EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 10
93-110
Year: 2018

MUCOADHESIVE MICROSPHERES: A PROMISING APPROACH FOR ORAL DRUG DELIVERY

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Article Received on 12/08/2018 **Article Revised on 02/09/2018** **Article Accepted on 22/09/2018**

ABSTRACT
Mucoadhesive microspheres are one of the most promising novel techniques for drug delivery. Mucoadhesive systems offer a sustained drug release method, thus enhancing drug absorption in a site-specific manner. Microspheres have very small sizes and provide efficient carrier capacities. Mucoadhesive systems therefore play a vital role in drug delivery systems. Mucoadhesive microspheres interact with mucous of gastrointestinal tract (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. Mucoadhesion is a two-step procedure, and its mechanism can be explained by combining theories of wetting, mechanical interlocking, electronic transfer, adsorption, fracture, and diffusion interpenetration, as deemed suitable. Mucoadhesive microspheres offer added advantages of reliability, safety, specificity, prolonged action, delayed release, and enhanced activity. These systems can be prepared by solvent evaporation, ionotropic gelation, emulsion solvent diffusion, spray drying, and solvent removal. The resulting microspheres are characterized using a number of parameters using in vivo and in vitro techniques. This review article gives an overview of mucoadhesive microspheres, preparation methods, characterization, applications, and recent developments.

KEYWORDS: Microspheres, mucoadhesion, mucoadhesion theories, mucoadhesive polymers and evaluation methods.

INTRODUCTION
Drug-related activity may be enhanced by novel drug delivery systems, such as the mucoadhesive microspheres. Since these systems are in intimate contact with absorption tissue and the mucous membrane, an increase in bioavailability and therefore local as well as systematic effects is noted as a result of dug release right on the action site. Despite the ability of restraining and localizing the system at GIT, the most preferred drug administration route continues to be oral because of its convenience. Microspheres have become a vital part of such oral systems because of their small size, ranging from 1 to 1000µm and high carrier capacity. Microspheres are drug cores with outer layers of an inert polymer. However, the main drawback of these systems is short residence time. Combining bioadhesion properties to microspheres results in mucoadhesive microspheres, which resolve this problem by providing enhanced and efficient contact with absorption membrane. Mucoadhesive microspheres efficiently target drugs to the absorption site by adhering to mucosal tissue of GIT. Microspheres are not only effective for long duration diseases, but they have also attracted interest for targeting anticancer drugs to the tumor. These systems also boost a high surface to volume ratio, and biodegradable polymers undergo selective uptake by the microfold cells (M cells) of payer patches in gastrointestinal (GI) mucosa. This uptake mechanism has been used for the delivery of high molecular weight drugs such as proteins, peptides, and antigens.[1]

Anatomy of mucosal membrane and mechanisum of mucoadhesion
Secretion volume of mucus is influenced by internal and external factors and can be either constantly or intermittently secreted. Mucus facilitates movement in the GI tract and secures it from harms that may occur due to intrinsic peristaltic movements and photolytic enzymes. The most important constituents of mucus are mucins or glycoproteins, as traits of gelatinous structure, cohesion and antiadhesion. Regardless of the body sites of secretion, usually glycoproteins are of almost similar structure. These are highly glycosylated proteins having molecular weights as high as 0.5 million. Almost 800-

4500 amino acid residues are contained in the polypeptide chain and are their characterization is done by two areas types-strongly glycosylated areas and areas lacking carbohydrate side chains. If glycolyzed, molecules become more resistant to proteolytic hydrolysis. Glycoproteins consist of a large number of loops, forming a branched three-dimensional network. Large mucus in oligomers owing to the formation of disulfide bonds are formed because of end domains of glycoprotein. These areas (C-and N-) contain greater than 10% cysteine. In each glycoprotein molecule, there are more than 200 carbohydrate chains are responsible for more than 80% molecular weight, each side chain having 2-20 sugar residues. The charge on these chains is negative at physiological pH values as they terminate with either sialic acid or fructose.

Figure 1 shows the mucous membrane structure at mouth. The mucous gelatinous layer provides a hood on epithelium. Below it, the connective tissue or lamina propria is present, having plentiful amount of blood and lymph vessels; and under it is a thin smooth muscle tissue layer. The mucus layer has variable thicknesses in different mucosal tissue surfaces, and it ranges from less than 1 *u*m in the oral cavity to 50–500 *u*m in the stomach. Secretion volume of mucus is influenced by internal and external factors and can be either constantly or intermittently secreted. Mucus facilitates movement in the GI tract and secures it from harms that may occur due to intrinsic peristaltic movements and proteolytic enzymes. The most important constituents of mucus are mucins or glycoproteins, as traits of gelatinous structure, cohesion, and antiadhesion owe to these. Human mucins are classified as secreted mucins and anchored mucins. Anchored mucins are those which are bound to membrane, whereas secreted mucus in further divided as soluble or gel forming. The glycosylated region, depending on count of repeat sequences, can measure 200-500 µm in length from cell surface. Mucus mainly protects and lubricates the supporting epithelial layer.[2]

The mechanism of mucoadhesion, of polymers or macromolecules with the surface of mucus membrane has not been properly understood yet. But it is known that the forces of attraction must overcome the forces of repulsion for successful utilization. For close contact and increased surface area, the diffusion of the substrate chains has to be promoted and, therefore, the mucoadhesive must properly spread on the substrate. For example, surface water can attract a partially hydrated polymer and result in its absorption by the substrate. While studying the mechanism of mucoadhesion, we can see it in figure 2. As a two-stage procedure. First, there is a contact stage followed by the consolidation stage. In the first stage, mucoadhesive and mucus membrane come into contact and in the second formulation spreads and swells, and deep contact starts with the mucus layer.

As shown in the figure 3 numerous theories have been presented to explain the mechanisms involved in mucoadhesion. These theories include mechanical-interlocking, electrostatic, diffusion–interpenetration, adsorption and fracture processes. Table 1 list undoubtedly the most widely accepted theories are founded surface energy thermodynamics and interpenetration/diffusion.[3]

Polymers for mucoadhesive microspheres

The polymeric attributes that are pertinent to high levels of retention at applied and targeted sites via mucoadhesive bonds include hydrophilicity, negative charge potential and the presence of hydrogen bond forming groups. Additionally, the surface free energy of the polymer should be adequate so that 'wetting' with the mucosal surface can be achieved. The polymer should also possess sufficient flexibility to penetrate the mucus network, biocompatible, non-toxic and economical.

The polymers that are commonly employed in the manufacturing of mucoadhesive drug delivery platforms that adhere to mucin-epithelial surfaces.

The ideal characteristics of mucoadhesive polymers are as below:

(1) Polymers that become sticky when placed in aqueous media and owe their bioadhesion to stickiness.

(2) Polymers that adhere through non-specific, non-covalent interactions that are primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).

(3) Polymers that bind to specific receptor sites on the cell surface.

As shown in the figure 4 the polymers are classified on the bases on of mucoadhesion properties which are source of the polymer, solubility of the polymer in water, charge and mechanisum of the bonding.

Methodologies used in preparation of mucoadhesive microspheres

The microspheres can be prepared by using any of the several methods described in the following section, but the choice mainly depends on the nature of the mucoadhesive polymer, the active pharmaceutical ingredient, the intended use and the therapy. Moreover, the method of preparation and its choice are equivocally determined by some formulation and technology related factors.

Solvent Evaporation

It is the most extensively used method of microencapsulation, first described by Ogawa and co-workers. In this method a buffered or plain aqueous solution of the drug contained a stabilizing or viscosity modifying agent. It was added to an organic phase having polymer solution. This resulting solution is kept for continuous stirring to form water in oil emulsion. This emulsion is then added to a large volume of water containing an emulsifier like poly vinyl alcohol (PVA) or poly vinyl pyrrolidine (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 gets evaporated, leaving solid microspheres. The obtained microspheres are washed, centrifuged and lyophilized.[4,5,6]

K.Kannan, P.K.Karar, R.Manavalan; prepared acetazolamide mucoadhesive microspheres using combination of Eudragit RL and Eudragit RS. The spherical nature of the particles is depending upon the concentration of the Eudragit polymer ratio and stirring speed.[7] Jayvadan K. Patel and Jayant R. Chavda; amoxicillin stomach-specific carbopol-934P containing mucoadhesive microspheres for anti-Helicobacter pylori infections. The microspheres are prepared by emulsion solvent evaporation method in which ethyl cellulose is used as carrier. It was observed that on increasing the amount of drug-to-polymer-to-polymer ratio the mucoadhesion was increases as the more free -COOH groups were available which are mainly responsible for binding with sialic acid groups in mucus. It was concluded that mainly carbopol-934P ratio influences the mucoadhesion.[8] Shiva Kumar Yellanki, Jeet Singh, Jawad Ali Syed et al; prepared amoxicillin trihydrate microspheres using this method which showed good mucoadhesion due to high amount of carrier polymer that is ethyl cellulose.[9] M. Cuna et al; prepared amoxycillin-loaded ion-exchange resin encapsulated in mucoadhesive polymers like polycarbophil and Carbopol 934 with oil-in-oil solvent evaporation technique. It was observed that encapsulation in like polycarbophil and Carbopol 934 was difficult as the distribution of the particles in the stomach for long period of time becomes more difficult.[10] R. Natarajan et al; atenolol mucoadhesive microspheres were prepared with the Carbopol 934P as mucoadhesive polymer and Eudragit RL100 as carrier polymer. As the carbopol 934P is highly viscous polymer to reduce the viscosity of the polymeric solution and olive oil is used as dispersion medium to minimize the aggregation of the microspheres.[11] Sang-Min cho et al; prepared chitosan and poly (acrylic acid) (PAA) mucoadhesive microspheres. The microspheres were formed due to electrostatic interaction between the carboxy groups of PAA and amine groups of the chitosan and these microspheres had higher affinity to the mucin than that of chitosan microspheres alone.[12] Paruvathanahalli Siddalingam Rajinikanth et al; clarithromycin microspheres were prepared by emulsification-solvent evaporation method in which ethyl cellulose as a matrix polymer and Carbopol 934P as mucoadhesive polymer. Floating-bioadhesive microspheres were prepared with use of calcium carbonate as gas forming agent to improve the gastric residency of the drug.[13] Adeola O. Adebisi et al; preapared clarithromycin microspheres with their surfaces functionalised with concanavalin A. Lecithin was conjugate to the microspheres using two staged carbodiimide activation though the conjugation which did not show significant influence on the drug release or buoyancy properties of the formulation but improves the mucoadhesion properties. The conjugated microspheres showed improved interaction with the porcine gastric mucin compared to unconjugated microspheres.[14] Bizhan Malaekeh-Nikouei et al; prepared chitosan-coated microspheres containing cyclosporine A. These microspheres were evaluated for percent of mucin adsorption to the surface of coated microspheres. Chitosan coating enhances the accessibility and localization to the absorptive membrane via bioadhesion.[15] Yunying Tao et al; prepared acyclovir loaded mucoadhesive microspheres using carbopol 974P NF. The studies showed that use of eggshell membrane was done to measure the in-vivo and in vitro mucoadhesion of the microspheres in place of stomach mucosa. The formulation was sustained release due gel forming ability of carbopol and solubility of the drug. Most of carboxy groups of the carbopol ionize at pH 3.6 which causes the repulsion between the anions and swelling of the polymer which influences the slow drug release.[16] Yasunori Miyazaki et al; used oppositely charged dextran derivatives and cellulose acetate butyrate (CAB) for the microsphere preparation. Maine purpose of the use of these natural oppositely charged polymers in the formulation was that they formed the polyion complexes after reacting with each other and swollen. Swelling of the polymers reduces the drug release and spreading the formulation over large surface area of the GI tract reduces the risk of dose dumping.[17] W. M. Obeidat et al; theophylline microspheres were evaluated for the effect of the polymer viscosity solution phase and other factors controlling the dissolution. Microspheres were prepared with two different cellulose acetate butyrate polymers (CAB381-2, CAB381 -20) having same chemical structure but different molecular weights. The experiment suggests that two different polymers having different viscosity in the acetone affect the release rate of the drug.[18] Arya RK et al; prepared famotidine mucoadhesive microspheres with the combination of the sodium carboxy methyl cellulose and sodium alginate. The combination of the both the polymers have significant effect on drug entrapment and release in per say to achieve the criteria of the gastroretention. Sodiumcarboxy methyl cellulose is a hydrophilic polymer due to which drug gets release immediately as the sodium alginate is use as rate controlling polymer. Alginates form high viscosity solution due to intermolecular bonding and holds the free water molecules inside the alginate matrix.[19,20] Gentamicin microspheres were prepared with hyaluronic acid and combination of hyaluronic acid and chitosan glutamate. The microspheres prepared with the hyaluronic acid alone showed more mucoadhesion than that of chitosan. Hyaluronic acid possesses plenty of hydrophilic functional groups and forms mucous glycoprotein bonds during mucoadhesion process.[21] While chitosan possesses positive charge, this would be expected to promote adhesion to both the negatively charged mucus and the underlying cell layer.[22] It was suggested that chitosan hydrates slower than hyaluronic acid in water and this would tend to oppose

mucoadhesion. Hence, the combination of the two polymers showed additional mucoadhesive capacity by penetration-enhancing effects of chitosan.[23] Jayvadan Patel et al; prepared propanol hydrochloride microspheres the concentration of emulsifying agent span 80 showed significant influence on the percentage of the mucoadhesion and drug entrapment efficiency.[24] Vandana Dhankar1 et al; single emulsion was employed to prepare ranitidine hydrochloride chitosan loaded microspheres showed that due to immediate solidification/cross-linking of the polymers occur when they come in contact with a glutaraldehyde solution. The drug will not get diffused into the surrounding aqueous medium and showed high encapsulation efficiency.[25] Yasunori Miyazaki et al; formulation theophylline microspheres was evaluated in three different formulation sustained release floating and mucoadhesive. The mucoadhesive formulation showed prolonged serum drug levels which indicates the superior levels of sustained drug delivery of the drug. The mucoadhesive polymers showed dextran sulphate and [2-(diethylamino) ethyl] dextran wasused as mucoadhesive polymers. Incorporation of these polymers in to the formulations plays important role in the water channels for the drug to diffuse out through.[26]

Emulsion solvent diffusion

Liu H, Pan W et al; prepared acyclovir mucoadhesive microspheres by emulsion solvent diffusion technique. Acyclovir rasinate were prepared by bath technique and these resinate used as core material in the preparation of mucoadhesive microspheres. Acyclovir (AV) is suspended in the ion-exchange resins. ion-exchange resins are high-molecular-weight polyelectrolytes, which can exchange mobile ions of similar charge with the surrounding medium. These resonates were prepared by bath method. The AV-loaded resins suspended in the polyethylene glycol (PEG-4000) water solution. These PEG coated AV-resinates was obtained by drying the suspension. Then the solution was added to carbopol 934 and ethanol solution which was agitated until well dispersed. The carbopol 934 was used as a main coating material. Then the suspension was added into the mixture consisting of 300 mL liquid paraffin and 20 mL Span80 drop by drop to form a suspension. The suspension was kept stirring at 40°C for 3 hours. The AV-resinate microspheres were then harvested by filtration with a 400-mesh sieve, washed with petroleum benzene, and dried at 40°C for 2 hours. The microspheres were proved to be gastric mucoadhesive and sustained-release with higher bioavailability [27]. Chun MK et al; acetaminophen microspheres were prepared by emulsion solvent diffusion and interpolymer complexation method. In the preparation poly(acrylic acid) (PAA) was used as mucoadhesion material. PAA is highly soluble polymer in order to reduce the water solubility.it is complex with proton accepting polymers such as poly (ethylene glycol), poly(ethylene glycol) macromer, poloxamer and poly(vinyl pyrrolidone) (PVP). The Poly(vinyl pyrrolidone) (PVP) forms intense hydrogen bonding interpolymer complex. It was concluded that adhesive force of microspheresis equivalent to the Carbopol. The concentration of corn oil used with span 80 in the emulsion did significantly affects particle size.[28] Myung-K wan chun et al; prepared microsphere with PAA and PVA. The complexation between PAA and PVA as a result of hydrogen bonding which was confirmed by the shift in the carbonyl absorption bands of bond PAA. The corn oil was used as external phase. As ethanol/ water mixture as internal phase is not miscible with the corn oil and the external phase. It was also observed that PAA and PVP aggregate and precipitate in ethanol and water in a relatively short period of time, resulting in the formation of a PVP/PAA inter polymer complex, suggesting that the intensity of hydrogen bonding between PAA and PVP is quite strong. The release rate of microspheres prepared with Carbopol 971 was compared with PVA microspheres. However, release rate of PVA/ PAA microspheres was much slower than that of Carbopol microspheres.[28]

Ionic gelation (hydrogel microspheres

Microspheres made of gel-type polymers, such as alginate, were produced by dissolving the polymer in an aqueous solution, suspending the active ingredient in the mixture and extruding through a precision device, producing microdroplets which were made to fall into a hardening bath, which was slowly stirred. The hardening bath usually contains calcium chloride solution, whereby the divalent calcium ions crosslink the polymer forming gelled microspheres. The method involved an "all-aqueous" system and avoided residual solvents in the microspheres.[29] The surface of these microspheres can be further modified by coating them with polycationic polymers, like polylysine after fabrication. The particle size of microspheres could be controlled by using various size extruders or by varying the polymer solution flow rates. Veenashailendrabelgamwar et al; developed atenol loaded microspheres with the mucoadhesive polymers including hydroxypropyl methylcellulose (HPMC) K15M and carbopol 971P. In this technique cross linking of sodium alginate with calcium chloride was done which are responsible for slow drug release. Sodium alginate is cross linked with $CaCl_2$ solution to release the drug in a controlled manner. Chemically, alginates are anionic block copolymer consisting monomers of d-mannuronic acid joined together by 1-4 glycosydic linkages. Bivalent alkaline earth metals like Ca_2+ undergoes ionic interaction with -COOH moiety of sodium alginate and results in cross linking of sodium alginate. On increasing the concentration of the $cacl_2$ions the cross linking of the polymer and compactness of the insoluble matrices resulting in more drug entrapment.[30] Mohammed G Ahmed et a; developed captopril microspheres by orifice gelation method with different polymers like hydroxy propyl methyl cellulose, carbopol 934P, chitosan and cellulose acetate phthalate. In various polymer ratio. Alginate-carbopol 934 P combination showed greater mucoadhesion compared to the other polymer combination.[31] Christina. et al; prepared

diclofenac sodium microspheres with sodium alginate in combination with Eudragit S100. Due to low solubility of sodium alginate and diclofenac sodium being practically insoluble in acidic medium, there was no observable release of diclofenac sodium in 0.1 N HCl. The microspheres showed sustained release effect. Up to 12 hours.[32] Figure 5 represents the systematic representation of microspheres preparation by ion gelation method.

Champak Kalita et al; prepared irinotecan microparticles using chitosan and alginate as a polyelectrolyte complex by ionotropic gelation method for sustained release of the drug.[33] Praveen Kumar Gaur et al; prepared gabapentin mucoadhesive microspheres with the use of Sodium alginate and sodium carboxymethylcellulose. It was observed that the microspheres prepared with the low concertation of polymer were of irregular shape due to poor molecular packing and cross-linking in comparison with the medium and high concentration polymers. Calcium chloride amount was considered to be at 1– 5% w/v to control the level of cross-linking between bivalent cation Ca_2+ acid group of alginate. The drug entrapment efficiency was being affected by both of the polymers but in a reciprocal mode. Entrapment efficiency was directly proportional to the amount of sodium alginate, while it was inversely proportional to the amount of sodiumcarboxy methyl cellulose.[34] Dilipkumar Pal et al; formulated mucoadhesive microspheres containing tamarind seed polysaccharide (TSP)-alginate for oral gliclazide delivery. It was proved that the drug entrapment efficiencies were appeared to decrease with increasing particle size. The release of gliclazide from TSP-alginate microspheres at gastric pH (pH 1.2) was comparatively slow and sustained than intestinal pH (pH 7.4). This was due to the shrinkage of alginate at acidic pH (as alginate is pH sensitive), which might slower the drug release from the gliclazide from TSP-alginate microspheres. The reason of the higher drug release in phosphate buffer, pH 7.4 was due to the higher swelling rate of these microspheres. In case of comparatively higher TSP containing microspheres, the more hydrophilic property of the TSP bonded better with water to form viscous gel structure, which might blocked the pores on the surface of microspheres and sustain the release profile of the drug.[35] Yueling Zhang et al; prepared insulin alginate-chitosan microspheres by membrane emulsification technique in combination with ion (Ca_2+) and polymer (chitosan) solidification. It was observed that under the pH conditions of gastrointestinal environment, only 32% of insulin released during the simulated transit time of drug which was 2 h in the stomach and 4 h in the intestine. While under the pH condition of blood environment, insulin release was stable and sustained for a long time (14 days). Furthermore, the chemical stability of insulin released from the microspheres was well preserved after they were treated with the simulated gastric fluid containing pepsin for 2 h. the proposed method showed good efficiency in oral administration of protein or peptide drugs.[36] Veena Belgamwar et al; metoprololtartarate microspheres were prepared with various mucoadhesive polymers ratios including HPMC of various grades like K4M, K15M, K100M, E50LV, Carbopol of grades 971P, 974P and polycarbophil. The microspheres prepared with HPMC K4M and Carbopol 971Pwas compared. The preliminary mucoadhesive strength studies performed for various polymers using rotating cylindrical method showed that HPMC had greater mucoadhesive properties than carbopol and polycarbophil.[37] Md. Lutful Amin et al; prepared metronidazole floating-mucoadhesive microsphere for sustained drug release at the gastric mucosa. The mechanism of the floating-mucoadhesive microspheres involves crosslinking of the carboxylate groups of the alginate molecules by divalent calcium ions. Sodium bicarbonate was used as the gas forming substance to incorporate floating property, which reacted with glacial acetic acid and formed carbon dioxide.

$NaHCO_3 + CH_3COOH = CH_3COONa + CO_2 + H_2O$

Production of carbon dioxide by sodium bicarbonate usually impedes the crosslinking of the alginate molecules. As Carbopol is viscous and possesses free carboxylate groups. It was used for additional crosslinking by calcium ions to increase bead strength and surface smoothness.[38] Jing-Yi Hou et al; prepared microparticles by an emulsification-internal gelatin method using a combination of chitosan and Ca_2+ as cationic components and alginate as anions. pH-sensitive mucoadhesive microparticles loaded with puerarin could enhance puerarin bioavailability. It was observed that in the puerarin mucoadhesive microparticles-pretreated groups, the microparticles reversed the decrease in Periodic acid–Schiff (*PAS*) staining induced by ethanol; significant increase in tumor necrosis factor(TNF-α), interleukin1β (IL-1β) and interleukin(IL-6) levels; and decreased the level of prostaglandin E_2 (PGE2) were observed.[39] AashimaHooda et al; prepared multiunit chitosan based floating system containing Ranitidine HCl by ionootropic gelation and physically cross-linking with sodium tripolyphosphate (sodium TPP). Sodium TPP is a polyanion, which can interact with the positively charged amino group of chitosan by electrostatic forces. The concentration of the sodium TPP was varied and irregular shaped particles were obtained when sodium TPP was used at a concentration of 2% w/v it was too low to cross-link with amine group of chitosan. As the sodium TPP was increased to 4%, the microspheres formed were spherical and discrete due to better cross-linking. Increased sodium TPP increases the concentration of sodium tripolyphosphate (TPP) ions (P3O105−) which was sufficient to interact with the available amino group of chitosan. As the sodium TPP was further increased to 6%, the microspheres formed were very brittle & soft that tends to break during drying. This can be attributed to the presence of excess of OH− ions along with sodium TPP ions (P3O105−) and these OH− ions compete with sodium TPP ions (P3O105−) to react with amino group of chitosan. The stirring speed

was also found to affect the formation of microspheres.[40]

Solvent Removal Method

Emulsification-solvent removal method is most likely used for water labile polymers such as polyanhydrides. The drug is dispersed in the volatile organic solvent such as methylene chloride. The mixture is suspended in the oils such as corn oil and liquid paraffin, emulsifiers like span 80 and organic solvents. Then petroleum ether is added and stripped until the solvent is extracted into the oil solution. The resulting microspheres can be dried into the vacuum. This is simple and fast process of microencapsulation which involves relatively little loss of polymer and drug. The microspheres formed are usually in range of 0.5-5.0 micro meters can be filtered, washed with petroleum ether and air dried.[41,42] N. Badri Viswanathan et al; prepared glycolide microspheres by using new in-oil drying method. Which involves the use of a combination of mixed solvent system for the polymer and an oil as processing medium to enable high entrapment efficiency. The obtained product yields non-porous particles which could find use in the preparation of microparticles with reduced initial burst release. The proposed mechanism involves precipitation of proteins/polypeptides by water-miscible solvent solution within the microspheres being formed by phase inversion. As showen in the figure 6 the glycolide microspheres were prepared by using new in-oil drying method.[43] ShadabMd et al; prepared acyclovir-loaded alginate mucoadhesive microspheres in the ratio of 1:4. The swelling capacity of the polymers is observed highest in the pH 6.8 and lowest in 1.2. The main reason behind this was observed as polymers that undergoes cross-linking with calcium ion is the -COOH group. In acidic solution, the -COOH group remains protonated and exerts an insignificant electrostatic repulsive force. As a result, the microspheres swell to a very less extent. At a higher pH 6.8, the -COOH group undergoes ionization, which exerts electrostatic repulsion between the ionized groups, and results in higher swelling. The higher the swelling of the polymers, the higher is the drug release from the alginate microspheres.[44] M. Nappinnail; prepared cefpodoxime microspheres with use of chitosan. The release profile of the chitosan in acidic medium was found to be optimum, which sustained drug release upto12 hours. Chitosan as a cationic polymer helps to increase the drug polymer ratio. The microspheres which were prepared helps to increase the bioavailability of the drug and provided wide protection in the intestine.[45] The chitosan may provide improved drug delivery via a mucoadhesive mechanism, it has also been shown to enhance drug absorption via the paracellular route through neutralisation of fixed anionic sites within the tight junctions between mucosal cells.[46]

Spray drying

Spray drying is based on the drying of atomized droplet in stream of hot air. In this method the first polymer subsequently, drug followed by suitable cross-linking agent are added. This solution or dispersion is subjected to atomization in a stream of hot air. Atomization results in the formation of free flowing particles. Addition of the plasticisers in the spray dried microspheres helps to improve the coalescence on the drug particles which helps in the formation of the spherical and smooth surfaced microspheres. The size of the microspheres can be controlled by the rate of spraying, the addition rate of polymer drug solution and the drying temperature. The spray drying method is mainly depends upon the polymer ratio. The method is simple, one-stage continuous process, reproducible, only slightly dependent upon solubility of drug and easy to scale up.[47,48]

Chirag Nagda et al., formulated aclofenac microspheres using three different polymers carbopol, chitosan, and polycarbophil, in different weight ratios. It was observed that increasing the drug to polymer ratio slightly increased the size of microspheres and increased in the atomization nozzle flow reduced the particle size. The high swelling capacity of the carbopol and chitosan microspheres could be attributed to their ionized ability to uncoil the polymer into an extended structure. The higher swelling capacity of the carbopol than chitosan was likely due to its higher molecular weight. The poor mucoadhesion of the polycarbophil was due to its non-ionic property. The excellent mucoadhesion of the chitosan is due to electrostatic attraction between chitosan and mucin. Although Carbopol microspheres had negative charge in phosphate buffer (pH 6.8), causing negative charge repulsion with mucus, numerous hydrophilic functional groups such as carboxyl groups in Carbopol molecules could form hydrogen bonds with mucous molecules, thus producing some adhesive force of this polymer.[49] Phruetchika Suvannasara et al., developed effective drug delivery devices for thetreatment of gastric and duodenal ulcers in the stomach4-carboxybenzenesulfonamide-chitosan.(4-CBS-chitosan) microspheres were successful prepared by electrospray ionisation to obtain microspheres with a relatively narrow size distribution, 4-CBS-chitosan microspheres showed a 1.9-fold higher acetazolamide (ACZ) entrapment efficiency (EE) than that of pure chitosan reaching an ~90% EE, as well as an improved EE upto 100%. ACZ in the 4-CBS-chitosan microspheres showed 1.9-fold higher encapsulated level of than in the chitosan, it was concluded that higher amount of ACZ was released over a longer period of time from the ACZ-loaded 4-CBS-chitosan particles than from the ACZ-loaded chitosan particles. The reason that the 4-CBS-chitosan had a higher ACZ EE than the native chitosan is likely to be due to the enhanced ionic inter-actions between ACZ and the modified chitosan. Accordingly, the higher level of sustained release of ACZ from the ACZ-loaded 4-CBS-chitosan in the simulated gastric fluid (SGF) than that of the chitosan microspheres could be explained by the protonation of the amino group of the4-CBS-chitosan to NH_3+ giving

an increased partial electrostatic interaction with the SO_2NH_2 groups of the ACZ.[50] Jignyasha a. Raval et al; prepared mucoadhesive chitosan microspheres containing amoxicillin trihydrate. Chitosan microspheres with small particle size and good sphericity were prepared by a spray-drying method followed by chemical treatment with a chemical crosslinking agent (glutaraldehyde). The microspheres prepared in the ratio of 1:2 (drug to chitosan) were dissolved in 0.5% acetic acid and then chemical treatment with glutaraldehyde (10 mL per 100 mg chitosan for 60 min) was given. Microspheres prepared by this method showed linear relationship between swelling and the in vitro drug release.[51] JiayuCai et al., developed Levofloxacin (LOF) spray dried microspheres combined with glutaraldehyde cross-linking agent. The drug loaded microspheres showed a golf ball-like particles with a size distribution range between 0.5 and 2 μm. Microspheres without cross linking agent showed rapid dissolution. The cross linking microspheres showed delayed release pattern however increase in the concentration of cross linking agent was not associated with the more sustained release profile.[52] D. Patel Dinal et al., prepared mucoadhesive chitosan microspheres of levosalbutamol sulphate. Mucoadhesion was found to increase with increased concentration of polymer. The mucoadhesive microspheres were prepared with the 0.62 um of swelling capacity and 99.8% swelling. It was observed that drug availability decreased by raising the polymer/drug weight ratio from 1:1 to 2:1. On increasing the chitosan polymer ratio it hydrates and produced a more viscous network in the gelled microspheres. The production of viscous network limits the drug diffusion and also influenced drug availability according to the swelling behaviour.[53] Yohkoakiyama et al., polyglycerol ester of fatty acids (PEGF) mucoadhesive microspheres were prepared. The comparative studies on mucoadhesion were done with carbopol coated microspheres, carbopol dispersion microspheres and PEGF microspheres without carbopol. It was observed that mucoadhesion of carbopol dispersion microspheres were more in stomach than the carbopol coated and PEGF microspheres. The reason behind the adhesion of the carbopol dispersion adhesion was that when they come in contact with the water the carbopol dispersion was strongly attached with the stomach mucosa leaving part of the swollen carbopol particles behind within the microspheres. Hence, carbopol dispersion microspheres were referred as adhesive micromatrix system.[54] Yohkoakiyamaet al**.,** prepared delapril hydrochloride microspheres by dispersing melted tetraglycerolpentastearate and tetraglycerolmonostearate in combination or tetraglyceroltristearate singly at high temperature. The in-vivo release profile was studied by deconvolution method. It was concluded that after the microspheres were administered, the pharmacological effect of delapril hydrochloride on the angiotensin I-induced pressor response was also sustained and showed consistency with the plasma concentration-time curve due the inhibition of presser response to angiotensin I is an index of anti-hypertensive activity.[55] Kumar.PPrem et al; prepared clarithromycin mucoadhesive microspheres by electrospray method with the use of carbopol 934P and ethyl cellulose polymers. In the starting the 65% of the drug was released in 15 min time and by the end of the 180 minutes almost 100% of the drug was release. To control the drug release at the initial time, point a low viscosity grade polymer hydroxypropyl cellulose (HPC) grade was used. Drug release depends on the thickness, and viscosity of gelled layer which is distance between the erosion and the swelling boundary. HPC increases the gelled layer and helps to increase the drug release time.[56]

Hot melt method

The primary objective of this method is microencapsulation, and it is suitable for water-labile polymers such as polyanhydrides; however, it cannot be used for thermolabile substances. The first step in this method is melting of polymer and subsequent mixing with solid drug particles having particle size less than 50 μm. This mixture is then suspended in silicone oil or some other immiscible solvent. It is continuously stirred while keeping temperature 5°C more than the polymer melting point. After stabilization, emulsion is cooled. Washing of solidified microspheres is performed by using petroleum ether. Resulting in microspheres of the diameter 1–1000 μm, and size distribution is controllable by varying the stirring rate. The major limitation of this method is that it is not suitable for thermolabile drugs.[57,58] KhokanBera et al; prepared Metformin HCl loaded mucoadhesive agar (*Gelidiumcartilagineum*) microspheres for sustained release by hot-cold congealing method. It was found that, the drug was released by diffusion from the matrix after hydration and swelling of the microspheres in the dissolution medium. The release metformin from the agar microspheres was depended upon pH of the gelation medium. It was noted that as the increase with pH the drug release was also increase.[59] Table 2 list the comparison various processes used for preparation of mucoadhesive microspheres.

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 absorption site, thereby increasing absorption and bioavailability of the drug. The methods used to evaluate mucoadhesive microspheres include the following.

In vitro techniques

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 biological tissue samples, such as synthetic

and natural mucus, frozen and freshly excised tissue etc. The different in vitro methods used are as follows.

Method based on measurement of tensile strength (Figure. 7A)

The Wilhelmy plate technique is an old concept used for the measurement of dynamic contact angles and involves the use of a micro tensiometer or a microbalance. The CAHN dynamic contact angle analyser (model DCA 322, CAHN instruments, Cerritos, California, USA) has been modified to perform adhesive microforce measurements.[60] 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 micro tensiometer.[60] 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 microspheres. 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 is 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 software system, three essential mucoadhesive parameters can be analysed. These include the fracture strength, deformation to failure and work of adhesion.[61] The CAHN instrument, although a powerful tool has inherent limitations in its measurement technique. It 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. The novel electromagnetic force transducer (EMFT) is a remote sensing instrument that uses a calibrated electromagnet to detach a magnetic loaded polymer microsphere from a tissue sample. 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 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 mucoadhesive drug delivery system to target-specific tissues. Recently, tensile test using texture analyser has been reported for studying the mechanical characteristics of mucoadhesiveness of polymers and dosage forms.[61] Several surface substrates such as porcine stomach tissue, chicken pouch tissue.[62] Bovine sublingual mucosa[63,64], bovine duodenal mucosa[64], mucin disc, and mucin gel have been used as a model substrate using texture analyser. The validation of the test using texture analyser has been performed under simulated gastric condition using pig gastric mucosa[65] or simulated buccal conditions using chicken pouch tissues, in order to elucidate test conditions and instrumental parameters influencing the mucoadhesive test results.

Method based on measurement of shear stress (Figure.7A)

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.[66] Adhesion tests based on the shear stress measurement involve two glass slides coated with the 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. As shown in the figure 7 Mikos and Peppas; designed the in vitro method of flow chamber.[3][67] 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 agoniometer, which also monitors the static and dynamic behaviour of the microparticle.[68,69]

Method based on measurement of peel strength (Figure. 7A)

The amount of force or energy required for tangential detachment of mucoadhesive formulation. The test has shown limited use for mucoadhesive formulations. However, for the patches it is of great value. The stress in this test is mainly focused at the edge of adhesive system.[70]

Novel mucoadhesion method for polymer

Mucin particle method

This method evaluates the mucoadhesion of polymers with commercially available porcine mucin particles. In this test mucin particles are suspended in a suitable buffer solution having a concentration 1% w/v and then are mixed with an appropriate amount of polymer solution. The change in the surface property of mucin particle was detected by measuring the Zeta potential with the zeta master (Malvern instrument, Worcestershire, UK). In one of the experiments when coarse mucin particle suspension was mixed with the solution of chitosan and carbopol the zeta potential of the mucin particle was changed but in another experiment when hydroxyl propyl methyl cellulose solution was added to the mucin suspension the zeta potential was unchanged. This result indicates that Carbopol and chitosan have mucoadhesive property. A modified mucin particle method can be performed using the submicron

sized mucin particle (200-300 nm) produced by sonication to the coarse mucin suspension. When the suspension is mixed with a polymer solution, the mucin particle may aggregate if the polymer has the mucoadhesive property and the extent of aggregation is directly proportional to the mucoadhesive property of the polymer.[71]

Biacore system

The system is based on principle underlying an optical phenomenon called surface plasmon resonance (SPR). The SPR response is the measurement of refractive index, which varies with the solute content in a solution that contains a sensor chip. When a detected molecule is attached to the surface of sensor chip, or when the analyte binds to the detected molecule, the solute concentration on the sensor chip surface increases, leading to an SPR response. When the analyte (mucin particle) binds to the ligand molecule (polymer) on the sensor chip surface, the solute concentration and the refractive index on that surface changes, increasing the resonance unit (RU) response. When they dissociate, the RU response falls. Later, the analyte can be removed from the ligand by using a regenerating agent. The response will then turn back to the equilibrium state as the beginning step.[72,73]

In vitro mucoadhesion

The test on mice stomach mucosa the mucoadhesive properties of microspheres were evaluated by the method designed by ranga and coworkers using stomach isolated from mice First, mice were fasted for 24 h and the stomach was dissected immediately after the mice were sacrificed. The stomach mucosa was removed and rinsed with physiological saline. Hundred particles of drug loaded formulation were scattered uniformly on the surface of the stomach mucosa. Then, the stomach mucosa with microspheres was placed in a chamber maintained at 93% relative humidity at room temperature. After 30 min, the tissues were taken out and fixed on a plate at an angle of 45°. The stomach mucosa was rinsed with simulated gastric fluid (pH 1.3, without enzymes) for 5 min at a rate of 22 mL/min. The microspheres remaining at the surface of stomach mucosa were counted, and the percentages of the remaining microspheres were calculated and the statistical significance of the differences between two groups was analysed using the two-tailed t-test.[74]

In vitro mucoadhesion test using eggshell membrane as substitute mucosa. Eggshell membranes were employed as a substitute model for in vitro mucoadhesion evaluation. The eggshell membranes were obtained from fresh chicken eggs. After emptying the egg of its content, the external shell was removed, and the underlying membrane was isolated. Then similar procedure was carried out as mice mucosa to measure the in vitro mucoadhesion of the microspheres. The number of microspheres remaining on the surface of eggshell membrane was counted, and the adhering percent was calculated and statistically analysed.[75]

Others in vitro tests to measure the adhesive strength are mucoadhesion studies via rotating cylinder[76], falling liquid film method[77], everted sac technique[78], In Vitro Wash- off Test[79], and novel rheological approach.[80]

In vitro release studies

No standard In vitro method has yet been developed for dissolution study of mucoadhesive microspheres. Morphology analysis and size determination of 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 tunnelling microscopy (STM). The volume mean diameter of the microspheres can be determined in the ultrapure water (Sation 9000, Barcelona, Spain) by laser diffraction (Fraunhofer model) (Coulter LS 230, Florida, USA) reported by Lemoine and associates.[81] The surface charge can be measured in terms of Zeta potential and the measurement can be done with Brookhaven Instrument Zeta PALS (Phase Analysis Light Scattering), Ultra-Sensitive Zeta Potential Analyzer (NY, USA).[82] The mucoadhesion mechanism of various mucoadhesive polymers can be studied by using atomic force microscopy (AFM).[83]

In vivo techniques

In vivo mucoadhesion measurements have consisted of transit time or relative bioavailability assays and measurement of residence time. The established methods for monitoring gastrointestinal transit time of radio-opaque or radiation emitting doses include X-ray and gamma scintigraphy. Relative bioavailability measurements are made by comparing the plasma level concentrations of drugs administered in mucoadhesive per oral dosage forms compared to standard per oral dosage forms and intravenous infusions. Each of these methods provides data that support or reject the mucoadhesive of a material, which can be correlated indirectly to parameters, measured in vitro.[84,85,86]

GI transit time is determined using radio-opaque microspheres. Radio-opaque marker, e.g., barium sulphate encapsulated in mucoadhesive polymer is used to study the GIT transit time. Mucoadhesive labelled with chromium (^{51}Cr), indium (^{113m}In), iodine ($^{123}I^-$), and technetium (^{99m}Tc) have been used to study the transit of the microsphere in the GIT.[87] Faeces collection (using an automated faeces collection machines) and X-ray inspection provides a non-invasive method of monitoring GI residence time without effecting normal GI motility.

Gamma scintigraphy technique

Several methods currently exist to study the fate of formulations in the rodents and primate's gastrointestinal tract, such as gamma scintigraphy and radiological studies.[87,88] The greatest advantage of gamma

scintigraphy over radiological studies is that it allows visualization over time of the entire course of transit of a formulation through the digestive tract, with reasonably low exposure of subjects to radiation. Location of microspheres on oral administration, extent of transit through the GIT, distribution and retention time of the mucoadhesive microspheres in GIT can be studied using the gamma scintigraphy technique. Some mucoadhesive microspheres are labelled with Tc-99m and administered to rabbits. The imaging is performed after 0.5, 2, 4, 6 and 24 h of dosing using, a large field view gamma camera (Siemens AG, Munich, Germany). In Gamma scintigraphy analysis, the section of GIT is critically analysed and much differentiation is present at 0.5 h and 2 h after oral administration.[89]

The percent radioactivity had significantly decreases ($t_{1/2}$ of 99mTc-pertechnetate is 5-6 h), and the presence of microspheres in GIT could not be assessed clearly after 24 h of administration due to negligible radioactivity. Studies on the behaviour of chitosan formulations in humans are few, and more studies are therefore needed to demonstrate what happens to chitosan formulations in the human gastrointestinal tract. In a recent study, we used neutron activation-based gamma scintigraphy to visualize the gastro-retentive properties of chitosan formulations in the human stomach. Sakkinen and co-worker shave described a gamma scintigraphy evaluation of the fate of microcrystalline chitosan granules in the fasted human stomach.[90]

Magnetic resonance imaging and fluorescence detection Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a non-invasive technique that is widely available for in vivo visualization and localization of solid oral dosage forms in the rat gastrointestinal tract. Compared to other imaging modalities MRI allows the representation of anatomical structures with different contrasts and high spatial resolution. To date, only a limited number of studies have utilized MRI to monitor events within pharmaceutical processes.[91] A majority of these MRI studies so far have dealt with implanted drug delivery systems or slow-release systems whereby degradation and erosion of delivery capsules or tablets were mainly studied. A minority of studies have dealt with MRI tracking of microspheres within the GI tract.[92,93] MRI was used for estimating gastric emptying times and determining the opening time point and location of different dosage forms in the intestine. This method compared mucoadhesive properties of polymers applied with different dosage forms in a reproducible way. The combination of magnetic resonance imaging and fluorescence analysis showed added advantage to facilitate comparison of mucoadhesive properties of polymers for gastro intestinal drug delivery in vivo. However, labelling techniques of oral solid dosage forms for MRI applications have not been well established as those of gamma scintigraphy and imagining of the whole GI tract under different conditions is still difficult. The detailed literature on MRI for in vivo mucoadhesion has been well reviewed elsewhere.[94]

Quantitative GIT distribution fluorescence microscopy

Fluorescence microscopy was performed to determine the extent of distribution and penetration of microsphere formulations. The excised tissue sections of GIT were blotted with tissue paper. The wiped tissue was fixed in fixative solution (3:1, absolute alcohol/ chloroform) for 3 h. The pieces were first transferred to absolute alcohol for 0.5 h and then in absolute alcohol and xylene for 1 h. Wax scrapings were added in this solution till saturation and were kept for 24 h. Paraffin blocks were made by embedding the tissue in hard paraffin and matured at 62±1.0°C. The sections (5 µm thickness) were cut using a microtome (Erma optical works, Tokyo, Japan) and examined under fluorescence microscope (Leica, DMRBE, Bensheim, Germany). The results of quantitative GI distribution study also showed significant higher retention of mucoadhesive microspheres in upper GI tract.[94] In vitro/in vivo correlation of mucoadhesive force for gastric retention. To investigate the mucoadhesive properties of the gastric environment, an in vivo quantitative mucoadhesive fracture strength test was developed to correlate the data established with in vitro experimentation. Mucoadhesive and non-mucoadhesive bio erodible polymers with potential for use in oral drug delivery were tested for mucoadhesive fracture strength both in vivo and in vitro. Surprisingly, no statistically significant difference was found between the mucoadhesive fracture strength of fast eroding polyanhydride and slowly eroding hydrophobic polymers in vivo but in vitro results was statistically different. The lack of IVIVC (in vitro/in vivo correlation) among mucoadhesive fracture strengths reflects the clinical finding that polymers that produced strong mucoadhesive forces in vitro may not achieve prolonged gastric retention in vivo due to differences between the in vitro screening conditions and the in vivo bioadhesive environment.[95] The new technique for comparing in vivo to in vitro mucoadhesion measurements quantitatively provides a means for analysing the correlation between in vitro and in vivo mucoadhesive performance indicator, fracture strength.[96]

Applications

Microspheres have many applications, and some of them are as follows.[97,98,99]

Microspheres are used to prepare controlled and sustained release dosage forms. Enteric-coated dosage forms can be prepared using microspheres. As a result, the medication selectively absorbs in intestine instead of stomach. Drugs can be protected from environmental hazards including humidity, light, oxygen, or heat. Microspheres do not provide perfect barrier, but a great deal of protection is offered. If there are any incompatible substances, we can use encapsulation. Drugs are very less likely to evaporate from microspheres, and therefore these can be used to

decrease the volatility. Many core materials are hygroscopic in nature, and microspheres can reduce these properties. Microencapsulation also reduces gastric irritation of drugs. Mucoadhesion avoids first pass metabolism. Additionally, significant cost reductions may be achieved and dose-related side effects may be reduced due to API localisation at the disease site.

Table 1: Mucoadhesion Theories.

Theory	Comment
The wettability theory	As shown in the figure 3a this theory is applicable to liquid or low viscosity mucoadhesive systems and "spread ability" of active pharmaceutical ingredient (API) across biological membrane. Critical parameters can be solid surface contact angle measurements. This process defines the energy required to counter the surface tension at the interface between the two materials allowing for a good mucoadhesive spreading and coverage of the biological substrate.
The fracture theory	As shown in the figure 3b this Theory relates to the force for polymer detachment from the mucus to the strength of their adhesive bond.
The electronic theory	As shown in the figure 3d this Theory refers to the adhesion occurring by means of electron transfer between the mucus. System arising through differences in their electronic structures. The electron transfer between the mucus and the mucoadhesive results in the formation of a double layer of electrical charges at the mucus and mucoadhesive interface
The diffusion-interlocking theory	Important factors which are involved in this theory are inter-movement are molecular weight, cross-linking density, chain mobility/flexibility and expansion capacity of both networks and temperature.

Table 2: Comparison of Various Processes Used For Preparation of Mucoadhesive Microspheres.

Methods	Size (um)	polymers	comments
Spray drying	1-10	Poly (lactide-coglycolide)	Primarily for microspheres used for intestinal imaging.
Solvent evaporation	1-100	Comparatively stable polymers like polyester and polystyrene	Labile polymers may degrade during the fabrication process due to presence of water.
Solvent removal	1-300	High melting point polymers like polyanhydrides,	Only organic solvents are used
Ionic gelation	1-300	chitosan, alginate.	Encapsulation of live cells done
Hot melt method	1-1000	Water labile polymers like polyanhydrides and polyesters	Smooth and dense external surface of microspheres

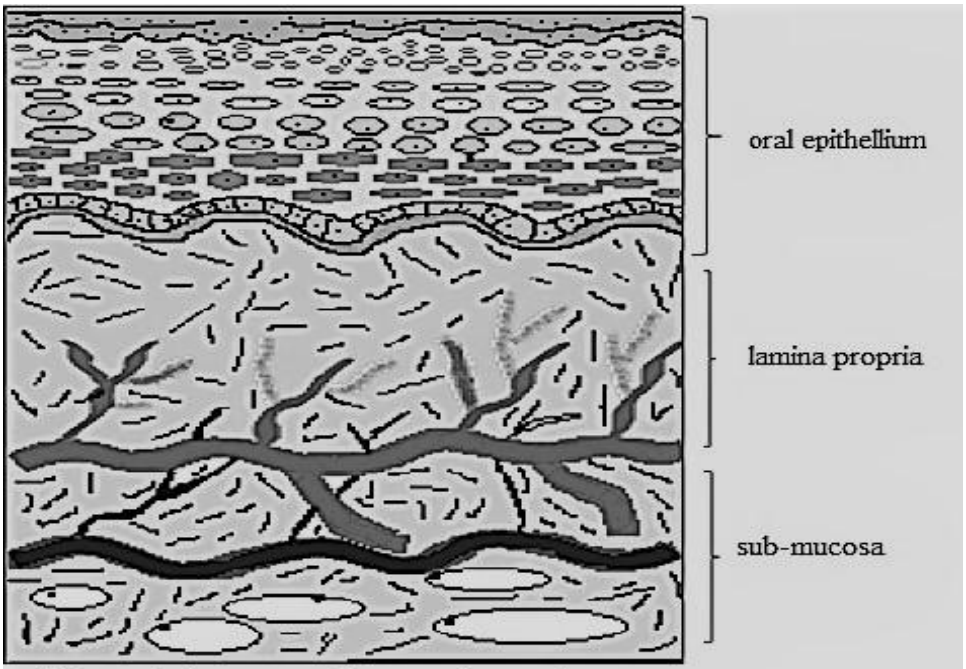

Figure 1. Anatomy of mucosal membrane

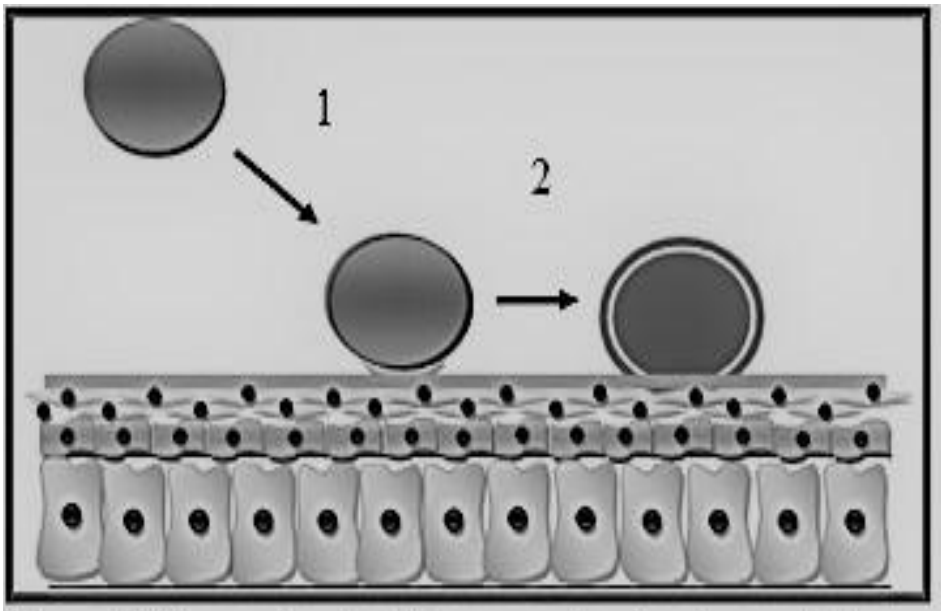

Figure 2. Stages involved in mucoadhesion 1.conact stage and 2.consollidation stage

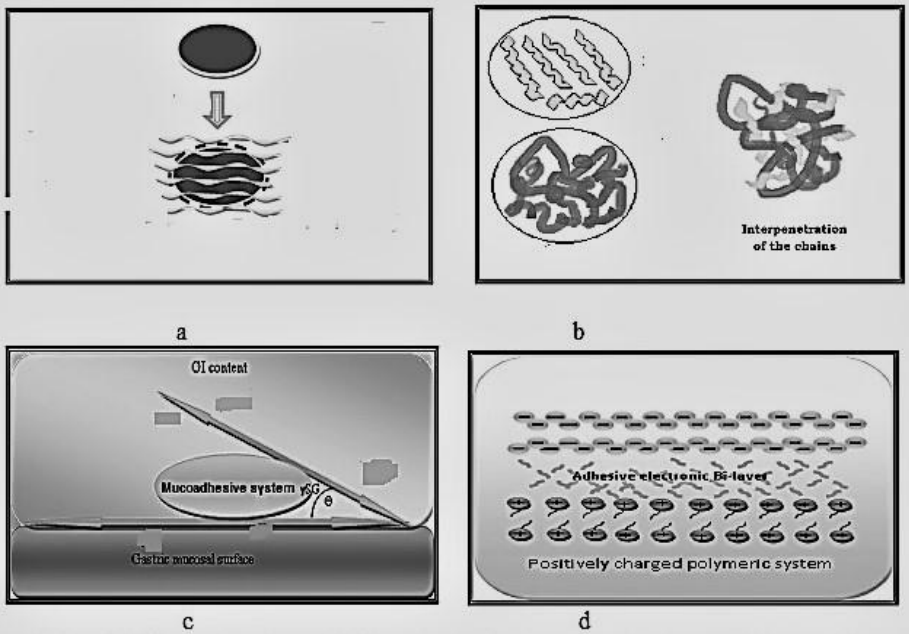

Figure 3. a) Wettability theory b) Electronic theory of mucoadhesion c) Relation between the contact angle mucoadhesive system and gastro mucosal surface and the interface. d) Electronic theory of mucoadhesion.

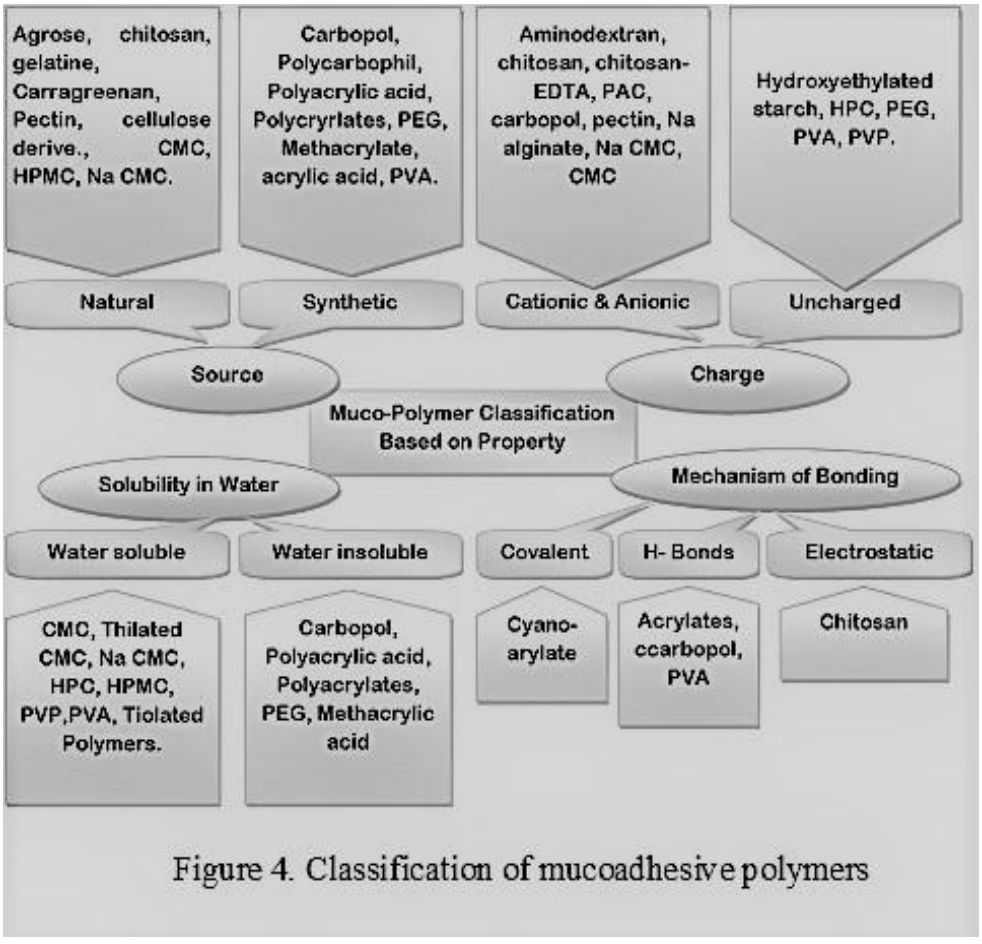

Figure 4. Classification of mucoadhesive polymers

Polyelectrolyte solution

↓

[Sodium Alginate (-)/Gellan gum (-)/CMC (-)/Pectin (-)/ Chitosan (+) + Drug]

Added drop wise under magnetic stirring by needle

↓

Counter ion solution

[Calcium chloride solution (+)/Sodium tripolyphosphate (-)]

↓

Microspheres

Figure 5 Schematic representation of microspheres preparation by ion gelation method .

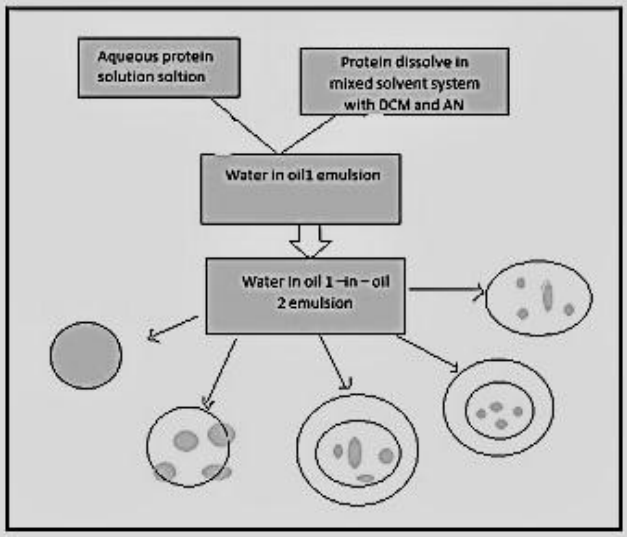

Figure 6. Glycolide microspheres by using new in-oil drying method

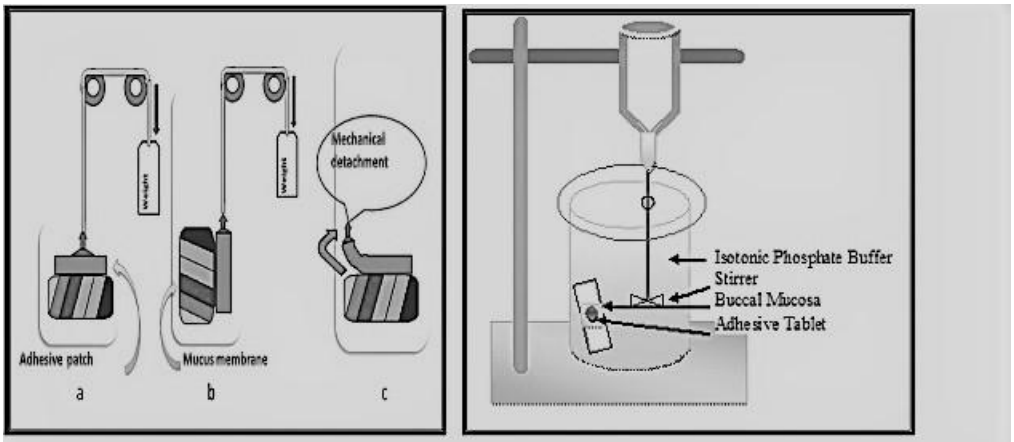

Figure 7. (a) Tensile strength test, (b) shear strength test, (c) peel strength test. B Apparatus for measuring shear strength.

CONCLUSION

Mucoadhesion is the property that can be used to adhere the microparticulate drug delivery system to the mucosal membrane. Mucoadhesive microspheres have emerged as a promising drug carrier system in pharmaceutical industry. Controlled and delayed drug release is possible using mucoadhesive microspheres, and GI mucosa is a viable target for these. Such systems offer increased residence time, safety, and protection for drugs, increased plasma concentration versatility. Mucoadhesive microspheres are one of the most ideal systems for the most preferred drug intake mode, i.e., oral, and to realize the dream of delivering otherwise orally inefficient drugs as well as drugs currently delivered through invasion only. Hence, it is concluded that mucoadhesive microspheres are the effective drug delivery systems for safe and prolong delivery of the drug.

Declaration of interest

The authors report no conflicts of interest.

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