

Journal of Pharmaceutical and Biomedical Analysis Letters

Online at www.pharmaresearchlibrary.com/jpbmal

JPBMAL, 2013; Vol.1(1), 47-54

Mucoadhesive Microsphere: A Review

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Available online 14 October 2013

Key words:

Mucoadhesive microspheres

Bioadhesion

Controlled drug delivery

Abstract: The conventional oral dosage forms have disadvantages regarding the short duration of delivery to system. A controlled release system designed to increase its residence time in stomach with contact with mucosa was achieved by the formulation of mucoadhesive microsphere of the drug. The aim of the present study is to provide an overview of various aspects of mucoadhesive microsphere based on various polymers, preparation methodology of mucoadhesive microspheres, different methods of evaluation and their applications in drug delivery. Microspheres constitute an important part of novel drug delivery system by virtue of their small size and efficient carrier 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. These have the disadvantage of having short residence time, so the bio-adhesive characteristics can be coupled to microspheres to develop mucoadhesive microspheres. Mucoadhesion can be defined as the state in which two materials, at least one of which is mucous membrane, are held together for a prolonged time period by means of interfacial forces. Mucoadhesive microspheres have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, controlled and sustained release of drug from dosage form and specific targeting of drugs to the absorption site.

Introduction

The oral route of drug administration constitutes the most convenient and preferred means of drug delivery to systemic circulation of body but has short-term limitations due to their inability to restrain and localize the system at gastro-intestinal tract. Mucoadhesive microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity. These are 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 polymers as coating material or have drug-polymer matrix particles. The success of these mucoadhesive microspheres is due to the increase residence time at site of absorption by means of providing an intimate contact of the drug delivery system with the absorbing membrane by coupling it with mucoadhesive polymers. Mucoadhesive microspheres have advantages like efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site [Hemlata Kaurav *et al.* 2012]. A primary object of using mucoadhesive formulations orally would be to achieve a substantial increase in length of stay of the drug in the GI tract. Stability problem in the intestinal fluid can be overcome. Therapeutic effect of drugs insoluble in the intestinal fluids can be improved. Mucoadhesive microspheres carrier systems are made from the biodegradable polymers in sustained drug delivery. They have carried applications and are prepared using assorted polymers. Bioadhesion is a phenomenon in which two materials at least one of which is biological and are held together by means of interfacial forces. The attachment could be between an artificial material and biological substrate such as adhesion between polymer and a biological membrane in case of polymer attached to the mucin layer of mucosal tissue. The term mucoadhesion is used when the mucosal layer lines a number of regions of body including a gastrointestinal tract, urogenital tract, the airways, the ears, nose and eye. These represent potential sites for attachment of bioadhesive system and hence the mucoadhesive drug delivery system could be designed for buccal, oral, vaginal, rectal, nasal and ocular route of administration.

Mechanism of Mucoadhesion:-

A complete understanding of how and why certain macromolecules attach to a mucus surface is not yet available, but a few steps involved in the process are generally accepted, at least for solid systems. Several theories have been proposed to explain the fundamental mechanism of adhesion [Harshad Parmar *et al.* 2010]. A General Mechanism of Mucoadhesion Drug Delivery system is show in Figure 1:

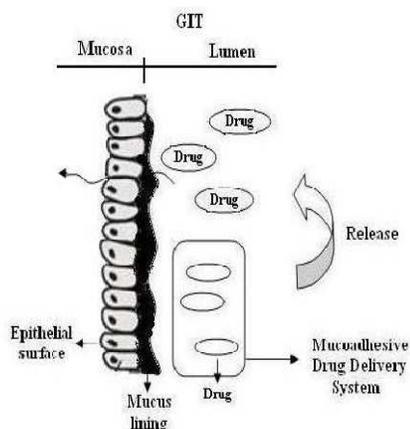


Figure 1: Mechanism of mucoadhesion

The mucoadhesive / mucosa interaction

Chemical Bonds

- a. Ionic bonds
- b. Covalent bonds
- c. Hydrogen bonds
- d. Van-der-Waals bonds
- e. Hydrophobic bonds.

Mucoadhesion Theories

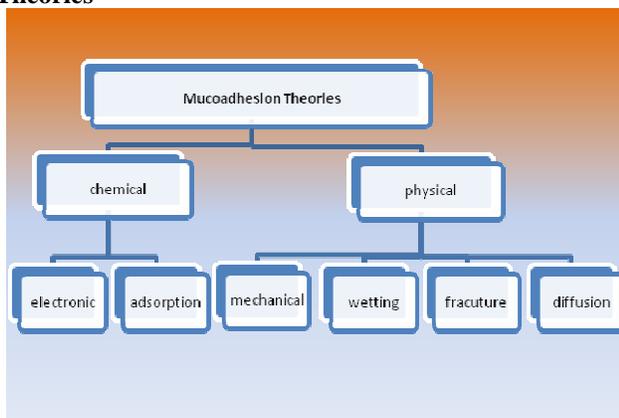


Figure 2: Theories of mucoadhesion

The phenomena of bioadhesion occur by a complex mechanism. Six theories have been proposed, which will explain the mechanism of bioadhesion. The theories are as follows:

- ❖ **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 determines the mucoadhesive strength.
- ❖ **Adsorption theory:** According to the adsorption theory, the mucoadhesive device adheres to the mucus by Van der Waals and hydrogen bonds, electrostatic attraction or hydrophobic interactions.
- ❖ **Wetting theory:** The wetting theory applies to liquid systems which 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.
- ❖ **Diffusion theory:** Diffusion theory describes the interpenetration of both polymer and mucin chains to a sufficient depth to create a semi-permanent adhesive bond. It is believed that the adhesion force increases with the degree of penetration of the polymer chains. This penetration rate depends on the diffusion coefficient, flexibility and nature of the mucoadhesive chains, mobility and contact time [Vinod KR *et al.* 2012].
- ❖ **Fracture theory:** This is perhaps the most-used theory in studies on the mechanical measurement of mucoadhesion. It analyses the force required to separate two surfaces after adhesion is established. This force,

S_m , is frequently calculated in tests of resistance to rupture by the ratio of the maximal detachment force, F_m , and the total surface area, A_0 , involved in the adhesive interaction :

$$S_m = F_m/A_0$$

- ❖ **Mechanical theory:** Mechanical theory considers adhesion to be due to the filling of the irregularities on a rough surface by a mucoadhesive liquid. Moreover, such roughness increases the interfacial area available to interactions thereby aiding dissipating energy and can be considered the most important phenomenon of the process.

Mucoadhesive Polymers

Mucoadhesive polymers are water-soluble and water insoluble polymers, which are swellable networks, jointed 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:

- a. Polymers that become sticky when placed in water and owe their mucoadhesion to stickiness.
- b. Polymers that adhere through nonspecific, non-covalent interactions that is primarily electrostatic in nature (although hydrogen and hydrophobic bonding may be significant).
- c. Polymers that bind to specific receptor site on tile self surface.

Characteristics of an ideal mucoadhesive polymer

- The polymer and its degradation products should be nontoxic and should be non-absorbable from the gastrointestinal tract.
- It should be nonirritant to the mucous membrane.
- It should adhere quickly to most tissue and should possess some site-specificity.
- It should allow daily incorporation to the drug and offer no hindrance to its release.
- The polymer must not decompose on storage or during the shelf life of the dosage form.

Molecular Characteristics

- Strong hydrogen bonding groups (-OH, -COOH).
- Strong anionic charges.
- Sufficient flexibility to penetrate the mucus network or tissue crevices.
- Surface tension characteristics suitable for wetting mucus/mucosal tissue surface.
- High molecular weight.

Polymers Used For Mucoadhesive System

Polymers that adhere to biological surfaces can be divided into four broad categories :

1. Polymers that adhere through non specific, non covalent interactions which are primarily electrostatic in nature
2. Polymers possessing hydrophilic functional groups that hydrogen bond with
3. Similar groups on biological substrates.
4. Polymers that bind to specific receptor sites on the cell or mucus surface.

Table 1: Polymers and their mucoadhesive strength

Polymers	Bioadhesion
Carbopol 934	+++
Carboxy methyl cellulose	+++
Poly(acrylic acid /divinyl benzene)	+++
Tragacanth	+++
Sodium alginate	+++
Hydroxy ethyl cellulose	+++
Guargum	++
Gelatin	++
Gum Karaya	++
Thermally modified starch	+
Pectin	+
Chitosan	+
Acacia	+
Polyethylene glycol	+
Psyllium amberlite-200 resin	+
Hydroxy propyl cellulose	+
Polyvinyl pyrrolidone	+
Hydroxy ethyl methacrylate	+

Hydrophilic polymers: it swells when put into an aqueous media (due to solubility in water) with subsequent dissolution of the matrix. The greater mucoadhesive property is found in polyelectrolyte's in comparison with neutral polymers [Brahmaiah *et al.* 2013].

Anionic polyelectrolyte's: Have been extensively used for designing mucoadhesive delivery systems due to their ability to exhibit strong hydrogen bonding with the mucin present in the mucosal layer. E.g. poly (acrylic acid) and carboxy methyl cellulose [Ludwig A. *et al* 2005].

Cationic Polyelectrolyte's: it has good biocompatibility and biodegradable properties thus used for developing mucoadhesive polymer. E.g. Chitosan, which will undergoes electrostatic interactions with the negatively charged mucin chains and exhibits mucoadhesive property.

Non-Ionic Polymers: Used for mucoadhesive properties and form viscous solutions when dissolved in water E.g. poloxamer, hydroxyl propyl methyl cellulose, methyl Cellulose, poly (vinyl alcohol) and poly (vinyl pyrrolidone).

Hydrogels: It can be defined as three-dimensionally cross linked polymer chains which have the ability to hold water within its porous structure. The water holding capacity of the hydrogels is mainly due to the presence of hydrophilic functional groups like hydroxyl, amino and carboxyl groups.

Thiolated polymers: Free thiol groups Present in the polymeric skeleton helps in the formation of disulphide bonds with mucin which have the cysteine-rich sub-domains e.g. chitosan–iminothiolane, poly(acrylic acid)–cysteine, poly(acrylic acid)–homocysteine, chitosan thioglycolic acid, chitosan–thioethylamidine, alginate–cysteine, poly(methacrylic acid)–cysteine and sodium carboxy methyl cellulose–cysteine [Sipai Altaf Bhai *et al.* 2013].

Lectin-based polymers: The specific affinity of lectins towards sugar or carbohydrate residues provides them with specific cyto-adhesive property and is being explored to develop targeted delivery systems.

Method of preparation of microspheres:

The microsphere can be prepared by using several techniques, but the choice of the technique depends on the nature of the polymer used, the drug, intended use and the duration of therapy. Factors are: 1) The particle size 2) The drug 3) Reproducibility of the release profile 4) No stability problem. 5) No toxic product associated with the final product.

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 [Parmar H *et al.* 2010].

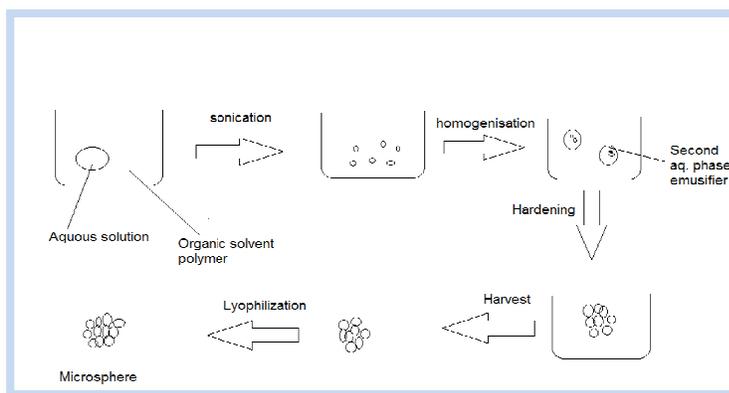


Figure 3: Solvent evaporation method for preparation of microspheres

Emulsion cross linking method

In this method drug is dissolved in aqueous gelatin solution which is previously heated for 1 hr at 40°C. The solution is added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35°C, results in w/o emulsion then further stirring is done for 10 min at 15°C 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°C for 10 min to block unreacted glutaraldehyde.

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 coacervates. 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 coacervates 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 speed 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 [Meena KP *et al.* 2011].

Ionic gelation

Alginate/chitosan particulate system for drug 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 Ca^{2+} / Al^{3+} . 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 [Prasanth V.V *et al.* 2011]

Orifice-Ionic Gelation Method

Sodium alginate and the mucoadhesive polymer are dispersed in purified water (50 ml) to form a homogeneous polymer mixture. Drug is added to the polymer matrix and mixed thoroughly to form a smooth viscous dispersion. Resulting dispersion is then sprayed into calcium chloride (10% w/v) solution by continuous stirring. Produced droplets are retained in the calcium chloride solution for 15 minutes to complete the curing reaction and to produce rigid spherical microspheres. The resulting microspheres are collected by decantation, and the product thus separated is washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then dried at 45°C for 12 hrs.

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 [Hemlata Kaurav *et al.*2012]

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 1-100 μ m. Microparticles 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.

Characterization/ evaluation of mucoadhesive microspheres

1. **Particle size analyser:** Suspension of microsphere (50 mg) in distilled water (5mL) containing 2% w/v of tween 80(to prevent microsphere aggregation), is sonicated in water bath and the particle size was expressed as volume mean diameter in micrometer [Prasanth V.V *et al.*2011].
2. **Optical microscopy:** This method was used to determine particle size by using optical microscope (Meizer OPTIK) The measurement was done under 450x (10x eye piece and 45x objective) and 100 particles were calculated.
3. **Scanning microscopy (SEM)electron:** Surface morphology was determined by the method SEM. In this microspheres were mounted directly on the SEM sample slab with the help of double sided sticking tape and coated with gold film under reduced pressure [Chawdary *et al.*2003]
4. **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:

$$\% \text{ Entrapment} = \text{Actual content} / \text{Theoretical content} \times 100$$

- In-vitro Mucoadhesivity:** The mucoadhesive property of microspheres can be evaluated by in-vitro wash off test for mucoadhesion. Pieces of intestinal mucosa (3cm×2cm) were mounted onto glass slides using cyanoacrylate glue. Microspheres were spread onto each wet rinsed tissue specimen and immediately thereafter the support was hung onto the arm of USP disintegration apparatus. By operating the disintegration test machine, the tissue specimen was given a regular up and down movement in 0.1 N HCl/ PBS pH 6.8 at 37°C taken in a 1 litre vessel of the machine. At the end of 30 minutes, 1 hour and then at hourly intervals, the machine was stopped and the microspheres adhering to the tissue, 0.1NHCl/PBS was centrifuged, dried and weight. The mucoadhesiveness of microspheres can be calculated [Yadav *et al.*2011].

$$\text{Percent mucoadhesion} = \left(\frac{\text{Weight of adhered microsphere}}{\text{Weight of applied microspheres}} \right) \times 100$$

- Swelling Index:** Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer. To ensure the complete equilibrium, exactly weighed amount of microspheres were allowed to swell in given buffer. The excess surface adhered liquid drops were removed by blotting and the swollen microspheres were weighed by using microbalance. The hydrogel microspheres then dried in an oven at 60° for 5 h until there was no change in the dried mass of sample.

$$\text{Swelling index} = \left(\frac{\text{Mass of swollen microspheres} - \text{mass of dry microspheres}}{\text{mass of dried microspheres}} \right) \times 100$$

Angle of contact: The angle of contact is measure to determine the wetting property of microparticulate carrier. It determines the nature of microspheres in terms of hydrophilicity-hydrophobicity. The angle of contact is measured at the solid/air/water interface. The angle of contact is measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 20 within a minute of deposition microspheres.

- 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).

Applications of microspheres

- Prolongs the residence time of the dosage form at the site of absorption. Controlled and sustained release dosage forms..
- Due to an increased residence time it enhances absorption and hence the therapeutic efficacy of the drug
- Excellent accessibility
- Rapid absorption because of enormous blood supply and good blood flow rates, increase in drug bioavailability due to first pass metabolism avoidance.
- Drug is protected from degradation in the acidic environment in the GIT by designing enteric coated mucoadhesive microspheres.
- Faster onset of action is achieved due to mucosal surface.
- It has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat. For example, vitamin A and K have been shown to be protected from moisture and oxygen through microsphere.
- Mucoadhesive microsphere method has also been proposed to prepare intrauterine contraceptive device.
- Therapeutic magnetic microspheres are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system.
- Vaccine delivery for treatment of diseases like hepatitis, influenza, pertusis, ricin toxoid, diphtheria, birth control. Microspheres in vaccine delivery have a specific advantage like improved antigenicity by adjuvant action, modulation of antigen release, stabilization of antigen.

Table.2: Past Research works on Mucoadhesive Microspheres

Drug	Reference	Bioadhesive polymer used	Application of polymer
Valsartan	Pansare <i>et al.</i>	HPMC K100, Ethyl Cellulose	Increased bioavailability
Tolterodine Tartrate	Swain <i>et al.</i>	Chitosan, Ethyl cellulose	Sustained release
Sitagliptin	Harsha <i>et al.</i>	Carbopol 934P	Increased GIT retention
Rizatriptan benzoate	Sharma <i>et al</i>	<i>Abelmoschus esculentus</i>	Increased nasal retention
Metformin HCl	Berak <i>et al.</i>	Agar	Sustained release

Cefalexin	Shivhare <i>et al.</i>	Sodium alginate, guar gum	Increased residence
Simvastatin	Brahmaiah <i>et al.</i>	HPMC K100M, carbopol 940P, sodium CMC	Extended release
Nateglinide	Jain <i>et al.</i>	PVA, PAA	Controlled release
Ibuprofen	Sudhamani <i>et al.</i>	Ethyl cellulose	Sustained release
Famotidine	Arya <i>et al.</i>	Sodium CMC, sodium alginate	prolonged drug release
Repaglinide	Yadav <i>et al.</i>	Eudrgit S100, chitosan	Duration of drug action increased
Theophylline	Namdeo <i>et al.</i>	Sodium alginate	extended release
Promethazine HCl	Iliger <i>et al.</i>	Chitosan, gelatin	Nasal drug delivery
Insulin	Critchely <i>et al.</i>	DSM-LPC	Nasal drug delivery
Desmopressin	Sakagami M <i>et al.</i>	Starch	increase in Cmax and bioavailability

Conclusion

Mucoadhesive systems offer a promising drug carrier system for the sustiend/controlled delivery of pharmaceuticals. It can be applied to adhere to mucosal tissues anywhere in body as on mucosal layer in eye, nose, oral cavity, respiratory system, urinary system and GIT. The drugs which have low bioavailability problems due to low solubility or first pass metabolism or intestinal enzymatic degradation can be delivered through preparing their mucoadhesive microsphere designed for increased retention time in GIT or for nasal or buccal delivery or stomach retentive delivery, respectively. Thus mucoadhesive microspheres are promising for the further research having the goal of achieving controlled/sustained release of drug with increase in bioavailability over longer period of time and target drug delivery in the body.

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