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Mucoadhesive Microspheres for Novel Drug Delivery System: A Review

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ABSTRACT

There are various approaches for the delivery of therapeutic substance to the target site in a controlled release fashion. One such approach is using microspheres as carriers for drugs or active pharmaceutical compound. However, the success of this drug delivery system is limited due to their short residence time at the site of absorption. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in stomach, thus offering the possibilities of localized as well as systemic controlled release of drugs. This article presents the advantages of Mucoadhesive microsphere, mechanism, theories involved in mucoadhesion, factor that affect the mucoadhesion, polymer in Mucoadhesive drug delivery system, methodology of preparation of Mucoadhesive microsphere, method of evaluation and their applications in drug delivery. Mucoadhesive drug delivery systems promises several advantages that arise from localization at a given target site, prolonged residence time at the site of drug absorption and an intensified contact with the mucosa increasing the drug concentration gradient.

Keywords: Microsphere, Mucoadhesion, Bioadhesion, Bioavailability.

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INTRODUCTION

The most desirable and convenient method of drug administration is the oral route due to the ease of administration and patient compliance. One limitation for oral delivery is poor bioavailability and for the drug candidates who show absorption window in the proximal gut and is the major obstacle to the development of controlled release formulation. A number of approaches have been developed to increase the residence time of dug formulation.[1]

Microsphere carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems.[2-4]

The problem frequently encountered with controlled release dosage forms is the inability to increase the residence time of the dosage form in the stomach and proximal portion of the small intestine, due to the rapid gastrointestinal transit phenomenon of the stomach which may consequently diminish the extent of absorption of many drugs since almost most of the drug entities are mostly absorbed from the upper part of the intestine, therefore it would be beneficial to develop a sustained release formulation which remain at the absorption site for an extended period of time.[5]

Microspheres constitute an important capacity. Microspheres are the carrier linked drug delivery system in which particle size is ranges from 1-1000 μm range in diameter having a core of drug and entirely outer layers of polymer as coating material. However, the success of these microspheres is limited due to their short residence time at site of absorption. It would, therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membrane. This can be achieved by coupling bioadhesion characteristics to microspheres and developing "Mucoadhesive microspheres.[6]

Drug action can be improved by developing new drug delivery system, such as the Mucoadhesive microsphere drug delivery system. Mucoadhesive microspheres remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at site of action leading to a bioavailability increase and both local and systemic effects.[7]

The gastroretentive drug delivery systems can be retained in the stomach for long time and improve the oral bioavailability of drugs that have an absorption window in a particular region of the gastrointestinal tract.[8]

Mucoadhesive system (Bioadhesion):

Mucoadhesive drug delivery systems are used to enhance drug absorption in a site-specific manner .[9] Mucoadhesion or bioadhesion can be defined as the state in which two materials, at least one of which is biological in nature, are held together for a prolonged time period by means of interfacial forces. In biological systems, bioadhesion can be classified into three types.

- Type 1: adhesion between two biological phases, for example, platelet aggregation and wound healing.
- Type 2: adhesion of a biological phase to an artificial substrate, for example tissue, cell adhesion to culture dishes and biofilm formation on prosthetic devices and inserts.
- Type 3: adhesion of an artificial substance to a biological substrate, for example, adhesion of synthetic hydrogels to soft tissues.

For drug delivery purpose, the term "Bioadhesion" implies attachment of a drug carrier system to a specific biological location. The biological surface can be epithelial tissue or the mucus coat on the surface of a tissue. If adhesive attachment is to a mucous coat, the phenomenon is referred to as "Mucoadhesion". Mucoadhesion is defined as the interaction between a mucin surface and a synthetic or natural polymer.[10]

Microspheres, in general, have the potential to be used for targeted and controlled release drug delivery; but coupling of bioadhesive properties to microspheres has additional advantages e.g. efficient absorption and bioavailability of the drugs due to high surface to volume ratio, a much more intimate contact with the mucous layer, specific targeting of drugs to the absorption site. Bioadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity.

Theories of mucoadhesion:[11,12]

The phenomena of Bioadhesion occur by a complex mechanism. Six theories have been proposed which can improve our understanding for the phenomena of adhesion and can also be extended to explain the mechanism of Bioadhesion. The theories include:

Electronic theory

Electronic theory is based on the premise that both mucoadhesive and biological materials possess opposing electrical charges. Thus, when both materials come into contact, they transfer electrons leading to the building of a double electronic layer at the interface, where the attractive forces within this electronic double layer determine the mucoadhesive strength.

Adsorption theory

According to the adsorption theory, after an initial contact between two surfaces, the material

adheres because of surface forces acting between the atoms in the two surfaces.

Two types of chemical bonds resulting from these forces can be distinguished.

1. Primary chemical bonds of covalent nature, which are undesirable in bioadhesion because their high strength may result in permanent bonds.
2. Secondary chemical bonds having many different forces of attraction, including electrostatic forces, Vander Waals forces, and hydrogen and hydrophobic bonds.

Wetting theory

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 Spreadibility .

The Spreadibility coefficient, *SAB*, can be calculated from the difference between the surface energies γB and γA and the interfacial energy γAB, as indicated in equation 1.

$$SAB = \gamma B - \gamma A - \gamma AB \quad (1)$$

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

$$WA = \gamma B + \gamma A - \gamma AB \quad (2)$$

Mechanical theory

The mechanical theory assumes that adhesion arises from an interlocking of a liquid adhesive (on setting) into irregularities on a rough surface. However, rough surfaces also provide an increased surface area available for interaction along with an enhanced viscoelastic and plastic dissipation of energy during joint failure, which are thought to be more important in the adhesion process than a mechanical effect.

Diffusion theory

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 .

Fracture theory

Fracture theory differs a little from the other five in that it relates the adhesive strength to the forces required for the detachment of the two involved surfaces after adhesion. This assumes that

the failure of the adhesive bond occurs at the interface. However, failure normally occurs at the weakest component, which is typically a cohesive failure within one of the adhering surfaces.

Polymers used in the formulation of Mucoadhesive microspheres:[13]

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, joined by cross-linking agents. These polymers possess optimal polarity to make sure that they permit sufficient wetting by the mucus and optimal fluidity that permits the mutual adsorption and interpenetration of polymer and mucus to take place. Mucoadhesive polymers that adhere to the mucin– epithelial surface can be conveniently divided into three broad classes.

- Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- Polymers that adhere through nonspecific, noncovalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- Polymers that bind to specific receptor site.

Table 1.Relative Mucoadhesive performance of some potential mucoadhesive pharmaceutical polymers:

S.No.	Mucoadhesive Polymers	Properties of polymer	Bioadhesion property
1.	Alginate Sodium	Anionic polymer Rapid swelling and dissolution	High mucoadhesive properties
2.	Chitosan	Cationic polymer, High to moderate swelling	Mucoadhesive properties
3.	Sodium carboxymethyl Cellulose (SCMC)	Anionic polymer, High swelling properties that does not plateau,	High mucoadhesive properties
4.	Carbopol	good water sorption property, forms a hydrogel upon hydration	High mucoadhesive properties
5.	Hydroxyethyl Cellulose (HEC)	Non ionic polymer, High swelling properties and rapid erosion,	Low mucoadhesive properties increased by the addition of SCMC
6.	Hydroxypropyl cellulose (HPC)	Non ionic polymer, Increased swelling in ethylcellulose/HPC films	Moderate mucoadhesive properties
7.	Hydroxypropylmethyl cellulose (HPMC)	Non ionic polymer, Rapid swelling that plateau	Moderate mucoadhesive properties
8.	Polyvinyl alcohol	Non ionic polymer, Moderate swelling	Mucoadhesive properties
9.	Poly vinyl Pyrrolidone	As film forming polymer, High swelling properties	Used as co-adjuvant to increase mucoadhesion
10.	Carrageenan	Poor and stable swelling	Moderate mucoadhesive properties
11.	Guar gum	As an additive, conveyed moderate swelling	Good mucoadhesive properties

12.	Poly ethylene oxide	Non ionic polymer,	High mucoadhesion with high molecular weight
13.	Xantham gum	Anionic polymer, High swelling properties	high mucoadhesive properties

Characteristics of an ideal Mucoadhesive polymer:[14]

- The polymer and its degradation products should be nontoxic and should be nonabsorbable from the GI tract.
- It should be nonirritant to the mucus membrane.
- It should preferably form a strong noncovalent bond with the mucin–epithelial cell surfaces.
- It should adhere quickly to most tissue and should possess some site specificity.
- It should allow easy incorporation of the drug and should offer no hindrance to its release.
- The polymers must not decompose on storage or during the shelf life of the dosage form.
- The cost of the polymer should not be high so that the prepared dosage form remains competitive.

PREPARATION METHODS OF MUCOADHESIVE MICROSPHERES:

Incorporation of solid, liquid or gases into one or more polymeric coatings can be done by micro encapsulation technique. The different methods used for various microspheres preparation depends on particle size, route of administration, duration of drug release and these above characters related to rpm, method of cross linking, drug of cross linking, evaporation time, co-precipitation etc. The various methods of preparations are:-

Phase separation Coacervation technique:

This process is based on the principle of decreasing the solubility of the polymer in organic phase to affect the formation of polymer rich phase called the coacervate. In this method, the drug particles are dispersed in a solution of the polymer and an incompatible polymer is added to the system which makes first polymer to phase separate and engulf the drug particles. Addition of non-solvent results in the solidification of polymer. Polylactic acid (PLA) microspheres have been prepared by this method by using butadiene as incompatible polymer. The process variables are very important since the rate of achieving the coacervate determines the distribution of the polymer film, the particle size and agglomeration of the formed particles. The agglomeration must be avoided by stirring the suspension using a suitable stirrer since as the process of microspheres formation begins the formed polymerize globules start to stick and form the agglomerates. Therefore the process variables are critical as they control the kinetic of the

formed particles since there is no defined state of equilibrium attainment.[15]

Emulsion cross linking method:

In this method drug is dissolved in aqueous gelatin solution which is previously heated for 1 hr at 40 0C. The solution is added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35 0C, results in w/o emulsion then further stirring is done for 10 min at 15 0C Thus the produced microspheres are washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then treated with 100mL of 10mm glyciene solution containing 0.1%w/v of tween 80 at 37 0C for 10 min to block unreacted glutaraldehyde. An example for this technique is Gelatin microspheres.

Solvent Evaporation:

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dispersed in a volatile solvent which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated if necessary to evaporate the solvent for the polymer of the core material is disperse in the polymer solution, polymer shrinks around the core. If the core material is dissolved in the coating polymer solution, matrix – type microcapsules are formed. The core materials may be either water soluble or water in soluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous. The comparison of mucoadhesive microspheres of hyaluronic acid, Chitosan glutamate and a combination of the two prepared by solvent evaporation with microcapsules of hyaluronic acid and gelatin prepared by complex coacervation were made.[6]

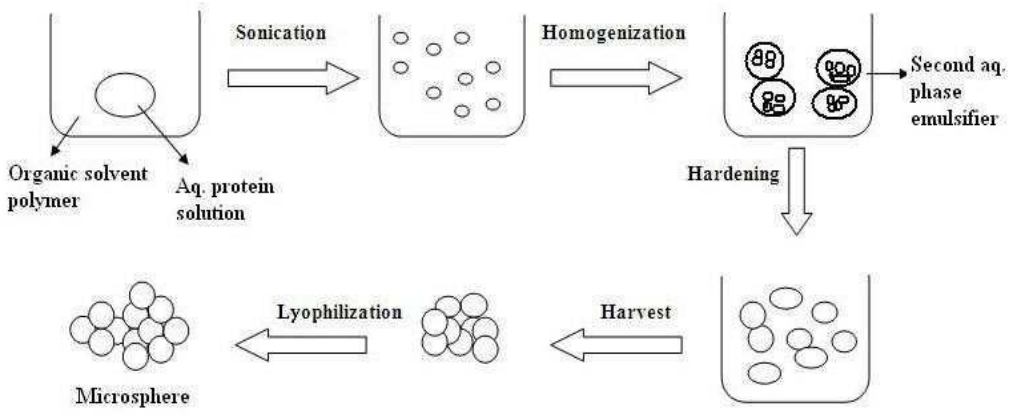

Figure 1: Solvent evaporation method for preparation of microspheres.

Ionic gelation:

Alginate/chitosan particulate system for diclofenac sodium release was prepared using this technique. In this method drug is added to aqueous solution of sodium alginate. In order to get the complete solution stirring is continued and after that it is added dropwise to a solution containing Ca2+ /Al3+. Microspheres which are formed were kept in original solution for 24 hr for internal gellification followed by filtration for separation. The complete release is obtained at pH 6.4-7.2 but the drug will not release in acidic pH.[16]

Spray Drying:

In Spray Drying the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100µm. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions. This process is rapid and this leads to the formation of porous micro particles.

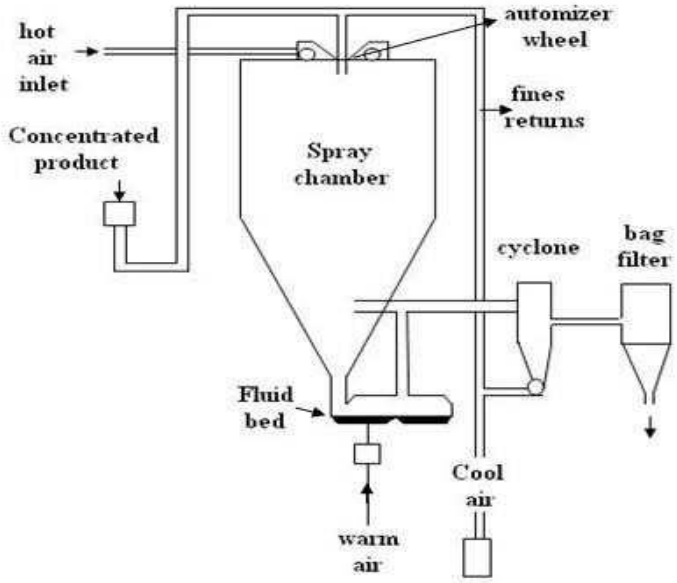

Figure 2: Spray drying method for preparation of microspheres.

Multiple emulsion polymerization technique:

Multiple emulsion method involves formation of(o/w) Primary emulsion (non aqueous drug solution in polymer solution) and then addition of primary emulsion to external oily phase to

form o/w/o emulsion followed by either addition of cross linking agent (glutaraldehyde) and evaporation of organic solvent. This method of preparation is ideal for incorporating poorly aqueous soluble drug, thus enhancing its bioavailability. The microspheres prepared by multiple emulsion technique make the poorly aqueous soluble drug such as ketorolac tromethamine more bioavailable.[15]

FACTORS AFFECTING MUCOADHESION:

Polymers usually diffuse into the mucosal layer and thereafter adhere to the layer by forming intermolecular entanglements. There are following factors which can affect mucoadhesion:

1. With the increase in the molecular weight (MW) of the polymer chain there is an increase in the mucoadhesiveness of a polymer.In general, polymers having MW ≥ 100, 000 have been found to have adequate mucoadhesive property for biomedical applications. A typical example is polyethylene glycol (PEG). PEG of 20,000 MW shows negligible mucoadhesive property while PEG of 200,000 MW exhibits improved mucoadhesiveness and the PEG of 400,000 MW has got excellent mucoadhesiveness.[17] Similarly, polyoxyethylene of 7,000,000 MW has exhibited excellent mucoadhesive property and could be tried for the development of buccal delivery systems.[18] Dextrans of 19,500,000 and 200,000 MW, poly(acrylic) acid of ~750,000 MW and polyethylene oxide of 4,000,000 MW also exhibit good bioadhesive property.
2. Polymer chain length plays an important role in bioadhesiveness. With the increase in the chain length of the polymers there is an increase in the mucoadhesive property of the polymer. Flexible polymer chains helps in the better penetration and entanglement of the polymer chains with that of mucosal layer thereby improving the bioadhesive property.
3. The flexibility of the polymer chains is generally affected by the crosslinking reactions and the hydration of the polymer network. Higher the crosslinking density, lower is the flexibility of the polymer chains. Keeping this in mind, teethering of long flexible chains onto the polymer matrices, with high crosslinking density, appears to be an excellent idea to improve the bioadhesive property. In a recent study, this phenomenon was utilized to device tethered poly (ethylene glycol)–poly (acrylic acid) hydrogels with improved mucoadhesive properties.[19]In addition to the reduced flexibility of the polymer chains, crosslinking results in the reduced diffusion of water into the crosslinked polymer matrix. But sufficient hydration of the polymer network is necessary for the complete opening of the interpolymeric pores within the polymer matrix in addition to the mobilization of the polymer chains.[20] Hence highly crosslinked polymeric matrix limits the interpenetration

of polymer and mucin chains amongst themselves which in turn results in the decrease in the mucoadhesive strength.[21]

4. Apart from the MW and chain length of the polymer chains, spatial arrangement of the polymer chains may also play an important role. As mentioned above, dextrans of 19,500,000 and 200,000 MW exhibit good Mucoadhesive properties. The efficiency of both the dextrans and PEG (MW: 200,000) have been found to possess similar bioadhesive strength. [17, 22]
5. Formation of hydrogen-bonds amongst the functional groups of the polymers and mucosal layer also plays an important role. In general, stronger the hydrogen bonding stronger is the adhesion. The functional groups responsible for such kind of interaction include hydroxyl, carboxyl and amino groups. Various polymers which have the ability to form strong hydrogen bonds include poly (vinyl alcohol), acrylic derivates, celluloses and starch.[22]
6. Apart from the hydrogen bond formation, the presence of functional groups within the polymer structure may render the polymer chains as polyelectrolytes. The presence of charged functional groups in the polymer chain has a marked effect on the strength of the bioadhesion and can be demonstrated by cell-culture-fluorescent probe technique.[23,24] Anionic polyelectrolytes have been found to form stronger adhesion when compared with neutral polymers.[25]
7. In addition to the above facts, the concentration of the polymer also plays a significant role in the process of mucoadhesion. At lower concentrations of the polymer chains, there is an inadequate and unstable interaction amongst the polymer and the mucosal layer resulting in poor Mucoadhesive properties. In general, polymer concentration in the range of 1-2.5 wt % may exhibit sufficient mucoadhesive property for biomedical applications. However for certain polymers, like poly (vinyl pyrrolidone) and poly (vinyl alcohol), solvent diffusion into the polymer network decreases at very high polymer concentration due to the formation of the highly coiled structure thereby limiting interpenetration of the polymer and mucin chains with the subsequent reduction in the Mucoadhesive property.[26]
8. Apart from the above-mentioned physico-chemical properties of the polymeric network, various environmental factors also play an important role in mucoadhesion. As mentioned previously, Mucoadhesive property is dependent on the presence of functional groups which can ionize so as to give a charge distribution on the polymer chains. The ionization of the functional group is dependent on the pH of the external medium. Hence

change in the pH of the external environment may play an important role in tailoring mucoadhesive property. As for example, chitosan (cationic polyelectrolyte) exhibit excellent mucoadhesive property in neutral or alkaline medium.[27]

9. The contact time amongst the polymer matrix and the mucosal layer can also govern the Mucoadhesive property. With the initial increase in the contact time there is an increase in the hydration of the polymer matrix and subsequent interpenetration of the polymer chains. The physiology of the mucosal layer may vary depending on the patho-physiological nature of the human body.
10. The physiological factors which play an important role in governing the mucoadhesive property of a polymer matrix include texture and thickness of mucosa.[22]

EVALUATION OF MUCOADHESIVE MICROSPHERES:

Particle size analysis:

The Mucoadhesive microspheres were examined by optical microscope. The freshly prepared suspension of microspheres was examined on an optical microscope and size of the microspheres was measured by using a pre-calibrated ocular micrometer and stage micrometer.

Drug entrapment efficiency:

The capture efficiency of the microspheres or the percent entrapment can be determined by allowing washed microspheres to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation:-

% Entrapment = Actual content/Theoretical content x 100

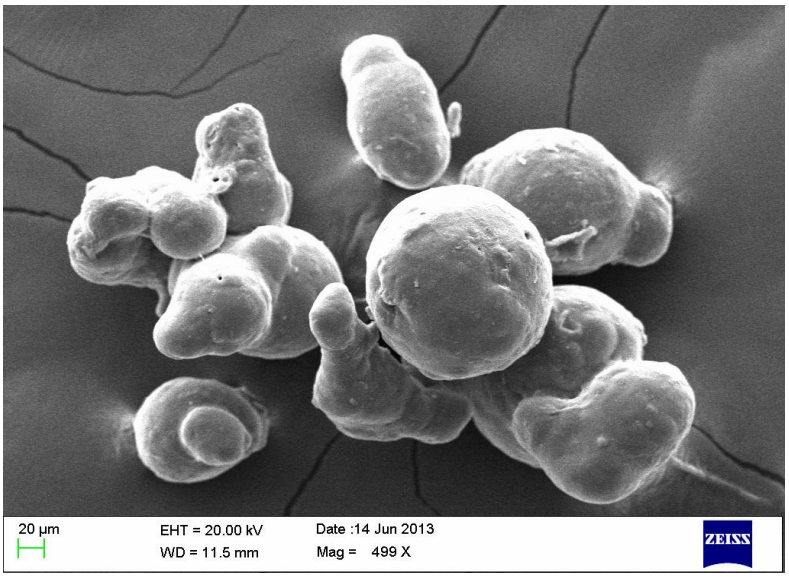

Figure 3- SEM Photograph showing population of Sodium alginate microspheres.

Surface topography by Scanning Electron:

Microscopy (SEM):SEM of the microspheres shows the surface morphology of the microspheres like their shape and size. The surface morphology and structure are visualized by scanning electron microscopy (SEM).The samples is prepared by lightly sprinkling the microspheres powder on a double side adhesive tape which already shucked to on aluminum stubs. The stubs is then placed into fine coat ion sputter for gold coating. After gold coating samples are randomly scanned for particle size and surface morphology.

***In vitro* Bioadhesivity Studies:**

Bioadhesivity testing is done by a novel in situ method. A freshly cut 5-6cm long piece of small intestine of rat is obtained and cleaned by washing with isotonic saline. The piece is cut open and the mucosal surface is exposed. Known weights of microspheres are added evenly on the mucosal surface. The intestinal piece is maintained at 80% (RH) relative humidity for 30mts in a desiccator. The piece is taken out and phosphate buffer pH 6 is allowed to flow over the intestinal piece for about 2 mts at a rate of 20ml/min. The perfusate is collected and dried to get the particles not adhered. The percent of bioadhesion is estimated by the ratio of amount applied to adhere micro matrices.[28]

***In vitro* drug release studies:**

In-vitro release studies can be performed according to USP XXII type 2 dissolution apparatus at suitable pH conditions. The temperature should be maintained at 37±0.5°C and the rotation speed of 100 rpm. Then 5 ml of sample should be withdrawn at various time intervals and replenished with an equal volume of fresh dissolution media. The drug content in the sample can be analyzed spectrophotometrically at specific wavelength (nm).[6]

Stability studies:

By placing the microspheres in screw capped glass container and stored them at following conditions:-

- Ambient humid condition
- Room temperature (27+/-2 0C)
- Oven temperature (40+/-2 0C)
- Refrigerator (5 0C -80C).

It is carried out of a 60 days and the drug content of the microsphere is analyzed.[16]

Swelling index:

This technique is used for Characterization of sodium alginate microspheres. Different solution (100mL) are taken such as (distilled water, buffer solution of pH (1.2, 4.5, 7.4) are taken and

alginate microspheres (100mg) are placed in a wire basket and kept on the above solution and swelling is allowed at 37 0C and changes in weight variation between initial weight of microspheres and weight due to swelling is measured by taking weight periodically and soaking with filter paper.[16]

The swelling index of the microsphere is calculated by using the formula:-

Swelling index= (mass of swollen microspheres - mass of dry microspheres/mass of dried microsphere.

Advantages of Mucoadhesive microspheres drug delivery system:[10]

- As a result of adhesion and intimate contact, the formulation stays longer at the delivery site improving API bioavailability using lower API concentrations for disease treatment.
- The use of specific bioadhesive molecules allows for possible targeting of particular sites or tissues, for example the gastrointestinal (GI) tract.
- Increased residence time combined with controlled API release may lead to lower administration frequency.
- Offers an excellent route, for the systemic delivery of drugs with high first-pass metabolism, there by offering a greater bioavailability.[29]
- Additionally significant cost reductions may be achieved and dose-related side effects may be reduced due to API localization at the disease site.[30]
- Better patient compliance and convenience due to less frequent drug administration.
- Uniform and wide distribution of drug throughout the gastrointestinal tract which improves the drug absorption.
- Prolonged and sustained release of drug.
- Maintenance of therapeutic plasma drug concentration.
- Better process ability (improving solubility, dispersibility, flowability).
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.[31]
- Drugs which are unstable in the acidic environment are destroyed by enzymatic or alkaline environment of intestine can be administered by this route e.g. buccal, sublingual, vagina.[32]

Applications of microspheres:

Some of the applications of microspheres are described in detail as following: -

1. Microsphere can be used to prepare enteric-coated dosage forms, so that the medicament will be selectively absorbed in the intestine rather than the stomach.
2. It has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat. Microsphere does not yet provide a perfect barrier for materials, which degrade in the presence of oxygen, moisture or heat, however a great degree of protection against these elements can be provided. For example, vitamin A and K have been shown to be protected from moisture and oxygen through microsphere.
3. The separations of incompatible substances, for example, pharmaceutical eutectics have been achieved by encapsulation. This is a case where direct contact of materials brings about liquid formation.
4. The stability enhancement of incompatible aspirin, chlorpheniramine maleate mixture is accomplished by microencapsulating both of them before mixing.
5. Microsphere can be used to decrease the volatility. An encapsulated volatile substance can be stored for longer times without substantial evaporation.
6. Microsphere has also been used to decrease potential danger of handling of toxic or noxious substances. The toxicity occurred due to handling of fumigants, herbicides, insecticides and pesticides have been advantageously decreased after microencapsulation.
7. The hygroscopic properties of many core materials may be reduced by microsphere.
8. Many drugs have been microencapsulated to reduce gastric irritation.[15]
9. Microsphere method has also been proposed to prepare intrauterine contraceptive device.
10. Therapeutic magnetic microspheres are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system. Mucoadhesive microspheres exhibit a prolonged residence time at the site of application and causes intimate contact with the absorption site and produces better therapeutic action.
11. Radioactive microspheres are used for imaging of liver, spleen, bone marrow, lung etc and even imaging of thrombus in deep vein thrombosis can be done.[16]

DRUGS WHICH HAVE BEEN GIVEN AS MICROSPHERES :

Table 2: Drugs which have been given as microspheres:

S.No	Drug	Polymer	Category	Ref.
1.	Metformin HCl	Sodium alginate	Antidiabetic	28
2.	Amoxicillin trihydrate	Ethyl Cellulose	Antibiotic	33
3.	Ibuprofen	Sodium alginate	Analgesic	34

4.	Trimetazidine Hcl	Chitosan	Antianginal	35
5.	Furosemide	Sodium alginate,Carbopol	Diuretic	36
6.	Insulin	Sodium alginate,Chitosan	Antidiabetic	37
7.	Furazolidine	Eudragit RS100, Carbopol 974P, HPMC	Antiulcer	38
8.	Acyclovir	Sodium alginate	Antiviral	39
9.	Atenolol Propranolol	Polyacrylic acid, Polyvinyl pyrrolidine	β Blockers	40
10.	Rantidine Hcl	Sodium alginate	Antacid	41
11.	Glipizide	Chitosan	Oral Hypoglycemic	42
12.	Captopril	Sodium alginate, HPMC, Chitosan, Carbopol 934P, Cellulose acetate phthalate	ACE Inhibitor	43
13.	Salbutamol sulphate	Carbopol, HPMC	Bronchodilator	44
14.	Torsemide	Sodium alginate , HPMC	Diuretic	45
15.	Ketorolac	Eudragit RS100, Eudragit RL100	Anti-inflammatory and Analgesic	46
16.	Acetazolamide	Eudragit RS, Eudragit RL	Diuretic	47
17.	Famotidine	SodiumCMC, Sod.alginate	Antiulcer	48

CONCLUSION:

To derive maximum therapeutic benefits from certain drug substances, it is desirable to prolong their residence time. Mucoadhesive microspheres will ensure the maintenance of effective plasma concentration over prolonged period of time by extending the release of drug release with enhanced bioavailability over longer periods of time, and for drug targeting to various sites in the body. Mucoadhesive drug delivery is a promising area for systemic delivery of orally inefficient drugs as well as an attractive alternative for noninvasive delivery of potent peptide and perhaps protein drug molecules. Mucoadhesive drug delivery systems are gaining popularity day by day in the global pharma industry and a burning area of further research and development. Drug delivery through Mucoadhesive microspheres is a promising area for continued research with the aim of achieving controlled release with enhanced bioavailability over longer periods of time and for drug targeting to various sites in the body.

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