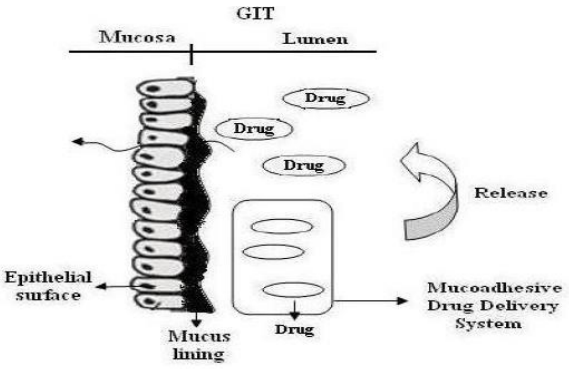

Figure 1. Mechanism of Mucoadhesion

Electronic theory - According to this theory, electron transfers occur upon contact of adhesive polymer with a mucus glycoprotein network because of difference in their electronic structures. This results in the formation of electrical double layer at the interface e.g. Interaction between positively charged polymers chitosan and negatively charged mucosal surface which becomes adhesive on hydration and provides an intimate contact between a dosage form and absorbing tissue.

Absorption theory - According to this theory, after an initial contact between two surfaces, the material adheres because of surface force acting between the atoms in two surfaces. Two types of chemical bonds resulting from these forces can be distinguished as primary chemical bonds of covalent nature and Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander Walls forces, hydrogen and hydrophobic bonds.

Diffusion theory - According to this theory, the polymer chains and the mucus mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chain penetrates the mucus depends on the diffusion coefficient and the time of contact. The diffusion coefficient in terms depends on the value of molecular weight between crosslinking and decreases significantly as the cross linking density increases.

Wetting theory - The wetting theory postulates that if the contact angle of liquids on the substrate surface is lower, then there is a greater affinity for the liquid to the substrate surface. If two substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive among the substrate surface.

Cohesive theory - The cohesive theory proposes that the phenomena of bioadhesion are mainly due to intermolecular interaction amongst like molecule. Based upon the above theories, the process of bioadhesion can broadly be classified into two categories namely chemical (electron and absorption theory) and physical (wetting, diffusion and cohesive theory).

POLYMERS USED IN MUCOADHESIVE DRUG DELIVERY SYSTEM

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place.

Hydrophilic polymers - The polymers within this category are soluble in water. Matrices developed with these polymers swell when put into an aqueous media with subsequent dissolution of the matrix. The polyelectrolytes extend greater mucoadhesive property when compared with neutral polymers (A. Ludwig, et.al., 2005).

Anionic polyelectrolytes, e.g. poly (acrylic acid) and carboxymethyl cellulose have been extensively used for designing mucoadhesive delivery systems due to their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer (S. Rossi, et.al., 2005). Chitosan provides an excellent example of cationic polyelectrolyte, which has been extensively used for developing mucoadhesive polymer due to its good biocompatibility and biodegradable properties (A. Portero, et.al., 2005). Chitosan undergoes electrostatic interactions with the negatively charged mucin chains thereby exhibiting mucoadhesive property. Structure of Chitosan is shown in Figure 2. The ionic polymers may be used to develop ionic complex with the counter-ionic drug molecules so as to have a drug delivery matrix exhibiting mucoadhesive property. Non-ionic polymers, e.g. poloxamer, hydroxypropyl methyl cellulose, methyl cellulose, poly (vinyl alcohol) and poly (vinyl pyrrolidone) have also been used for mucoadhesive properties (A. Ludwig, et.al., 2005).

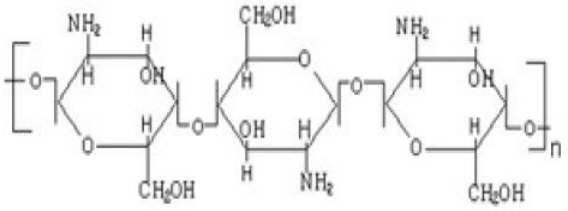

Figure. 2. Chemical structure of Chitosan

Hydrogels - Hydrogels can be defined as three-dimensionally crosslinked polymer chains which have the ability to hold water within its porous structure. The water holding capacity of the hydrogels is mainly due to the presence of hydrophilic functional groups like hydroxyl, amino and carboxyl groups. Hydrogels prepared by the condensation reaction of poly (acrylic acid) and sucrose indicated an increase in the mucoadhesive property with the increase in the crosslinking density and was attributed to increase in the poly (acrylic acid) chain density per unit area. Acrylates have been used to develop mucoadhesive delivery systems which have the ability to deliver peptide bioactive agents to the upper small intestine region without any change in the bioactivity of the peptides. Wheat germ agglutinin helped in improving the intestinal residence time of the delivery system by binding with the specific carbohydrate moieties present in the intestinal mucosa.

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) in addition to the paracellular uptake of the bioactive agents (P.L. Soo, et.al., 2002, R. Saviae et.al., 2003,). 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

Lectin-based polymers - Lectins are proteins which have ability to reversibly bind with specific sugar carbohydrate residues and are found in both animal and plant kingdom. The specific affinity of lectins towards sugar or carbohydrate residues provides them with specific cyto-adhesive property and is being explored to develop targeted delivery systems. Lectins extracted from legumes have been widely explored for targeted delivery systems. Various lectins which have shown specific binding to the mucosa include lectins extracted from *Ulex europaeus* I and *Lens culinarius* (J. Hietanen, et.al., 2007). A short list of Mucoadhesive polymers is given in Table no. 1

Synthetic polymers	Natural polymers
Cellulose derivatives	Tragacanth
polycarbophil	Sodium alginate
Poly (ethylene oxide).	Karaya gum
Poly (vinyl pyrrolidone).	Guar gum
Poly (vinyl alcohol).	Gelatin
Poly (hydroxyethyl methylacrylate)	Chitosan
Hydroxyl propyl cellulose	Soluble starch

Table No 1. List of Natural and Synthetic polymers.

APPLICATIONS OF MUCOADHESIVE MICROSPHERES:

1. Mucoadhesive microsphere is one potential strategy for prolonging GRT. Mucoadhesive microspheres interact with mucous of GIT and are considered to be localized or trapped at the adhesive site by retaining a dosage form at the site of action, or systemic delivery by retaining a formulation in intimate contact with the absorption site which may result in prolonged gastric residence time as well as improvement in intimacy of contact with underlying absorptive membrane to achieve better therapeutic performance of drugs.

2. Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria, birth control. Microsphere in vaccine delivery have a specific advantage like improved antigenicity by adjuvant action, modulation of antigen release, stabilization of antigen.

3. Mucoadhesive microspheres as a novel carrier system to improve drug delivery by various routes of administration like buccal, oral, nasal, ocular, vaginal and rectal, either for systemic or for local effects.

4. Mucoadhesive microspheres are used as targeted drug delivery system for various diseases. Mucoadhesive microspheres are involved in various clinical as well as pharmaceutical aspects.

CONCLUSION

Mucoadhesive microsphere prepared by different method was evaluated for their mucoadhesive properties. The microsphere prepared by glutaraldehyde and thermal cross linking showed good stability in HCl as compared with microsphere prepared by tripolyphosphate and emulsification ionotropic gelation. Microspheres have the potential to be used for targeted and controlled release drug delivery but coupling of mucoadhesive properties to microspheres has additional advantages such as efficient absorption, enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drugs to the absorption site. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs.

In future by combining with various other strategies mucoadhesive microspheres can find the central place in novel drug delivery. Microsphere drug delivery system provides opportunities for designing new controlled and delayed released oral formulations. Variety of opportunities offered by microspheres like protection and masking, reduction in dissolution rate, spatial targeting of the active

ingredient. This approach facilitates reduce drug concentration at the site other than target organ or tissue, delivery of small quantities of potent drugs and protection of labile compounds before and after administration. Microspheres are ideal targeting drug delivery system with high safety profile.

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