REVIEW ARTICLE

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# Mucoadhesive Microspheres and Microcapsules: Current Status

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**Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesive microspheres and microcapsules 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/or better therapeutic performance of drugs. In recent years such mucoadhesive microspheres have been developed for oral, buccal, nasal, ocular, rectal and vaginal routes for either systemic or local effects. The principles underlying the development of mucoadhesive microspheres and the research work carried out on these systems are reviewed here.**

## MUCOADHESIVE MICROSPHERES AND MICROCAPSULES

Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the health care system. Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, Nanoparticles and liposomes, which modulate the release and absorption characteristics of the drug. Microspheres constitute an important part of these particulate DDS by virtue of their small size and efficient carrier characteristics. However, the success of these novel DDS is limited due to their short residence time at the site of absorption. It would, therefore, be advantageous to have means for providing an intimate contact of the DDS with absorbing membranes. It can be achieved by coupling mucoadhesion characteristics to microspheres and developing novel delivery systems referred to as mucoadhesive microspheres.

## MUCOADHESION AND MUCOADHESIVE DRUG DELIVERY SYSTEMS

Mucoadhesive drug delivery systems are delivery systems which utilize the property of bioadhesion of certain polymers which become adhesive on hydration[1] and hence can be used for targeting a drug to a particular region of the body for extended periods of time[2]. Bioadhesion is a phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces[3]. The attachment could be between an artificial material and biological substrate, such as adhesion between a polymer and a biological membrane. In the case of polymer attached to the mucin layer of a mucosal tissue, the term mucoadhesion is used. The mucosal layer lines a number of regions of the body including the gastrointestinal tract, the urogential tract, the airways, the ear, nose and eye. These represent potential sites for attachment of bioadhesive system and hence, the mucoadhesive drug delivery systems could be designed for buccal, oral, vaginal, rectal, nasal and ocular routes of administration.

## ADVANTAGES OF MUCOADHESIVE SYSTEMS

Mucoadhesive systems have three distinct advantages when compared to conventional dosage forms. First, the mucoadhesive systems are readily localized in the region applied to improve and enhance the bioavailability of drugs. Greater bioavailability of piribedil[4], testosterone and its esters[5], vasopressin[6], dopamine[7], insulin[8] and gentamycin[9] was observed from mucoadhesive dosage systems. Second, these dosage forms facilitate intimate contact of the

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formulation with underlying absorption surface. This allows modification of tissue permeability for absorption of macromolecules, such as peptides and proteins. Inclusion of penetration enhancers such as sodium glycocholate[10], sodium taurocholate and L- lysophosphotidyl choline (LPC)[11] and protease inhibitors in the mucoadhesive dosage forms resulted in the better absorption of peptides and proteins and third, the mucoadhesive dosage forms also prolong residence time of the dosage form at the site of application and absorption to permit once or twice a day dosing[12].

## MUCOADHESIVE MICROSPHERES

Mucoadhesive microspheres include microparticles and microcapsules (having a core of the drug) of 1-1000 μm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it, respectively[13]. Microspheres, in general, have the potential to be used for targeted and controlled release drug delivery; but coupling of mucoadhesive properties to microspheres has additional advantages, e.g. 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, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesives and antibodies on the surface of the microspheres.

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. Application of mucoadhesive microspheres to the mucosal tissues of ocular cavity, gastric and colonic epithelium is used for administration of drugs for localized action. Prolonged release of drugs and a reduction in frequency of drug administration to the ocular cavity can highly improve the patient compliance. The latter advantage can also be obtained for drugs administered intra-nasally due to the reduction in mucociliary clearance of drugs adhering to nasal mucosa. Microspheres prepared with mucoadhesive and bioerodable polymers undergo selective uptake by the M cells of Peyer patches in gastrointestinal (GI) mucosa. This uptake mechanism has been used for the delivery of protein and peptide drugs, antigens for vaccination and plasmid DNA for gene therapy. Moreover, by keeping the drugs in close proximity to their absorption window in the GI mucosa, these mucoadhesive microspheres improve the absorption and oral bioavailability of drugs like furosemide and riboflavin. The concept of a non-invasive single shot vaccine, by means of mucosal immunization, offers controlled release of antigens and thus forms another exquisite application of mucoadhesive microspheres.

## POLYMERS USED FOR MUCOADHESIVE MICROSPHERES

The properties of the mucoadhesive microspheres, e.g. their surface characteristics, force of mucoadhesion, release pattern of the drug, and clearance, are influenced by the type of polymers used to prepare them. Suitable polymers that can be used to form mucoadhesive microspheres include soluble and insoluble, non-biodegradable and biodegradable polymers. These can be hydrogels or thermoplastics, homopolymeres, copolymers or blends, natural or synthetic polymers.

## CLASSIFICATION OF POLYMERS

### Hydrophilic polymers, hydrogels and thermoplastic polymers:

Hydrophilic polymers are the water-soluble polymers that swell indefinitely in contact with water and eventually undergo complete dissolution. Hydrogels are water swellable materials, usually a cross-link polymer with limited swelling capacity. Thermoplastic polymers include the non-erodible neutral polystyrene and semi crystalline bioerodible polymers, which generate the carboxylic acid groups as they degrade, e.g. polyanhydrides and polylactic acid. Various synthetic polymers used in mucoadhesive formulations include polyvinyl alcohol, polyamides, polycarbonates, polyalkylene glycols, polyvinyl ethers, esters and halides, polymethacrylic acid, polymethylmethacrylic acid, methylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose and sodium carboxymethylcellulose.

Various biocompatible polymers used in mucoadhesive formulations include cellulose-based polymers, ethylene glycol polymers and its copolymers, oxyethylene polymers, polyvinyl alcohol, polyvinyl acetate and esters of hyaluronic acid. Various biodegradable polymers used in mucoadhesive formulations are poly (lactides), poly(glycolides),poly(lactide-co-glycolides), polycaprolactones, and polyalkyl cyanoacrylates. Polyorthoesters, polyphosphoesters, polyanhydrides, polyphosphazenes are the recent additions to these polymers.

### Specific site directed bioadhesives- the next generation:

The specific mucosal surfaces can be targeted using site-specific chemical agents that are anchored onto the polymeric DDS. The first generation mucoadhesive poly-

TABLE 1: SPECIFIC LIGANDS TO THE GLYCOSAL GROUPS ON CELL MEMBRANES FOR TARGETING MUCOADHESIVE MICROSPHERES

| Glycosyl groups on cell membranes | Specific ligands | Specific site |
|---|---|---|
| Mannose | *Galanthus nivalis* agglutinin (GNA) | Epithelial cells in stomach, caecum, and colon |
| N-Acetylglucosamine | Wheat germ agglutinin (WGA) | Epithelial cells in stomach, caecum, colon and absorptive enterocytes in small intestine |
| | *Lycopersicon esculentum* or tomato lectin (LEA) | Strong binding to M cells |
| N-Acetylglucosamine | Lectin ML-1 from Visum album | Endocytosed by villus enterocytes and goblet cells strong binding to epithelial cells in small intestine |
| Phytohaemagglutinin | *Phaseolus vulgaris* isoagglutinin | Surface cells of the stomach |
| Fucose | Aleuria aurentia agglutinin (AAA) | Specific binding and transcytosis by M cells |

mers lack specificity and can bind to any mucosal surface. This limits their use for fabrication of mucoadhesive drug delivery system for a particular tissue. However, the development of polymers and microspheres grafted with mucus or cell-specific ligands have increased therapeutic benefit and made site-specific drug delivery possible Table 1. Any ligand with a high binding affinity for mucin can be covalently linked to the microspheres and be expected to influence the binding of microspheres. Targeting of the drugs can be achieved by using the following ligands.

**Lectins:**

Lectins can be defined as proteins of non-immune origin that bind to carbohydrates specifically and non covalently. Lectins can increase the adherence of microparticules to the intestinal epithelium and enhance penetration of drugs. They may be used to target therapeutic agents for different gut components or even for different cells (e.g. complex-specific lectins for parietal cells or fucose-specific lectins for M cells). A bioinvasive mechanism has been described for the activity of lectins as targeting moieties. After binding to specific cells, the lectins undergo cellular uptake and subsequently can also exhibit strong binding to nuclear pore membranes[14]. Polystyrene microparticules coated with tomato lectin were shown to be specifically adhesive to enterocytes[15]. Tomato lectin is a potential targeting moiety due to its low toxicity and high specificity, but its inactivation due to cross-reactivity with mucus limits its usefulness. The potential of tomato lectin can, however, be tapped by exploiting its cellular uptake for drug delivery[16]. The other useful lectin ligands include lectins isolated from: *Abrus precatroius, Agaricus bisporus, Anguilla anguilla, Arachis hypogaea, Pandeiraea simplicifolia*, and *Bauhinia purpurea*. Lectin-mediated drug delivery is being regarded as a promising approach for peroral specific mucoadhesive formulations. The use of lectins for targeting drugs to tumor tissue is currently under intensive investigation as the human carcinoma cell lines exhibit higher lectin binding capacity than the normal human colonocytes[15].

**Bacterial adhesions:**

Bacteria are able to adhere to epithelial surfaces of the enterocytes with the aid of fimbriae. Fimbriae are long, lectin like proteins found on the surface of many bacterial strains. Their presence has been correlated with pathogencity, e.g adherence of *Escherichia coli* to the brush border of epithelial cells mediated by K99 fimbriae is a prerequisite for subsequent production and cellular uptake of *E. coli* enterotoxin. Thus, the DDS based on bacterial adhesion factors could be an efficient mechanism to increase adhesion of mucoadhesive microspheres to epithelial surfaces[17]. Another study[18] envisaging the importance of bacterial adhesion has been carried out using invasion, which is a membrane protein from *Yersinia pseudotuberculosis*.

Cellular uptake of polymeric nanospheres functionalized with invasion has been observed using confocal laser scanning microscopy.

**Amino acid sequences:**

Certain amino acid sequences have complementary parts on the cell and mucosal surfaces and when attached to microparticles can promote binding to specific cell surface glycoproteins. The cell surface glycoproteins are altered in the presence of disease conditions and these altered protein sequences can be targeted by complementary amino acid sequences attached to the drug delivery device.

**Antibodies:**

Antibodies can be produced against selected molecules present on mucosal surfaces. Due to their high specificity, antibodies can be a rational choice as a polymeric ligand for designing site-specific mucoadhesives. This approach can be useful for targeting drugs to tumor tissues.

## PREPARATION OF MUCOADHESIVE MICROSPHERES

**Solvent evaporation:**

It is the most extensively used method of microencapsulation, first described by Ogawa *et al.*[19]. A buffered or plain aqueous solution of the drug (may contain a viscosity building or stabilizing agent) is added to an organic phase consisting of the polymer solution in solvents like dichloromethane (or ethyl acetate or chloroform) with vigorous stirring to form the primary water in oil emulsion. This emulsion is then added to a large volume of water containing an emulsifier like PVA or PVP to form the multiple emulsions (w/o/w). The double emulsion, so formed, is then subjected to stirring until most of the organic solvent evaporates, leaving solid microspheres. The microspheres can then be washed, centrifuged and lyophilize to obtain the free flowing and dried microspheres.

**Hot melt microencapsulation:**

This method was first used by Mathiowitz and Langer[20] to prepare microspheres of polyanhydride copolymer of poly[bis(*p*-carboxy phenoxy) propane anhydride] with sebacic acid. In this method, the polymer is first melted and then mixed with solid particles of the drug that have been sieved to less than 50 μm. The mixture is suspended in a non-miscible solvent (like silicone oil), continuously stirred, and heated to 5° above the melting point of the polymer. Once the emulsion is stabilized, it is cooled until the polymer particles solidify. The resulting microspheres are washed by decantation with petroleum ether. The primary objective for developing this method is to develop a microencapsulation process suitable for the water labile polymers, e.g. polyanhydrides. Microspheres with diameter of 1-1000 μm can be obtained and the size distribution can be easily controlled by altering the stirring rate. The only disadvantage of this method is moderate temperature to which the drug is exposed.

**Solvent removal:**

It is a non-aqueous method of microencapsulation, particularly suitable for water labile polymers such as the ployanhydrides. In this method, drug is dispersed or dissolved in a solution of the selected polymer in a volatile organic solvent like methylene chloride. This mixture is then suspended in silicone oil containing span 85 and methylene chloride[21]. After pouring the polymer solution into silicone oil, petroleum ether is added and stirred until solvent is extracted into the oil solution. The resulting microspheres can then be dried in vacuum.

**Hydrogel microspheres:**

Microspheres made of gel-type polymers, such as alginates, are produced by dissolving the polymer in an aqueous solution, suspending the active ingredient in the mixture and extruding through a precision device, producing micro droplets which fall into a hardening bath that is slowly stirred. The hardening bath usually contains calcium chloride solution, whereby the divalent calcium ions crosslink the polymer forming gelled microspheres. The method involves an all-aqueous system, which eliminates residual solvents in microspheres. Lim and Moss[22] developed this method for encapsulation of live cells, as it does not involve harsh conditions, which could kill the cells. The surface of these microspheres can be further modified by coating them with polycationic polymers, like polylysine after fabrication. The particle size of microspheres can be controlled by using various size extruders or by varying the polymer solution flow rates.

**Spray drying:**

In this process, the drug may be dissolved or dispersed in the polymer solution and spray dried. The quality of spray-dried microspheres can be improved by the addition of plasticizers, e.g. citric acid, which promote polymer coalescence on the drug particles and hence promote the formation of spherical and smooth surfaced microspheres. The size of microspheres can be controlled by the rate of spraying, the

feed rate of polymer drug solution, nozzle size, and the drying temperature. This method of microencapsulation is particularly less dependent on the solubility characteristics of the drug and polymer and is simple, reproducible, and easy to scale up[23].

**Phase inversion microencapsulation:**

The process involves addition of drug to a dilute solution of the polymer (usually 1-5%, w/v in methylene chloride). The mixture is poured into an unstirred bath of strong non-solvent (petroleum ether) in a solvent to non-solvent ratio of 1:100, resulting in the spontaneous production of microspheres in the size range of 0.5-5.0 μm can then be filtered, washed with petroleum ether and dried with air[24]. This simple and fast process of microencapsulation involves relatively little loss of polymer and drug.

## EVALUATION OF MUCOADHESIVE MICROSPHERES

The best approach to evaluate mucoadhesive microspheres is to evaluate the effectiveness of mucoadhesive polymer to prolong the residence time of drug at the site absorption, thereby increasing absorption and bioavailability of the drug. The methods used to evaluate mucoadhesive microspheres include the following.

**Measurement of adhesive strength:**

The quantification of the mucoadhesive forces between polymeric microspheres and the mucosal tissue is a useful indicator for evaluating the mucoadhesive strength of microspheres. *In vitro* techniques have been used to test the polymeric microspheres against a variety of synthetic and natural mucus, frozen and freshly excised tissue etc. The different *in vitro* methods include the following.

**Tensile stress measurement, Wilhelmy plate technique:**

The wilhelmy plate technique is traditionally used for the measurement of dynamic contact angles and involves the use of a microtensiometer or microbalance. The Cahn dynamic contact angle analyzer (model DCA 322, Cahn Instruments, Cerritos) has been modified to perform adhesive micro force measurements. The DCA 322 system consists of an IBM compatible computer and microbalance assembly[25]. The microbalance unit consists of stationary sample and tare loops and a motor powered translation stage. The instrument measures the mucoadhesive force between mucosal tissue and a single microsphere mounted on a small diameter metal wire suspended from the sample loop in microtesiometer[26]. The tissue, usually rat jejunum, is mounted within the tissue chamber containing Dulbecco's phosphate buffered saline containing 100 mg/dl glucose and maintained at the physiologic temperature. The chamber rests on a mobile platform, which is raised until the tissue comes in contact with the suspended microsphere. The contact is held for 7 min, at which time the mobile stage is lowered and the resulting force of adhesion between the polymer and mucosal tissue recorded as a plot of the load on microsphere versus mobile stage distance or deformation. The plot of output of the instrument is unique in that it displays both the compressive and the tensile portions of the experiment. By using the Cahn soft ware system, three essential mucoadhesive parameters can be analyzed. These include the fracture strength, deformation to failure and work of adhesion.

Fracture strength is the maximum force per unit surface area required to break the adhesive bond. Deformation to failure is the distance required to move the stage before complete separation occurs. This parameter is dependent on the material stiffness and the intensity of strength of adhesion. Work of adhesion is a function of both the fracture strength and the deformation to failure. It tends to be the strongest indicator of the bioadhesive potential.

This technique allows the measurement of mucoadhesive properties of a candidate material in the exact geometry of the proposed microsphere delivery device and the use of a physiological tissue chamber mimics the *in vivo* conditions. From a single tensile experiment, 11 mucoadhesive parameters can be analyzed out of which 3 are direct predictors of the bioadhesive potential[27].

The Cahn instrument, although a powerful tool has inherent limitations in its measurement technique, makes it better suited for large microspheres (with a diameter of more than 300 μm) adhered to tissue *in vitro*. Therefore, many new techniques have been developed to provide quantitative information of mucoadhesive interactions of the smaller microspheres.

**Novel electromagnetic force transducer (EMFT):**

The EMFT is a remote sensing instrument that uses a calibrated electromagnetic to detach a magnetic loaded polymer microsphere from a tissue sample[28]. It has the unique ability to record remotely and simultaneously the tensile force information as well as high magnification video images of mucoadhesive interactions at near physiological conditions. The EMFT measures tissue adhesive forces by

monitoring the magnetic force required to exactly oppose the mucoadhesive force. To test a microsphere, it must first be attached to the sample of tissue; magnetic force is then generated by an electromagnet mounted on the microscope vertically above the tissue chamber. After the computer has calculated the position of microsphere, the tissue chamber is slowly moved down, away from the magnet tip. As the tissue slowly descends away from the magnet, the video analysis continuously calculates the position of microsphere until the latter is completely pulled free of the tissue. The computer can display the results either as raw data or convert it to a force versus displacement graph. The primary advantage of the EMFT is that no physical attachment is required between the force transducer and the microsphere. This makes it possible to perform accurate mucoadhesive measurements on the small microspheres, which have been implanted *in vivo* and then excised (along with the host tissue) for measurement. This technique can also be used to evaluate the mucoadhesion of polymers to specific cell types and hence can be used to develop MDDS to target-specific tissues.

**Shear stress measurement:**

The shear stress measures the force that causes a mucoadhesive to slide with respect to the mucus layer in a direction parallel to their plane of contact[29]. Adhesion tests based on the shear stress measurement involve two glass slides coated with polymer and a film of mucus. Mucus forms a thin film between the two polymer coated slides, and the test measures the force required to separate the two surfaces. Mikos and Peppas[30] designed the *in vitro* method of flow chamber. The flow chamber made of Plexiglass is surrounded by a water jacket to maintain a constant temperature. A polymeric microsphere placed on the surface of a layer of natural mucus is placed in a chamber. A simulated physiologic flow of fluid is introduced in the chamber and movement of microsphere is monitored using video equipment attached to a goniometer, which also monitors the static and dynamic behavior of the microparticule[27].

**Adhesion number:**

Adhesion number for mucoadhesive microspheres is determined as the ratio of the number of particles attached to the substrate to the total number of applied particles, expressed as a percentage. The adhesion strength increases with an increase in the adhesion number.

**Falling liquid film method:**

It is a simple, quantitative in situ method, wherein an excised intestinal segment cut lengthwise, is spread on a plastic flute and positioned at an incline. The suspension of microsphere is allowed to flow down the intestinal strip. Particle concentrations entering the segment from the dilute suspension reservoir and leaving the intestinal segment can be determined with the help of coulter counter to quantify the steady state fraction of particles adhered to the intestinal mucosa. The percent of particles retained on the tissue is calculated as an index of mucoadhesion[31].

**Everted sac technique:**

The everted intestinal sac technique is a passive test for mucoadhesion and involves polymeric microspheres and a section of the everted intestinal tissue. It is performed using a segment of intestinal tissue excised from the rat, everted, ligated at the ends and filled with saline. It is then introduced into a tube containing a known amount of the microspheres and saline, and agitated while incubating for 30 min. Sac is then removed, microspheres are washed and lyophilized, and the percentage of binding to the sac is calculated from difference in the weight of the residual spheres from the original weight of the microspheres.

The advantage of the technique is that no external force applied to the microspheres being tested; microspheres are freely suspended in buffer solution and made to come in contact with the everted intestinal tissue randomly. The Cahn technique and the everted intestinal sac technique, both predict the strength of mucoadhesion in a very similar manner. Santos *et al.*[26] established a correlation between the two *in vitro* mucoadhesion assay methods which thereby allows one to confidentially utilize a single mucoadhesion assay to scan a variety of mucoadhesive polymers.

## *IN VIVO* TECHNIQUES OF EVALUATION

**Measurement of the residence time:**

Measurements of the residence time of mucoadhesives at the application site provide quantitative information on their mucoadhesive properties. The GI transit times of many mucoadhesive preparations have been examined using radioisotopes and fluorescent labeling techniques.

**GI transit using radio-opaque microspheres:**

It is a simple procedure involving the use of radio-opaque markers, e.g. barium sulfate, encapsulated in mucoadhesive polymers to determine the effects of mucoadhesive polymers on GI transit time. Faeces collection (using an automated faeces collection machine) and X-ray inspection provide a non-invasive method of moni-

TABLE 2: RESEARCH WORK ON MUCOADHESIVE MICROSPHERES AND MICROCAPSULES

| Drug | Polymer | Route | Purpose/Result |
|---|---|---|---|
| Acyclovir[34] | Chitosan | Ocular | Slow release rates increased AUC |
| Methyl prednisolone[35] | Hyaluronic acid | Ocular | Slow release rates, sustained drug concentration in tear fluids |
| Gentamicin[36] | DSM+ LPC | Nasal | Increase nasal absorption |
| Insulin[36] | DSM+ LPC | Nasal | Effective delivery of insulin into the systemic circulation via nasal route |
| Human growth hormone (hGH)[37] | DSM+ LPC | Nasal | Rapid and increased absorption |
| Desmopressin[38] | Starch | Nasal | Addition of LPC causes a five folds increase in Cmax and two folds increase in bioavailability |
| Haemagglutinin (HA) obtained from influenza A virus[39] | HYAFF | Nasal | With mucosal adjuvant:-ed serum IgG antibody response as compared to i.m. immunization |
| Beclomethasone[40] | HPC | Nasal | Increasing the bioavailability |
| Gentamicin[41] | HA/Chitosan | Nasal | Improving the bioavailability |
| Gentamicin[42] | HPMC | Nasal | Increasing the absorption |
| Furosemide[43] | AD-MMS (PGEFs) | GI | Increased bioavailability<br>Higher AUC<br>Effective absorption from the absorption window |
| Riboflavin | AD-MMS (PGEFs) | GI | ——— |
| Amoxicillin | AD-MMS (PGEFs) | GI | Greater anti *H. pylori* activity |
| Delapril hydrochloride (prodrug)[44] | PGEFs | GI | MRT of drug is increased plasma concentrations of the active metabolite are sustained |
| Amoxicillin[45] | Polycarbopol /Carbopol 934/Ion exchange resin | GI | Greater anti *H. pylori* activity |
| Cephradine[46] | Chitosan/ethylcellulose | GI | Prolonged the intestinal absorption |
| Vancomycin[47] | PGEF coated with Eudragit S 100 | Colonic | Well absorbed even without absorption enhancers |
| Insulin[47] | PGEF coated with Eudragit S 100 | Colonic | Absorbed only in the presence of absorption enhancers, e.g. EDTA salts |
| Nerve growth factor (nGF)[48] | HYAFF | Vaginal | Increased absorption from HYAFF microspheres as compared to aqueous solution of the drugs |
| Insulin[49] | HYAFF | Vaginal | Increased absorption from HYAAF microspheres as compared to aqueous solution of the drugs |

| Drug | Polymer | Route | Purpose/Result |
|---|---|---|---|
| Salmon calcitonin[33] ous | HYAFF | Vaginal | Increased absorption from HYAAF microspheres as compared to aque-solution of the drugs |
| Acriflavine[50] | MC/Sodium CMC/Alginate/ Carbopol 974 | Vaginal | Controlled release |
| Pipedimic acid[51] | CMC as mucopolysaccharide+ EudragitRL as matrix polymer | Vesical | ——— |
| Indomethacin[52] | Alginate+ Sodium CMC/MC/ Carbopol/HPMC | Oral | Slow release rates |
| Glipizide[53] | Alginate+ Sodium CMC/MC/ Carbopol/HPMC | Oral | Slow release rates |

AD-MMS: adhesive micromatrix system., AUC: area under curve., CMC: carboxy methyl cellulose., DSM: degradable starch microspheres., EDTA: ethylenediaminetetraacetic acid., GI: gastrointestinal., HYAFF: hyaluronic acid esters., IgG: immunoglobulin G., i.m.: intramuscular., LPC: lysophosphatidylcholine., MRT: mean residence time., PEGs: polyglycerol esters of fatty acids., MC: methylcellulose., HPC: hydroxypropylcellulose., HPMC: hydroxypropylmethylcellulose., HA: hyaluronic acid and alginate: sodium alginate.

toring total GI residence time without affecting normal GI motility. Mucoadhesives labeled with Cr-51, Tc-99m, In-113m, or I-123 have been used to study the transit of the microspheres in the GI tract[32].

**Gamma scintigraphy technique:**

Distribution and retention time of the mucoadhesive intravaginal microspheres can be studied using the gamma scintigraphy technique. A study has reported the intensity and distribution of radioactivity in the genital tract after administration of technetium labeled hyaluronic acid esters (HYAFF) microspheres. Dimensions of the vaginal cavity of the sheep can be outlined and imaged using labeled gellan gum and the data collected is subsequently used to compare the distribution of radiolabelled HYAFF formulations. The retention of mucoadhesive-radiolabelled microspheres based on HYAFF polymer was found to be more for the dry powder formulation than for the pessary formulation after 12 h of administration to vaginal epithelium[33].

The combination of sheep model and gamma scintigraphy method has been proved to be an extremely useful tool for evaluating the distribution, spreading and clearance of vaginally administered mucoadhesive drug delivery systems (MDDS), including microbicides.

**Surface characterization of the mucoadhesive microspheres:**

Surface morphology of microspheres and the morphological changes produced through polymer degradation can be investigated and documented using scanning electron microscopy (SEM), electron microscopy and scanning tunneling microscopy (STM). To assess the effect of surface morphology on the mucoadhesive properties, the microsphere samples are lyophilized and analyzed under SEM at 150X and 1000X. The smooth texture of the microsphere surface leads to weak mucoadhesive properties, while the coarser surface texture improves the adhesion through stronger mechanical interactions. The morphological surfaces changes occurring due to the hydrolytic degradation of the polymers, e.g. polyanhydrides can be studied after incubating the microspheres in the PBS buffer for different intervals of time[32].

## RECENT MUCOADHESIVE MICROSPHERE AND MICROCAPSULE RESEARCH

During the last one decade much research work has been done on mucoadhesive microspheres and microcapsules for various routes of drug administration. The primary objectives are to provide an intimate contact of the

dosage form with the absorbing surface and to increase the residence time of the dosage form at the absorbing surface to prolong drug action. Though oral route is the most commonly employed route of drug administration, it is not suitable for drugs which are susceptible to gut and/or hepatic metabolism and also for drugs which cause gastrointestinal side effects. As such mucoadhesive dosage forms are developed for other routes of drug administration such as buccal, nasal and vaginal routes which avoid the disadvantages of oral route. The bioavailability and duration of action of drugs administered by these routes are increased by use of the principle of mucoadhesion. Research work on mucoadhesive microspheres and microcapsules is summarized in Table 2.


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