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REVIEW ARTICLE

A Review on Mucoadhesive Microspheres as a Novel Drug Delivery System

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ABSTRACT

The objective of this article is to review the principles underlying the development and evaluation of mucoadhesive microspheres and the research work carried out on these systems. Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesion is commonly defined as the adhesion between two materials, at least one of which is a mucosal surface. Mucoadhesive microspheres may be designed to enable 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. This review article aims to provide an overview of the various aspects of mucoadhesion, mucoadhesive materials, factors affecting mucoadhesion, evaluating methods, and various mucoadhesive drug delivery systems.

KEYWORDS

Mucoadhesion, Mechanism of mucoadhesion, Microspheres, Site specific.

INTRODUCTION

Microspheres

Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm. Substances can be incorporated within microspheres in the liquid or solid state during manufacture or subsequently by absorption. Microparticles or microspheres are general terminologies that involve both microcapsule & micromatrix.[21] Microcapsules, where the entrapped substance is completely surrounded by a distinct capsule wall, and micromatrices, where the entrapped substance is dispersed throughout the microsphere matrix.[1]

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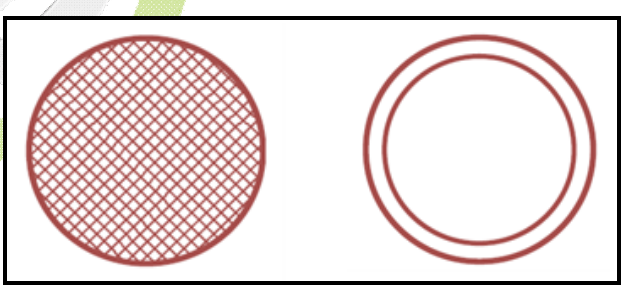


Figure 1: Schematic Diagram Illustrating Microspheres. (A) Microcapsule consisting of an Encapsulated Core Particle and (B) micromatrix consisting of Homogeneous Dispersion of Active Ingredient in Particle

Mucoadhesive Microspheres

"Mucoadhesive microspheres can be achieved by coupling mucoadhesion characteristics to microspheres and developing novel delivery systems referred to as "mucoadhesive microspheres."[6,22] 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,[24] bacterial adhesions[25] and antibodies,[26] etc. on the surface of the microspheres.

The potential application of microspheres in pharmaceutics has a great deal of attention over the past several years.[4] Microencapsulation is one process used to control and retard drug release and hence it prolongs therapeutic activity[2]. It offers greater effectiveness, lower toxicity, lower dosing and more lasting stability than conventional formulations. 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.[23]

Advantages of Mucoadhesive Microspheres[8]

As a result of adhesion and intimate contact, the formulation stays longer at the delivery site and thus improve API bioavailability. It can be allowed the disease treatment at lower API concentrations for. It offers an excellent route for the systemic delivery of drugs with high first-pass metabolism, there by offering a greater bioavailability.[27] The use of specific bioadhesive molecules allows possible targeting of drug molecules at particular sites or tissues, for example the gastrointestinal (GI) tract. It Increase residence time of formulation at target site and control API release which may lead to lower administration frequency.[23] Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site.[28] So, it will improve patient compliance and convenience due to less frequent drug administration.[23] It cause Uniform and wide distribution of drug throughout the gastrointestinal tract which improves the drug absorption. It provides Prolonged and sustained release of drug. It maintains therapeutic plasma drug concentration. Reduction in fluctuation in steady state levels produce better control of disease condition and reduced intensity of local or systemic side effects.[29] the processability is better (improving solubility, dispersibility, flowability). It increase safety margin of high potency drugs due to better control of plasma levels. Drugs which are unstable in the acidic environment or destroyed by enzymatic or alkaline environment of intestine can be administered by this route e.g. buccal, sublingual, vagina.

Methods of Preparation of Mucoadhesive Microspheres

Mucoadhesive microspheres can be prepared by using different techniques like:[3]

Complex Coacervation

In this method the coating material phase, prepared by dissolving immiscible polymer in a suitable vehicle and the core material is dispersed in a solution of the coating polymer under constant stirring. Microencapsulation was achieved by utilizing one of the methods of phase separation, that is, by changing the temperature of the polymer solution; by changing the pH of the medium, by adding a salt or an incompatible polymer or a non-solvent to the polymer solution; by inducing a polymer polymer interaction. Generally coating is hardened by thermal cross linking or desolvation techniques, to form a self sustaining microsphere.[9,30] Principle of this method is under suitable conditions when solutions of two hydrophilic colloids were mixed, result into a separation of liquid precipitate.

Hot Melt Microencapsulation

The polymer is firstly melted and then the solid drug particles are added to it with continuous mixing. The prepared mixture is then suspended in a non-miscible solvent like silicone oil with stirring and heated at the temperature above the melting point of the polymer with continuous stirring so as to get stabilized emulsion. The formed emulsion is cooled to solidify polymer

particles followed by filtration and washing of the microspheres with petroleum ether. [9,31]

Emulsion Solvent Evaporation Method

In this method, polymer is dissolved in an organic solvent, frequently methylene chloride. Then drug is dissolved or dispersed in it. The solution containing the polymer and the drug may be dispersed in an aqueous phase to form droplets. Continuous mixing and elevated temperatures may be employed to evaporate the more volatile organic solvent and leave the solid polymer–drug particles suspended in an aqueous medium. The particles are finally filtered from the suspension.[1] If the drug is water soluble then organic solvent immiscible solvent is used as the external phase instead of aqueous phase.[11]

Solvent Removal

The method involves dissolving the polymer into volatile organic solvent and the drug is dispersed or dissolved in it, this solution is then suspended in the silicone oil containing span 85 and methylene chloride under stirring, then petroleum ether is added and stirred until solvent is extracted into the oil solution. The obtained microspheres were then subjected for vacuum drying.[9,32] This is a non-aqueous method of microencapsulation and is most suitable for water labile polymers such as the polyanhydrides.

Ionotropic Gelation

Using this method Microspheres are formed by dissolving the gel-type polymers, such as alginate, in an aqueous solution followed by suspending the active ingredient in the mixture and extruding the solution through needle to produce micro droplets which fall into a hardening solution containing calcium chloride under stirring at low speed. Divalent calcium ions present in the hardening solution crosslink the polymer, forming gelled microspheres. [9,33]

Phase Inversion Method

In this method drug is added into dilute polymeric solution, in methylene chloride; and resultant mixture is poured into an unstirred bath of strong non-solvent, petroleum ether, in a ratio of 1: 100. Microspheres produced are then clarified, washed with petroleum ether and air dried. [9,34,35]

Spray Drying

By this method the size of microspheres can be controlled by manipulating the rate of spraying, feeding rate of polymer drug solution, nozzle size, and the drying temperature. This method involves dissolving/dispersing of the drug into the polymer solution which is then spray dried. [9,36,37,38]

Mechanism of Mucoadhesion[9,39]

As stated, mucoadhesion is the attachment of the drug along with a suitable carrier to the mucosal layer. Mucoadhesion is a complex phenomenon which involves wetting, adsorption and interpenetration of polymer chains. Mucoadhesion has the following Mechanism-

1. Intimate contact between a mucoadhesive delivery system and mucosal membrane (wetting or swelling phenomenon)

2. Penetration of the mucoadhesive delivery system into the tissue or into the surface of the mucous membrane (interpenetration)[40]

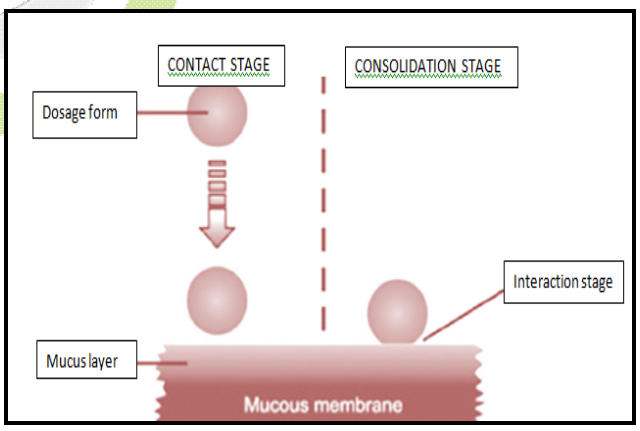


Figure 2: Mechanism of Mucoadhesion

Mucoadhesion Theories

Mucoadhesion is a complex process and numerous theories have been presented to explain the mechanisms involved.[10,41]

Wetting Theory of Mucoadhesion[17]

The wetting theory applies to liquid systems that present affinity to the surface in order to spread

over it. This affinity can be found by using measuring techniques such as the contact angle. The general rule states that lower the contact angle greater will be the affinity. The contact angle should be equal or close to zero to provide adequate spreadability [Figure 3].

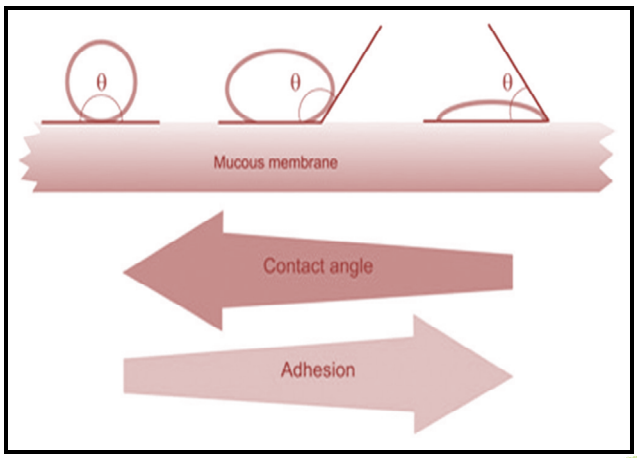


Figure 3: Schematic Diagram Showing Influence of Contact Angle between Device and Mucous Membrane on Mucoadhesion

The spreadability coefficient, S_{AB}, can be calculated from the difference between the surface energies γ_B and γ_A and the interfacial energy γ_{AB}, as indicated in following equation.[47]

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

The greater the individual surface energy of mucus and device in relation to the interfacial energy, the greater the adhesion work, W_A, i.e. the greater the energy needed to separate the two phases.

$$W_A = \gamma_B + \gamma_A - \gamma_{AB}$$

The Electronic Theory[10]

This theory describes adhesion occurring by means of electron transfer between the mucus and the mucoadhesive system arising through differences in their electronic structures. The electron transfer between the mucus and the mucoadhesive results in the formation of a double layer of electrical charges at the mucus and mucoadhesive interface. The net result of such a process is the formation of attractive forces within this double layer.[42] Controversy has surrounded this theory arising from the statement that electrostatic forces are an important cause of bond adhesion, rather than merely a result of high joint strength.[43]

The Fracture Theory[10]

According to this theory, the adhesive bond between systems is related to the force required to separate both surfaces from one another. This ‘‘fracture theory” relates the force for polymer detachment from the mucus to the strength of their adhesive bond. The work fracture has been found to be greater when the polymer network strands are longer or if the degree of cross-linking within such as system is reduced.[44] This theory allows the determination of fracture strength (r) following the separation of two surfaces via its relationship to Young’s modulus of elasticity (E), the fracture energy (e) and the critical crack length (L) through the following equation:[45]

$$\sigma = (E \times \varepsilon/L)^{1/2}$$

The Adsorption Theory[10]

In this instance, adhesion is defined as being the result of various surface interactions (primary and secondary bonding) between the adhesive polymer and mucus substrate. Primary bonds due to chemisorption result in adhesion due to ionic, covalent and metallic bonding, which is generally undesirable due to their permanency.[43] Secondary bonds arise mainly due to van der Waals forces, hydrophobic interactions and hydrogen bonding. Whilst these interactions require less energy to ‘break’ they are the most prominent form of surface interaction in mucoadhesion processes as they have the advantage of being semi-permanent bonds.[46]

Diffusion Theory[17]

According to diffusion theory, the polymer chains and the mucus mix to a sufficient depth to create a semi-permanent adhesive bond. The exact depth to which the polymer chains penetrate the mucus depends on the diffusion coefficient and the time of contact. This diffusion coefficient, in turn, depends on the value of molecular weight between crosslinks and decreases significantly as the cross-linking density increases [Figure 4].

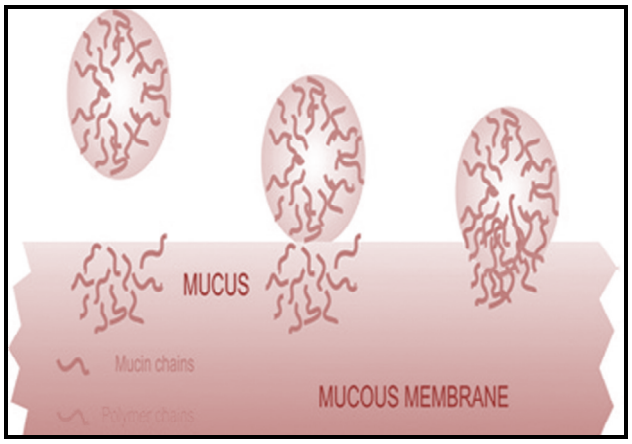


Figure 4: Secondary interactions resulting from interdiffusion of polymer chains of bioadhesive device and of mucus

Materials Used in the Formulation of Mucoadhesive Microspheres

Mucoadhesive microspheres are made up by using mucoadhesive polymers.[9] Mucoadhesive delivery systems are being explored for the localization of the active agents to a particular site. Polymers have played a significant role in designing such systems so as to enhance the residence time of the active agent at the desired location. Polymers used in mucosal delivery system may be of natural or synthetic origin.[13]

***Synthetic Polymers*[17, 18]**

Poly (acrylic acid) polymers (carbomers, polycarbophil), Cellulose derivatives (MC, EC, HPMC, Sodium CMC), Polylactic acid and Polyglycolic acid

***Natural Polymers*[19, 20]**

Xanthan gum, Soluble starch, Tragacanth, Sodium alginate, Gelatin, Pectin, Chitosan, albumin, etc.

Mucoadhesive polymers that adhere to the mucin-epithelial surface can be conveniently divided into three broad classes:[9]

- ✓ Polymers that become sticky on placing them in water and achieve their mucoadhesion due to stickiness.
- ✓ Polymers that adhere through nonspecific, noncovalent interactions that is primarily electrostatic in nature.
- ✓ Polymers that bind to specific receptor site on tile self surface.

***Characteristics of an Ideal Mucoadhesive Polymer*[7,48]**

- ✓ It should be nonirritant to the mucus membrane.
- ✓ The chain length of polymers must be long enough to promote the interpenetration and it should not be too long that diffusion becomes a problem, but as the cross linking increases, the chain mobility decreases which reduces the mucoadhesive strength.
- ✓ It should adhere quickly to most tissue and should possess some site specificity.
- ✓ The polymer and its degradation products should be nontoxic and should be no absorbable from the GI tract.
- ✓ It should preferably form a strong no covalent bond with the mucin epithelial cell surfaces.
- ✓ It should allow easy incorporation of the drug and should offer no hindrance to its release.
- ✓ It should posses sufficient high viscosity.
- ✓ The polymers must not decompose on storage or during the shelf life of the dosage form.
- ✓ The cost of polymer should not be high so that the prepared dosage form remains competitive.

Optimum PH – mucoadhesion is optimum at low pH conditions but at higher pH values a change in the conformation occurs into a rod like structure making those more available for inter diffusion and interpenetration.

Factors Affecting Mucoadhesion

***Polymer Related Factors*[49, 50, 51]**

A. Hydrophilicity

Bioadhesive polymers possess numerous hydrophilic functional groups, such as hydroxyl and carboxyl. These groups allow hydrogen bonding with the substrate, swelling in aqueous

media, thereby allowing maximal exposure of potential anchor sites. In addition, swollen polymers have the maximum distance between their chains leading to increased chain flexibility and efficient penetration of the substrate. [14]

B. Molecular Weight

The interpenetration of polymer molecules is favored by low molecular- weight polymers, whereas entanglements are favored at higher molecular weights. The optimum molecular weight for the maximum mucoadhesion depends on the type of polymer, with bioadhesive forces increasing with the molecular weight of the polymer up to 1,00,000. Beyond this level, there is no further gain.[14,52]

C. Cross-linking and Swelling

Cross-link density is inversely proportional to the degree of swelling.[53] The lower the cross-link density, the higher the flexibility and hydration rate; the larger the surface area of the polymer, the better the mucoadhesion. To achieve a high degree of swelling, a lightly cross-linked polymer is favored. However, if too much moisture is present and the degree of swelling is too great, a slippy mucilage results and this can be easily removed from the substrate.[54] The mucoadhesion of cross-linked polymers can be enhanced by the inclusion in the formulation of adhesion promoters, such as free polymer chains and polymers grafted onto the preformed network.[14, 49]

D. Spatial Conformation

Besides molecular weight or chain length, spatial conformation of a polymer is also important. Despite a high molecular weight of 19,500,000 for dextrans, they have adhesive strength similar to that of polyethylene glycol (PEG), with a molecular weight of 2,00,000. The helical conformation of dextran may shield many adhesively active groups, primarily responsible for adhesion, unlike PEG polymers, which have a linear conformation. [14,50]

E. Concentration of Active Polymer

There is an optimum concentration of polymer corresponding to the best mucoadhesion. In highly concentrated systems, beyond the optimum concentration the adhesive strength drops significantly. In concentrated solutions, the coiled molecules become solvent-poor and the chains available for interpenetration are not numerous. This result seems to be of interest only for more or less liquid mucoadhesive formulations. For solid dosage forms such as tablets, the higher the polymer concentration, the stronger the mucoadhesion.[14,55,56]

Environment Related Factors

A. pH of Polymer-Substrate Interface

pH can influence the formal charge on the surface of the mucus as well as certain ionizable mucoadhesive polymers. Mucus will have a different charge density depending on pH due to the difference in dissociation of functional groups on the carbohydrate moiety and the amino acids of the polypeptide backbone. Some studies had shown that the pH of the medium is important for the degree of hydration of cross-linked polycyclic acid, showing consistently increased hydration from pH 4 through pH 7, and then a decrease as alkalinity or ionic strength increases, for example polycarbophil does not show a strong mucoadhesive property above pH 5 because uncharged, rather than ionized, carboxyl group reacts with mucin molecule, presumably through numerous hydrogen bonds. However, at higher PH, the chain is fully extended due to electrostatic repulsion of the carboxyl ate anions.[13]

B. Applied Strength

To place a solid mucoadhesive system, it is necessary to apply a defined strength. Whatever the polymer, poly (acrylic acid/divinyl benzene) or carbopol 934, the adhesion strength increases with the applied strength or with the duration of its application, up to an optimum. The pressure initially applied to the mucoadhesive tissue contact site can affect the depth of interpenetration. If high pressure is applied for a sufficiently long period of time, polymers become mucoadhesive even though they do not have attractive interactions with mucin.[13]

C. Initial Contact Time

Contact time between the mucoadhesive and mucus layer determines the extent of swelling and interpenetration of the mucoadhesive polymer chains. More mucoadhesive strength increases as the initial contact time increases.[13]

Physiological Factors

A. Mucin Turnover

The natural turnover of mucin molecules from the mucus layer is important for at least two reasons. Firstly, the mucin turnover is expected to limit the residence time of the mucoadhesives on the mucus layer. No matter how high the mucoadhesive strength, they are detached from the surface due to mucin turnover. Secondly, mucin turnover results in substantial amounts of soluble mucin molecules. These molecules interact with mucoadhesives before they have chance to interact with the mucus layer. Mucin turnover may depend on the other factors such as the presence of food.[12,57]

B. Disease state

The physiochemical properties of the mucus are known to change during disease conditions such as the common cold, gastric ulcers, ulcerative colitis, cystic fibrosis bacterial, and fungal infections of female reproductive tract, and inflammatory conditions of the eye.[12,57]

Sites for Mucoadhesive Drug Delivery Systems [13, 15, 58]

Buccal Cavity

At this site, first-pass metabolism is avoided, and the nonkeratinized epithelium is relatively permeable to drugs. Due to flow of saliva and swallowing, materials in the buccal cavity have a short residence time and so it is one of the most suitable areas for the development of bioadhesive devices that adhere to the buccal mucosa and remain in place for a considerable period of time.

Gastrointestinal Tract

The gastrointestinal tract has been the subject of intense study for the use of bioadhesive formulations to improve drug bioavailability. The problem associated is that the polymeric bioadhesive formulations bind the intestinal mucus, which is constantly turning over and are transported down the gut by peristalsis. Another problem is that with conventional formulations such as tablets, the active ingredient may diffuse relatively rapidly away from the bioadhesive.

Nasal Cavity

Ease of access, avoidance of first-pass metabolism and a relatively permeable and well-vascularised membrane, contribute to make the nasal cavity an attractive site for drug delivery. Although the surface area is not large (between 150- 200 cm^2), one major disadvantage of nasal mucosa is the rapid removal of substances by mucociliary action (with a residence time half-life of 15-30 min). This makes it a prime target for bioadhesive formulations to prolong the residence time to allow drug release and absorption

Eye

One major problem for drug administration to the eye is rapid loss of the drug and or vehicle as a result of tear flow, and so it is a target for prolonging the residence time by bioadhesion. The bioadhesive polymers are finding increasing use in ophthalmic formulations, but often as viscosity enhancers rather than as bioadhesives.

Vagina

The vagina is a highly suitable site for bioadhesive formulations and it is here that the success of the concept can be seen convincingly. The bioadhesion increases the retention time (up to 72 h) and a smaller amount of the active ingredient can be used, reducing any adverse effects.

Characterization / Evaluation of Muco-adhesive Microspheres

Interaction Study by TLC/ FTIR

A. FTTR (Fourier Transform Infra Red)

The drug polymer interaction and also degradation of drug while processing for microencapsulation can be determined by FTIR.

In this method the pellets of drug and potassium bromide are prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra are scanned in the wave number range of 4000- 600 cm-1. FTIR study is carried on pure drug, physical mixture, formulations and empty microspheres. [8,59]

B. Thin Layer Chromatographic Studies

The drug stability in the prepared microspheres can also be tested by the TLC method. The Rf values of the prepared microspheres can be compared with the R_f value of the pure drug. The values indicate the drug stability.[8]

Production Yield

The yields of production of microspheres of various batches were calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymers. Yields were calculated as per the formula mentioned below:[64]

$$\text{Production Yield} = \frac{\text{practical weight of microspheres}}{\text{Theoritical weight of microspheres}} \times 100$$

Particle Size and Shape and Surface Morphology

Light microscopy (LM) and scanning electron microscopy (SEM) both can be used to determine the size, shape and outer structure of microspheres.[9]

Bulk Density/ Tapped Density

The microspheres fabricated are weighed and transferred to a 10-ml glass graduated cylinder. The cylinder is tapped using an autotrap until the microsphere bed volume is stabilized. The density is estimated by the ratio of microsphere weight to the final volume of the microsphere bed. [8]

Angle of contact

The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microspheres in terms of hydrophilicity or hydrophobicity. This thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The angle of contact is measured by fixed height funnel method.[8,59]

Entrapment Efficiency

The entrapment efficiency of the microspheres or the percent entrapment can be determined by keeping the microspheres into the buffer solution and allowing lysing. The lysate obtained is filtered or centrifuged and then subjected for determination of active constituents as per monograph requirement. The percent entrapment efficiency is calculated using following equation: [9,60]

% Entrapment = Actual content/Theoretical content x 100

Swelling Index

Swelling index illustrate the ability of the mucoadhesive microspheres to get swelled at the absorbing surface by absorbing fluids available at the site of absorption ,which is a primary requirement for initiation of mucoadhesion32. The percent swelling value can be determined using following equation.[9,61]

Percent swelling = $D_T - D_0 / D_0 \times 100$

Where, D_0 = weight of dried microspheres

D_T = weight of swelled microspheres

In- Vitro Release Study

Standard IP/BP/USP dissolution apparatus is used to study in-vitro release profile in the dissolution media that is similar to the fluid present at the absorption site as per monograph, using rotating basket or paddle type dissolution apparatus. [9,62]

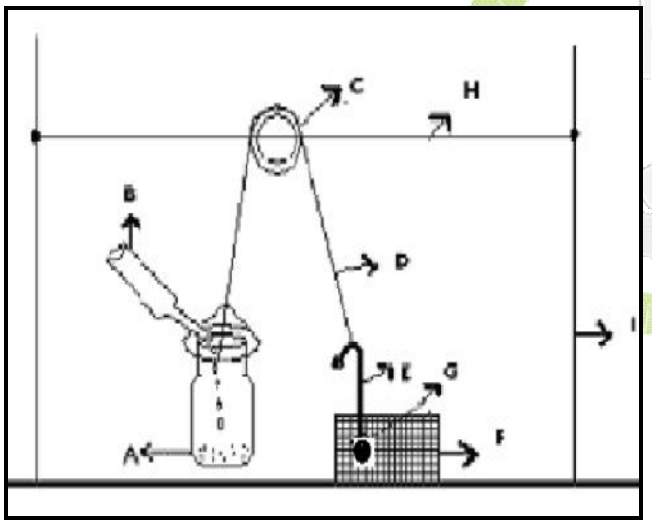
In Vitro Mucoadhesive Strength Measurement[28]

A modified balance method was used for determining the mucoadhesive strength. The cellophane membrane was cut into pieces previously treated with 0.1 N NaOH. Two pieces of cellophane membrane were tied to the two wooden pieces separately from that one wooden piece was fixed on the sieve and other piece was tied with the balance on right hand side. The right and left wooden were balanced

by adding extra weight on the left hand wooden. 100 mg of microsphere was placed between these wooden pieces containing cellophane membrane, and extra weight from the left pan was removed to sandwich the two pieces of cellophane membrane and some pressure was applied to remove the presence of air. The balance was kept in this position for 5 minutes. Water was added slowly at 1ml/min to the left–hand pan until the microsphere detached from the egg membrane surface. The water (ml) required to detach the microsphere from the cellophane membrane surface gave the measure of mucoadhesive strength. The mucoadhesive strength was calculated by using following equations,

$$\text{Force of adhesion } (N) = \frac{\text{mucoadhesion strength (gm)} \times 9.81}{1000}$$

$$\text{Bond strength} = \frac{\text{force of adhesion}}{\text{disk surface area}}$$



A= Plastic bottle B= Pipette C= Pulley
D= Thread E= Pin F= Sieve
G=Wooden pieces H= Stainless steel rod
I= Stand J=*In-situ* gel

Ex-Vivo Mucoadhesion Study

The mucoadhesive property of the microspheres is evaluated on goat's intestinal mucosa by using phosphate buffer, as per monograph. Weighed microspheres are spread onto wet rinsed tissue specimen and immediately thereafter the slides are hung onto the arm of a USP tablet disintegrating test machine with suitable support at 37^0C. The weight of microspheres leached out at different intervals is measured. The % mucoadhesion is calculated by the following equation[9,63]

$$\%\ Mucoadhesion = (Wa - W1)/(Wa) \times 100$$

Where, Wa is the weight of microspheres applied

W1 is the weight of microspheres leached out

CONCLUSION

Novel drug delivery systems achieved a great interest in recent years in the field of modern pharmaceutical formulations. Mucoadhesive microspheres drug delivery system have been gaining a lot of interest of various researchers and scholars, because of their advantages of controlled and sustained release action, and versatility as a drug carrier. Mucoadhesive microspheres offer unique carrier system for many pharmaceuticals. There is no doubt that mucoadhesion has moved into a new area with these new specific targeting compounds (lectins, thiomers, etc.) with researchers and drug companies looking further into potential involvement of more smaller complex molecules, proteins and peptides, and DNA for future technological advancement in the ever-evolving drug delivery arena. Mucoadhesive microspheres have been proved as a promising tool in delivery of drugs to a particular site in controlled or sustained manner, as they deliver the drug to a particular site for longer duration, the absorption of drug increased and hence, the bioavailability of the drug get increased. Therefore, it can be say that in future also mucoadhesive microspheres will play an important role in the development of new pharmaceuticals employing more advanced techniques and materials.

REFERENCES

1. Swarbrick J, Burgess DJ, Hickey AJ, Encyclopedia of pharmaceutical technology, 3rd edn, informa healthcare, New York, 2000, 2315-2336.

2. Bakan JA, Anderson JL, Microencapsulation: The Theory and Practice of Industrial Pharmacy, Philadelphia; 1976, 420-38.
3. Benita S, Microencapsulation: Methods and Industrial applications, 2nd edn, 2002, 183-205.
4. Delgado M, Spanka C, Kerwin LD, Wentworth PJ, Janda KD, "A tunable hydrogel for encapsulation and controlled release of bioactive proteins", Biomacromolecules, 2002, 3, 262-71.
5. Khan S, Tiwari T, Rao N, Joshi A, Dubey B, "Microspheres: A Review", World Journal of Pharmacy and Pharmaceutical Sciences, 2012, 1, 125-145.
6. Kora P, Rama C, Rao Y. "Mucoadhesive Microspheres for Controlled Drug Delivery", Biological Pharmaceutical Bulletin, 2004, 27(11), 1717-1724.
7. Mule MS, Kshirsagar RV, "Gastroretentive Mucoadhesive Microsphere: A Review", Indo American Journal of Pharmaceutical Research, 2011, 1(6), 483-505.
8. Kaurav H, HariKumar HL, Kaur A, "Mucoadhesive Microspheres as carriers in Drug Delivery: a Review", International Journal of Drug Development & Research, 2012, 4(2), 21-34.
9. Garg A, Upadhyay P, "Mucoadhesive Microspheres: A Short Review", Asian Journal of Pharmaceutical and Clinical Research, 2012, 5(3), 24-27.
10. Andrews GP, Thomas PL, Jones DS, "Mucoadhesive polymeric platforms for controlled drug delivery", European Journal of Pharmaceutics and Biopharmaceutics, 2009, 71, 505-518.
11. Robinson JR, Lee VHL, Jantzen G, Banker GS, Design and fabrication of oral controlled release drug delivery systems, 3rd edn, Marcel Dekker, New York, 1996, 112-127.
12. Lohani and Chaudhary, (Mucoadhesive microspheres: A novel approach to increase Gastroretention). Chronicles of Young Scientists, 2012; 3(2): 121-128.
13. Kumar S, Reddy J, Sekhar C, "Polymers In Mucoadhesive Microsphere Drug Delivery Systema Review", Journal of Global Trends in Pharmaceutical Sciences, 2011, 2(3), 249-263.
14. Shaikh R, Singh TR, Garland MD, Woolfson, Donnelly RF, "Mucoadhesive Drug Delivery Systems", Journal of Pharmacy and Bioallied Sciences, 2011, 3(1), 89-100.
15. Lee JW, Park JH, Robinson JR, "Bioadhesive-Based Dosage Forms: The Next Generation", Journal of Pharmaceutical Sciences, 2000, 89, 850-866.
16. Sachan NK and Bhattacharya A, "Basics and Therapeutic Potential of Oral Mucoadhesive Microparticulate Drug Delivery Systems", International Journal of Pharmacy and Clinical Research, 2009, 1, 10-14.
17. Yapel AP, Albumin medicament carrier system, US Patent 4147767, 1979.
18. Sharma S, Bajaj A, Kumar S, Singh Y, Kumar H, "Microspheres review" World Journal of Pharmaceutical research, 2012, 1(4), 975-992.
19. Redmon MP, Hickey AJ, DeLuca PP, "Prednisolone-21-acetate poly (glycolic acid) microspheres: influence of matrix characteristics on release" Journal of Controlled Release, 1989, 9, 99-109.
20. Izumikawa S, Yoshioka S, Aso Y, Takeda J, "Preparation of poly (L-lactide) microspheres of different crystalline morphology and effect of crystalline morphology on drug release rate", Journal of Controlled Release, 1991, 15(2), 133-140.
21. Mathiowitz E, Kreitz, MR, Microencapsulation: In Encyclopedia of Controlled Drug Deliver, John Wiley & Sons, Inc, New York, 1999, 493–546.

22. Mathiowitz E, Chickering DE, Jacob JS, Bioadhesive microspheres and their use as drug delivery and imaging systems, US Patent 6197346, 2001.

23. Robinson JR, Lee VH, Controlled Drug Delivery: Fundamentals and Applications, 2nd edn, Marcel Dekker, New York, 1987, 8.

24. Lehr CM, Bouwstra JA, Kok W, Noach AB, de Boer AG, Junginger HE, "Bioadhesion by means of specific binding of tomato lectin", Pharmaceutical Research, 1992, 9(4), 547-553.

25. Yuehuei H, Friedman JR, Hand Book of Bacterial Adhesion: Principles, Methods and Application, Humana Press, New Jersey, 2000, 644.

26. Wright. S, Huang L, "Antibody directed liposomes as drug delivery Vehicles", Advanced Drug Delivery Review, 1989, 3, 343-389.

27. Punitha S, Girish Y, "Polymers in mucoadhesive buccal drug delivery system", International Journal of Research and Pharmaceutical Sciences, 2010, 1(2), 170-186.

28. Patel VM, Prajapati BG, Patel MM "Design and characterization of chitosan containing mucoadhesive buccal patches of propranolol hydrochlorid", Acta Pharmaceutica, 2007, 57, 61–72.

29. Ganga S, "Mucosal Drug Delivery", Pharmainfo.net, 2007, 5.

30. Zhang L, Liu Y, Wu Z, Chen H, "Preparation and characterization of coacervate microcapsules for the delivery of antimicrobial oyster peptides", Drug Development and Industrial Pharmacy, 2009, 35(3), 369-278.

31. Mathiowitz E, Langer R, "Polyanhydride microspheres as drug carriers I. Hot-melt microencapsulation", Journal of Controlled Release, 1987, 5(1), 13-22.

32. Mathiowitz E, Chickering DE, Lehr CM, Bioadhesive Drug Delivery Systems: Fundamentals, Novel Approaches and Development, Marcel Dekker, New York, 1999, 459-475.

33. Lim F, Moss RD, "Microencapsulation of living cells and tissues", Journal of Pharmaceutical Sciences., 1981, 70(4), 351-354.

34. Chickering DE, Santos CA and Mathiowitz E, "Adaptation of a microbalance to measure bioadhesive properties of microspheres" In: Mathiowitz E, Chickering DE, Lehr CM, Bioadhesive Drug Delivery Systems: Fundamentals, Novel Approaches and Development, Marcel Dekker, New York, 1999, 131-145.

35. Costa MS, Margarida Cardoso MM, "Effect of uniform sized polymeric microspheres prepared by membrane emulsification technique on controlled release of anthracycline anti-cancer drugs", Desalination, 2006, 200, 498–500.

36. Bodmeier R, Chen HG, "Preparation of biodegradable poly(+/-)lactide microparticles using a spray-drying technique" Journal of Pharmcy and Pharmacology, 1988, 40(11), 754-757.

37. Oliveira de BF, Santana MHA, "Spray-dried chitosan microspheres crosslinked with d,l-glyceraldehyde as a potential drug delivery system: preparation and characterization" Submitted for presentation at the 14th International Drying Symposium (IDS 2004). Sao Paulo, Brazil, August 2004, 1166-1173.

38. Yassin AE, Alanazi FK, El-Badry M, Alsarra IA, Barakat NS, Alanazi FK, "Preparation and characterization of spironolactone-loaded gelucire microparticles using spray-drying technique" Drug Development and Industrial Pharmacy, 2009, 35(3), 297-304.

39. Alagusundaram M, Chetty MS, Umashankari K, Badarinath AV, Lavanya C, Ramkanth S, "Microspheres as a novel drug

delivery system: A review", International Journal of ChemTech Research, 2009, 1(3), 526-534.

40. Carvalho FC, Bruschi ML, Evangelista RC, Gremiao MPD, "Mucoadhesive drug delivery systems", Brazilian Journal of Pharmaceutical Sciences, 2010, 46, 1-17.
41. Muthukumaran M, Dhachinamoorthi D, Chandra KBS, Sriram NA, "Review On Polymers Used In Mucoadhesive Drug Delivery System", In. J Pharm Ind Res, 2011, 1(2), 122-127.
42. Dodou, P. Breedveld, P. Wieringa, "Mucoadhesives in the gastrointestinal tract: revisiting the literature for novel applications", European Journal of Pharmaceutics and Biopharmaceutics, 2005, 60, 1–16.
43. A.J. Kinloch, "The science of adhesion" Journal Material Science, 1980, 15, 2141–2166.
44. Ahagon A, Gent AN, "Effect of interfacial bonding on the strength of adhesion", Journal of Polymer Science Polymer Physics, 1975, 13, 1285–1300.
45. Gu JM, Robinson JR, Leung SH, "Binding of acrylic polymers to mucin/ epithelial surfaces: structure–property relationships", Critical Review in Therapeutic Drug Carrier Systems, 1988, 5, 21–67.
46. Jiménez-Castellanos MR, Zia H, Rhodes CT, "Mucoadhesive drug delivery systems" Drug Development and Industrial Pharmacy, 1993, 19, 143–194.
47. Smart JD, "The basics and underlying mechanisms of mucoadhesion", Advanced Drug Delivery Review, 2005, 57, 1556-68.
48. Lachman L, Lieberman H, Kangi, The Theory and Practice of Industrial Pharmacy, 3rd edn, Varghese publishing house, Mumbai, 1991, 296- 302.
49. Peppas NA, Little MD, Huang Y, Bioadhesive Controlled Release Systems, In: Wise DL, editor. Handbook of pharmaceutical controlled release technology, Marcel Dekker, New York, 2000, 255-69.
50. Jimenez-Castellanos MR, Zia H, Rhodes CT, "Mucoadhesive drug delivery systems", Drug Development and Industrial Pharmacy, 1993, 19, 143-94.
51. Ahuja A, Khar RK, Ali J, "Mucoadhesive drug delivery systems", Drug Development and Industrial Pharmacy, 1997, 23, 489-515.
52. Gurny R, Meyer JM, Peppas NA, "Bioadhesive intraoral release systems: Design, testing and analysis", Biomaterials, 1984, 5, 336-40.
53. Gudeman L, Peppas NA, "Preparation and characterisation of ph- sensitive, interpenetrating networks of poly(vinyl alcohol) and poly(acrylic acid)", Journal of Applied Polymer Science, 1995, 55, 919-28.
54. McCarron PA, Woolfson AD, Donnelly RF, Andrews GP, Zawislak A, Price JH, "Influence of plasticiser type and storage conditions on the properties of poly(methyl vinyl ether-co-maleic anhydride) bioadhesive films", Journal of Applied Polymer Science, 2004, 91, 1576-89.
55. Duchene D, Touchard F, Peppas NA, "Pharmaceutical and medical aspects of bioadhesive systems for drug administration", Drug Development and Industrial Pharmacy, 1988, 14, 283-18.
56. Peppas NA, Buri PA, "Surface, interfacial and molecular aspects of polymer bioadhesion on soft tissues", Journal of Controlled Release, 1985, 2, 257-75.
57. Lehr CM, Poelma FG, Junginger HE, Tukker JJ, "An estimate of turnover time of intestinal mucus gel layer in the rat in situ loop", International Journal of Pharmaeutics, 1991, 70, 235-40.
58. O'Neill JL, Remington TL, "Drug-induced esophageal injuries and dysphagia", The Annals of Pharmacotherapy, 2003, 37, 1675–1683.

59. Meena KP, Dangi JS, Samal PK, Namedo KP, "Recent advances in microsphere manufacturing technology", International Journal of Pharmacy and Technology, 2011, 3(1), 854-855.

60. Alagusundaram M, Chetty MS, Umashankari K, Badarinath AV, Lavanya C, Ramkanth S, "Microspheres as a novel drug delivery system: A review", International Journal of ChemTech Research, 2009, 1(3), 526-534.

61. Rajput G, Majmudar F, Patel J, Thakor R, Rajgor NB, "Stomach-specific mucoadhesive microsphere as a controlled drug delivery system", Systematic Review in Pharmacy, 2010, 1(1), 70-78.

62. Sonani NG, Hiremath SP, Dasankoppa FS, Jamakandi VG and Sreenivas SA, "Design and evaluation of gastroretentive mucoadhesive cephalexin tablets", Pharmaceutical Development and Technology, 2010, 15(2), 178-183.

63. Chakraborty S, Dinda SC, Ch. Patra NC, Khandai M, "Fabrication and Characterization of Algino-Carbopol Microparticulate System of Aceclofenac for Oral Sustained Drug Delivery", International Journal of Pharmaceutical Science Review Research, 2010, 4(2), 192-199.

64. Naik DR, Raval A, "Comparative Study of Acyclovir Microencapsulation by Novel Solvent Evaporation-Matrix Erosion and Spray Drying Techniques", International Journal of Pharmaceutical Sciences and Nanotechology, 2012, 5(1), 1627-1637.