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REVIEW ARTICLE

MUCOADHESIVE MICROSPHERES: A 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.

Keywords: Mucoadhesion, mucoadhesive microspheres,mucoadhesive polymers,application.

INTRODUCTION

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 [1]. 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 [2].

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 [4].

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

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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.

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 [5].

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 [6]. 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 [7, 8].

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 [9]. mucoadhesion is defined as the interaction between a mucin surface and a syntheticor natural polymer [10]. 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 [11]. 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 [12.]

MECHANISM 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 absorbed by the substrate because of the attraction by the surface water [13].

The mechanism of mucoadhesion is generally divided into two steps: the contact stage and the consolidation stage. The first stage is characterized by the contact between the mucoadhesive and the mucus membrane, with spreading and swelling of the formulation, initiating its deep contact with the mucus layer [14].

Theories of mucoadhesion:

The phenomena of bioadhesion occur by a complex mechanism. Above theories have been proposed, which will explain the mechanism of bioadhesion [15,16,17].

Electronic theory: Involves the formation of an electric double layer at the mucoadhesive interface by the transfer of electrons between the mucoadhesive polymer and the mucin glycoprotein network. For example: 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.

Wetting Theory: States 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 such substrate surfaces are brought in contact with each other in the presence of the liquid, the liquid may act as an adhesive amongst the substrate surfaces.

Adsorption 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 likes electrostatic forces, Vander Walls forces, hydrogen and hydrophobic bonds.

Diffusion Theory of Mucoadhesion

Diffusion theory describes that polymeric chains from the bioadhesive interpenetrate into glycoprotein mucin chains and reach a sufficient depth within the opposite matrix to allow formation of a semi-permanent bond [18]. The process can be visualized from the point of initial contact. The existence of concentration gradients will drive the polymer chains of the bioadhesive into the mucus network and the glycoprotein mucin chains into the bioadhesive matrix until an equilibrium penetration depth is achieved.

ADVANTAGES OF MUCOADHESIVE MICROSPHERES DRUG DELIVERY SYSTEM

Mucoadhesive systems have three distinct advantages when compared to conventional dosage forms.

1. Readily localized in the region applied to improve and enhance the bioavailability of drugs. E.g. testosterone & its esters, vasopressin, dopamine, insulin and gentamycin etc.

2. Facilitate intimate contact of the formulation with underlying absorption surface. This allows modification of tissue permeability for absorption of macromolecules. e.g. peptides and proteins.

3. Prolong residence time of the dosage form at the site of application and absorption to permit once or twice a day dosing [19].

4. Offers an excellent route, for the systemic delivery of drugs with high first-pass metabolism, there by offering a greater bioavailability [20].

5. Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site[21].

DISADVANTAGES OF MUCOADHESIVE MICROSPHERES DRUG DELIVERY SYSTEM

1. The release from the formulations may get modified.

2. The release rate may vary from a variety of factors like food and the rate of transit though gut, mucin turnover rate etc.

3. Differences in the release rate can be found from one dose to another.

4. Any loss of integrity in release pattern of the dosage form may lead to potential toxicity.

5. These kinds of dosage forms cannot be crushed or chewed.

TYPES OF MUCOADHESIVE POLYMERS

First generation mucoadhesive polymers

First-generation mucoadhesive polymers may be divided into three main sub-categories, namely: Anionic polymers, Cationic polymers and non-ionic polymers. Among these anionic and cationic polymers have been exhibits the greatest mucoadhesive strength [22].

Anionic polymers

Anionic polymers are the most widely employed mucoadhesive polymers within pharmaceutical formulation due to their high mucoadhesive functionality and low toxicity. These include alginates, carrageenan, 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 [23].

Polycarbophil and carbomer (Carbopol, PAA derivatives have been studied extensively as mucoadhesive platforms for drug delivery to the GI tract. [24,25]. Carbomers are cross-linked with allyl sucrose or allylpentaerythritol, whereas polycarbophil polymers are cross-linked with divinyl glycol. Both compounds have the same acrylic backbone but vary in their cross-link density that is often tailored to suit pharmaceutical or cosmetic performance.

Cationic polymers

Chitosan is a cationic polysaccharide, the most abundant polysaccharide in the world, next to cellulose [26]. The most explored mucoadhesive polymers, chitosan is gaining increasing importance due to its good biocompatibility, biodegradability and due to their favourable toxicological [27].The linearity of chitosan molecules also ensures sufficient chain flexibility for interpenetration [28]. Chitosan may provide improved drug delivery *via* mucoadhesive mechanism; it has also been shown to enhance drug absorption *via* the paracellular route through neutralization of fixed anionic sites within the tight junctions between mucosal cells [29, 30].

Novel second-generation mucoadhesives polymers.

Second generation includes lectins and thiolated polymers.

Lectin these are generally defined as proteins or glycoprotein complexes of non-immune origin that are able to bind sugars selectively in a non-covalent manner [31]. Lectins are capable of attaching themselves to carbohydrates on the mucus or epithelial cell surface and have been extensively studied, notably for drug-targeting applications [32, 33]. These second-generation bioadhesives not only provide for cellular binding, but also for subsequent endo- and transcytosis.

Thiolated polymers, also designated thiomers, are hydrophilic macromolecules exhibiting free thiol groups on the polymeric backbone. Due to these functional groups, various features of polyacrylates and cellulose derivatives were strongly improved [34]. The presence of thiol groups in the polymer allows the formation of stable covalents bonds with cysteine-rich subdomains of mucus glycoproteins leading to increased residence time and improved bioavailability [35]. Other advantageous mucoadhesive properties of thiolated polymers include improved tensile strength, rapid swelling, and water uptake behavior. .e.g-various thiolated polymers include chitosan-thioglycolic acid,chitosan-thioethylamidine, alginate-cysteine.

CHARACTERISTICS OF MATERIAL WHICH ARE USED FOR THE FORMULATION OF MUCOADHESIVE MICROSPHERES [36].

1. The polymer and its degradation products should be nontoxic and should be non absorbable from the gastrointestinal tract
2. It should be nonirritant to the mucus membrane
3. It should preferably form a strong noncovalent bond with the mucin epithelial cell surfaces
4. It should adhere quickly to most tissue and should possess some site specificity

5. It should allow easy incorporation of the drug and should offer no hindrance to its release
6. The polymers must not decompose on storage or during shelf life of the dosage form
7. The cost of polymer should not be high so that the prepared dosage form remains competitive

METHODS OF PREPARATION OF MUCOADHESIVE MICROSPHERES:

1. Emulsion cross-linking method.
2. Single emulsion techniques.
3. Ionotropic gelation.
4. Phase inversion method.
5. Spray drying and spray congealing method.
6. Solvent removal method.
7. Hot melt method.

1. Emulsion cross- linking method

It was described by Thanoo and associates. This method utilizes the reactive functional group of polymer to crosslink with aldehyde group of cross linking agent. In this method water-in-oil (w/o) emulsion was prepared by emulsifying the polymer aqueous solution in the oily phase. Aqueous droplets were stabilized using a suitable surfactant like span 80 or dioctyl sodium sulphosuccinate. The stable emulsion was cross linked by using an appropriate cross-linker like gluteraldehyde to harden the droplets. Microspheres were filtered and washed repeatedly with hexane or petroleum ether to remove traces of oils. They were finally washed with water to remove cross linkers and then dried at room temperature for 24h [37].

2. Single Emulsion Technique [38].

The microspheres of natural polymers are prepared by single emulsion technique. The polymers and drug are dissolved or dispersed in aqueous medium followed by dispersion in organic medium e.g. oil, results in formation of globules, and then the dispersed globule are cross linked by either of heat or by using the chemical cross-linkers. The chemical cross-linkers used are formaldehyde, glutaraldehyde, diacid chloride etc.

Ionotropic Gelation [39].

Using this method Microspheres are formed by dissolving the gel-type polymers, such as alginate, in an aqueous solution followed by suspending the active ingredient in the mixture and extruding the solution through needle to produce micro droplets which fall into a hardening solution containing calcium chloride under stirring at low speed. Divalent calcium ions present in the hardening solution crosslink the polymer, forming gelled microspheres.

Phase Inversion Method

The method involves addition of drug into dilute polymeric solution, in methylene chloride; and resultant mixture is poured into an unstirred bath of strong non-solvent, petroleum ether, in a ratio of 1: 100. Microspheres produced are then clarified, washed with petroleum ether and air dried [40].

Spray Drying [41, 42].

This method involves dissolving/dispersing of the drug into the polymer solution which is then spray dried. By this method the size of microspheres can be controlled by manipulating the rate of spraying, feeding rate of polymer drug solution, nozzle size, and the drying temperature.

Solvent removal method

It is a non-aqueous method of microencapsulation, also suitable for water labile polymers such as the polyanhydrides. Carino and co-workers used this method for preparing microspheres. In this method, drug was dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride. This mixture was then suspended in silicone oil containing Span 85 and methylene chloride. After pouring the polymer solution into silicone oil, petroleum ether was added and stirred until solvent was extracted into the oil solution. The resulting microspheres were then dried under vacuum [43].

Hot melt method

In this method, the polymer was first melted and then mixed with solid particles of the drug that had been sieved to less than 50 μ*m* . The mixture was suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5 °C above the melting point of the polymer. When the emulsion was stabilized it was left for cooling until the polymer particles solidified. The resulting microspheres were washed with petroleum ether. The main objective for developing this method was to develop a microencapsulation process suitable for the water labile polymers, e.g., polyanhydrides. Microspheres with diameter of 1-1000 μ*m* could be obtained and the size distribution could be easily controlled by changing the stirring rate. The major limitation of this method is that it is not suitable for thermolabile substances [44].

DRUG LOADING TECHNIQUES IN MICROSPHERES [45].

The drugs are loaded in the microspheres principally using two methods i.e. during the preparation of the microsphere or after the preparation of the microsphere by incubating them with the drug solution. The active components may be loaded by means of the physical entrapment, chemical linkage and surface absorption. It was found that maximum of drug loading in microspheres may be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables like presence of additives, method of preparation, heat of polymerization, agitation intensity etc. The loading of drug after the preparation of microspheres may be achieved by incubating them with high concentration of the drug in a suitable solvent. Here drug may be loaded in the microspheres via penetration

or diffusion of the drug through the pores present in the microsphere as well as by absorption

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[46].

Literature review on mucoadhesive microspheres

Sr.no	Drug used	Indication	Polymer used	Result	Ref
1	Nifidipine	Anti-hypertensive	HPMC, Carbapol	Mucoadhesive microspheres of nifidipine showed good controlled release properties and polymer used showed good entrapment efficiency	47
2	Ramipril	Hypertension Myocardial-infraction	Chitosan, Ethylcellulose	Mucoadhsive microspheric preparation of Ramipril prolonged the Gastrointestinal residence time and slow release of drug	48
3	Repaglinide	Antidiabetic	EudragitRS100chitosan	It has been concluded that drug loaded mucoadhesive microspheres are suitable delivery systems for Repaglinide	49
4	Cephalexin	Treatment of respiratory tract infection	Sodium alginate, Guargum	Improved bioavailability of cephalexin and decrease the frequency of dosage form administration	50
5	Simvastatin	Hypolipidemic	Carbopol 940P, sodium CMC, Guargum, HPMC, sodium alginate, ethyle cellulose, methyl cellulose, xanthan gum	Mucoadhesive microspheres of simvastratin were prepared and drug release was diffusion controlled	51
6	Rantidine hydrochloride	Gastroretentive	Chitosan and sodiumcarboxy methyl Celluloe	Mucoadhesive microspheres of rantidine hydrochloride were prepared	52
7	Amoxicillin	Anti-helicobactor pylori for gastric and duodenal ulcer	Carboxyvinyl polymer	Amoxicillin administration in the form of amoxicillin mucoadhesive microspheres more effectively cleared H.pylori than in the form of suspention.	53
8	Propanolol hydrochloride	hypertension	Sodium carboxy methyl cellulose, carbopol 934P, HPMC	It has been concluded that mucoadhesive microspheres can successfully design for sustain delivery of propanolol hydrochloride and improve patient compliance	54
9	Glipizide	Anti diabetic	Sodium alginate	By using sodium alginate mucoadhesive microspheres of glipizide should increase thelength of stay of glipizide for the treatment of diabetes.	55

CONCLUSION:

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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