

STOMACH SPECIFIC MUCOADHESIVE MICROSPHERES AS CONTROLLED DRUG DELIVERY SYSTEM-A REVIEW

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ABSTRACT

Stomach-specific mucoadhesive microspheres as a controlled drug delivery system have been developed to increase gastric retention time of the dosage forms. This article presents the polymers use for mucoadhesive microspheres, factor affecting the mucoadhesion, and developments in the techniques for *in vitro* and *in vivo* evaluation of mucoadhesive microspheres have also been discussed. Mucoadhesive microspheres, in general, have the potential to be used for 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. 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. The application of mucoadhesive microspheres to the mucosal tissues of gastric epithelium is used for administration of drugs for localized action. Mucoadhesive microspheres are widely used because they release the drug for prolong period, reduce frequency of drug administration and improve the patient compliance.

Keyword: Mucoadhesive Microspheres, Polymers, Mucoadhesion, Controlled Release

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation [1]. It is due to various advantages of this route like ease of administration, patient compliance and flexibility in the formulations [2]. However, this approach is be devilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility [3]. Furthermore, the relatively brief gastric emptying time (GET) in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose [4]. Therefore, control of placement of a drug delivery system (DDS) in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem [5].

These considerations have led to the development of a unique oral controlled release dosage form with gastro-retentive properties. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract [6].

Mucoadhesive microspheres adhere to the mucus layer for prolonging the residence time in the GI tract and release the loaded drug in a sustained manner. The intimate contact of the mucoadhesive polymer with the mucus surface can result in an increased drug retention time and drug concentration in the GI tract this should have an improved therapeutic effect for the gastric disease, mucoadhesive microspheres can be employed to deliver medication in a rate controlled and sometimes targeted manner. Medication is released from microspheres by drug leaching from the polymer or by degradation of the polymer matrix [7-8].

An ideal dosage form is one, which attains the desired therapeutic concentration of drug in plasma and maintains constant for entire duration of treatment. This is possible through administration of a conventional dosage form in a particular dose and at particular frequency [9]. In most cases, the dosing intervals much shorter than the half life of the drug resulting in a number of limitations associated with such a conventional dosage form are as follows [10]

- Poor patient compliance; increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.

- A typical peak plasma concentration time profile is obtained which makes attainment of steady state condition difficult.
- The unavoidable fluctuation in the drug concentration may lead to under medication or over medication as the steady state concentration values fall or rise beyond in the therapeutic range.
- The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index whenever overmedication occurs.

OVERVIEW OF STOMACH

The stomach is a J-shaped enlargement of the GIT whose function is to store and mix food with gastric secretions before emptying its load (chyme) through the pyloric sphincter and into the small intestine at a controlled rate suitable for digestion and absorption [11]. When empty, the stomach occupies a volume of about 50 ml, but this may increase to as much as 1 liter when full [12].

The stomach is located in the upper left hand portion of the abdomen just below the diaphragm. It occupies a portion of the epigastric and left hydrochondriac region. The main function of the stomach is to store the food temporarily, grind it and then release it slowly into the duodenum. Due to its small surface area, very little absorption takes place from the stomach. It provides a barrier to the delivery of drugs to the small intestine [13].

The stomach has four main regions [9] (Figure 1)

- Cardia
- Fundus
- Body
- Pylorus

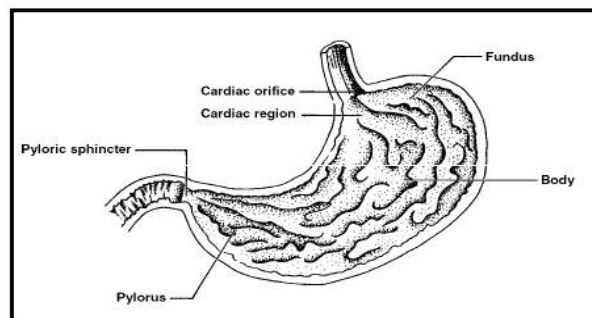


Fig. 1: Shows anatomy of stomach

The stomach wall is composed of four layers: mucosa, submucosa, muscularis and serosa [14].

The mucus layer

Mucus is a translucent and viscid secretion, which forms a thin, continuous gel blanket adherent to mucosal epithelial surface. The mean thickness of this layer varies from about 50-450 μm in humans [15]. The exact composition of the mucus layer varies substantially, depending on the species, the anatomical location and pathological states. However, it has general composition shown in Table 1[16].

Table 1: Showing composition of mucous

S. No.	Components	% Amount
1	Water	95
2	Glycoprotein and lipids	0.5-5.0
3	Minerals salts	1
4	Free proteins	0.5-1.0

From an engineering point of view, mucus is an outstanding water-based lubricant whose properties are extensively exploited within nature [17].

Function of mucus layer [18]

The primary functions of the mucus layer are: -

Protective- Resulting particularly from its hydrophobic

Barrier- The role mucus layer as barrier in tissue absorption of drugs and other substances is well known as it influence the bioavailability of the drug

Adhesion- Mucus has strong cohesion properties and firmly binds to the epithelial cells surface as continuous gel layer.

Lubrication- An important role of the mucus layer is to keep the mucosal membrane moist. Continuous secretion of mucus from the goblet cells is necessary to compensate for the removal of mucus layer due to digestion, bacterial degradation and solubilization of mucin molecules.

Mucoadhesion

Adhesion can be defined as the bond produced by contact between a pressure sensitive adhesive and a surface [19-20].

Mucoadhesion stages [21]

- 1) An intimate contact between a bioadhesive and a membrane.
- 2) Penetration of the bioadhesive into the crevice of the tissue surface.
- 3) Mechanical interlocking between mucin and polymer.

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. If adhesive attachment is to a mucus coat, the phenomenon is referred to as mucoadhesion. Bioadhesion can be modeled after a bacterial attachment to tissue surfaces, and mucoadhesion can be modeled after the adherence of mucus on epithelial tissue [22].

In biological systems, four types of bioadhesion could be distinguished [23]

1. Adhesion of a normal cell on another normal cell.
2. Adhesion of a cell with a foreign substance.
3. Adhesion of a normal cell to a pathological cell.
4. Adhesion of an adhesive to a biological substance.

For adhesion to occur, molecules must bond across the interface. These bonds can arise in the following way [24-25]

1. Ionic bonds—where two oppositely charged ions attract each other via electrostatic interactions to form a strong bond (e.g. in a salt crystal).

2. Covalent bonds—where electrons are shared, in pairs, between the bonded atoms in order to fill the orbital in both. These are also strong bonds.
3. Hydrogen bonds—here a hydrogen atom, when covalently bonded to electronegative atoms such as oxygen, fluorine or nitrogen, carries a slight positive charge and is therefore attracted to other electronegative atoms. The hydrogen can therefore be thought of as being shared, and the bond formed is generally weaker than ionic or covalent bonds.
4. Van-der-Waals bonds—these are some of the weakest forms of interaction that arise from dipole-dipole and dipole-induced dipole attractions in polar molecules, and dispersion forces with non-polar substances.
5. Hydrophobic bonds—more accurately described as the hydrophobic effect, these are indirect bonds (such groups only appear to be attracted to each other) that occur when non-polar groups are present in an aqueous solution. Water molecules adjacent to non-polar groups form hydrogen bonded structures, which lowers the system entropy.

Theories of adhesion

There are six general theories of adhesion, which have been adapted for the investigation of mucoadhesion [26-29].

Electronic theory suggests that electron transfer occurs upon contact of adhering surfaces due to differences in their electronic structure. This is proposed to result in the formation of an electrical double layer at the interface, with subsequent adhesion due to attractive forces.

Wetting theory is primarily applied to liquid systems and considers surface and interfacial energies. It involves the ability of a liquid to spread spontaneously onto a surface as a prerequisite for the development of adhesion. The affinity of a liquid for a surface can be found using techniques such as contact angle goniometry to measure the contact angle of the liquid on the surface, with the general rule being that the lower the contact angle, the greater the affinity of the liquid to the solid. The spreading coefficient (SAB) can be calculated from the surface energies of the solid and liquids using the equation:

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

Where γ_A is the surface tension (energy) of the liquid A, γ_B is the surface energy of the solid B and γ_{AB} is the interfacial energy between the solid and liquid. SAB should be positive for the liquid to spread spontaneously over the solid. The work of adhesion (WA) represents the energy required to separate the two phases, and is given by:

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

The greater the individual surface energies of the solid and liquid relative to the interfacial energy, the greater the work of adhesion.

Adsorption theory describes the attachment of adhesives on the basis of hydrogen bonding and van der Waals' forces. It has been proposed that these forces are the main contributors to the adhesive interaction. A subsection of this, the chemisorptions theory, assumes an interaction across the interface occurs as a result of strong covalent bonding.

Diffusion theory describes inter diffusion of polymers chains across an adhesive interface. This process is driven by concentration gradients and is affected by the available molecular chain lengths and their mobility. The depth of interpenetration depends on the diffusion coefficient and the time of contact. Sufficient depth of penetration creates a semi-permanent adhesive bond.

Mechanical theory assumes that adhesion arises from an interlocking of a liquid adhesive 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.

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.

MUCOADHESIVE POLYMERS

There are two broad classes of mucoadhesive polymers: hydrophilic polymer and hydrogels. In the large classes of hydrophilic polymers those containing carboxylic group exhibit the best mucoadhesive properties [30-31], poly vinyl pyrrolidone (PVP), Methyl cellulose (MC), Sodium carboxy methylcellulose (SCMC) Hydroxy propyl cellulose (HPC) and other cellulose derivative.

Hyrogels are the class of polymeric biomaterial that exhibit the basic characteristics of an hydrogels to swell by absorbing water interacting by means of adhesion with the mucus that covers epithelia i.e.

Anionic group – Carbopol [32], Polyacrylates and their cross-linked modifications

Cationic group - Chitosan and its derivatives

Neutral group - Eudragit- NE30D etc.

Characteristics of an Ideal Mucoadhesive Polymer [33-35]

1. The polymer and its degradation products should be nontoxic and should be no absorbable from the GI tract.
2. It should be nonirritant to the mucus membrane.
3. It should preferably form a strong no covalent bond with the mucin-epithelial cell surfaces.
4. It should adhere quickly to most tissue and should possess some site specificity.
5. It should allow easy incorporation of the drug and should offer no hindrance to its release.
6. The polymers must not decompose on storage or during the shelf life of the dosage form.
7. The cost of polymer should not be high so that the prepared dosage form remains competitive.
8. It should be inert and compatible with the environment
9. The polymer should be easily available in the market and economical.
10. It should allow easy incorporation of drug in to the formulation.

Table 2: Showing properties of some mucoadhesive polymers

Mucoadhesive Polymers	Properties of polymer
Chitosan [36-37]	Cationic polymer, High to moderate swelling and mucoadhesive properties
Alginate Sodium [38-39]	Anionic polymer, Rapid swelling and dissolution, High mucoadhesive properties
Polyvinyl alcohol [40-41]	Non-ionic polymer, Moderate swelling and mucoadhesive properties
Poly vinyl Pyrrolidone [42-43]	Non-ionic polymer, As film-forming polymer, High swelling properties Used as co-adjuvant to increase mucoadhesion
Agar [44]	Poor and stable swelling properties
Acacia [45]	Very poor mucoadhesion.
Guar gum [46]	As an additive, conveyed moderate swelling and good mucoadhesive properties
Carrageenan (λ) [47]	Poor and stable swelling and moderate mucoadhesive properties
Sodium carboxymethyl Cellulose (SCMC) [48-49]	Anionic polymer, High swelling properties that does not plateau, High mucoadhesive properties
Hydroxyethyl Cellulose (HEC) [50-51]	Non-ionic polymer, High swelling properties and rapid erosion, Low mucoadhesive properties increased by the addition of SCMC
Hydroxypropyl cellulose (HPC) [52-53]	Non-ionic polymer, Increased swelling in ethylcellulose/HPC films, Moderate mucoadhesive properties
Hydroxypropylmethyl cellulose (HPMC) [54-55]	Non-ionic polymer, Rapid swelling that plateaus, Moderate mucoadhesive properties
Poly ethylene oxide [56-57]	Non-ionic polymer, High mucoadhesion with high molecular weight
Xantham gum [58]	Anionic polymer, High swelling properties and high mucoadhesive properties

FACTOR AFFECTING MUCOADHESION

A. Polymer Related Factors [59]

- a. Molecular weight- The interpenetration of polymer molecules into the mucus layer is variable, for low molecular weight polymers penetration is more than high molecular weight polymers because entanglements are favored in high molecular weight polymers.
- b. Concentration of active polymer- For solid dosage forms such as tablets, the higher the concentration of polymer, the stronger the bioadhesion force.
- c. Spatial Conformation- Bioadhesive force is also dependent on the conformation of polymers, i.e., helical or linear. The helical conformation of polymers may shield many active groups, primarily responsible for adhesion, thus reducing the mucoadhesive strength of the polymer.

- d. Degree of Hydration- Another important factor affecting the mucoadhesive strength of polymeric components is the degree of hydration. In this respect many polymers will exhibit adhesive properties under conditions where the amount of water is limited. However in such a situation, adhesion is thought to be a result of a combination of capillary attraction and osmotic forces between the dry polymer and the wet mucosal surface which act to dehydrate and strengthen the mucus layer. Although this kind of "sticking" has been referred to as mucoadhesion it is important to clearly distinguish such processes from "wet-on-wet" adhesion in which swollen mucoadhesive polymers attach to mucosal surfaces. Hydration is essential for the relaxation and interpenetration of polymer chains, excess hydration could lead to decreased mucoadhesion and/or retention due to the formation of slippery mucilage. In this situation cross linked polymers that only permit a certain degree of hydration may be advantageous for providing a prolonged mucoadhesive effect [59].

- e. Chain flexibility of polymer- Chain flexibility is important for interpenetration and enlargement. As water-soluble polymers become more and more cross linked, the mobility of the individual polymer chain decreases, also as the cross linking density increases, the effective length of the chain which can penetrate into mucus decrease even further and mucoadhesive strength is reduced [60].
- f. Functional Group Contribution- The attachment and bonding of bioadhesive polymers to biological substrates occurs mainly through interpenetration followed by secondary non-covalent bonding between substrates. Given that secondary bonding mainly arises due to hydrogen bond formation, it is well accepted that mucoadhesive polymers possessing hydrophilic functional such as, carboxyl (COOH), hydroxyl (OH), amide (NH₂) and sulphate groups (SO₄H) may be more favorable in formulating targeted drug delivery platforms. Typically, physical entanglements and secondary interactions (hydrogen bonds) contribute to the formation of a strengthened network; therefore polymers that exhibit a high density of available hydrogen bonding groups would be able to interact more strongly with mucin glycoprotein [61].
- g. Swelling- The swelling characteristic is related to the polymer itself, and also to its environment. Interpenetration of chains is easier as polymer chains are disentangled and free of interactions. More the swelling of polymeric matrix higher the adhesion time of polymers.

B. Environmental – Related Factors [62-65]

- a. pH- pH influences the charge on the surface of both mucus and polymers. Mucus will have a different charge density depending on pH, because of difference in dissociation of functional groups on carbohydrate moiety and amino acids of the polypeptide backbone, which may affect adhesion.
- b. Applied strength- To place a solid bioadhesive system, it is necessary to apply a defined strength. Whichever the polymer may be the adhesion strength of those polymers increases with the increase in the applied strength.
- c. Initial contact time- The initial contact time between mucoadhesive and the mucus layer determines the extent of swelling and the interpenetration of polymer chains. The mucoadhesive strength increases as the initial contact time increases.
- d. Selection of the model substrate surface- The handling and treatment of biological substrates during the testing of mucoadhesive is an important factor, since physical and biological changes may occurs in the mucus gels or tissues under the experimental conditions.

C. Physiological factors

Mucin turnover and disease state of mucus layer are physiological variables, which may affect bioadhesion.

CHARACTERIZATION OF MICROSPHERES

Particle size, Shape and Morphology

All the microspheres were evaluated with respect to their size and shape using optical microscope fitted with an ocular micrometer and a stage micrometer. The particle diameters of more than 100 microspheres were measured randomly by optical microscope [66-68]. Scanning Electron photomicrographs of drug-loaded microspheres were taken. A small amount of microspheres was spread on gold stub. Afterwards, the stub containing the sample was placed in the Scanning electron microscopy (SEM). A Scanning electron photomicrograph was taken at an acceleration voltage of 20KV.

Entrapment Efficiency [69-70]

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

$$\% \text{ Entrapment} = \text{Actual content} / \text{Theoretical content} \times 100 \dots (\text{Eq.1})$$

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. The swelling index of the microsphere was calculated by using the formula [71-72]

$$\text{Swelling index} = (\text{mass of swollen microspheres} - \text{mass of dry microspheres}) / \text{mass of dried microspheres} \times 100 \dots (\text{Eq.2})$$

Mucoadhesion

The Mucoadhesive properties of the microsphere were evaluated by in vitro wash-off test [73]. A 1-cm by 1-cm piece of rat stomach mucosa was tied onto a glass slide (3-inch by 1-inch) using thread. Approximately 100 microspheres were spread onto wet rinsed tissue specimen and the prepared slide was hung onto one of the grooves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus was switched on and the tissue specimen was given up and down movements for 12h in the beaker of the disintegrating test apparatus, which contained the simulated gastric fluid (pH 1.2). The microspheres remaining at the surface of gastric mucosa were then counted, and the percentage of the remaining microspheres was calculated. The % Mucoadhesion was calculated by the formula shown in the Eq. 3,

$$\text{Percentage mucoadhesion} = \frac{\text{Weight of adhered microspheres}}{\text{Weight of applied microspheres}} \times 100 \dots (\text{Eq. 3})$$

In-Vitro Release Study

USP type II dissolution test apparatus was used for studying the drug release properties of microspheres. Weighed Microspheres were taken in muslin cloth and tied on the paddle which was suspended in the media under test. The test were carried out in HCl pH 1.2 (900ml) equilibrated at 37±0.5°C. The paddles were rotated at 100 rpm. At specific time points 5ml of dissolution media was withdrawn and replaced with 5ml of fresh dissolution medium. The collected samples were analyzed spectrophotometrically. Concentrations were calculated using calibration curves developed in respective media. Taking into account, the loss of drug in aliquot replaced, the correction factor was used as given below [74].

$$C_i = A_i + \frac{V_s}{V_t} \sum_{i=1}^{n-1} A_i \left(\frac{V_t}{V_t - V_s} \right) \dots \dots \dots (\text{Eq. 4.9})$$

Where, C_i = Corrected absorbance, V_s = Sample of dissolution media withdrawn, V_t = Total volume of dissolution media. Dissolution release profiles were plotted with percentage drug released at different time intervals. t₉₀ was calculated from the dissolution data. t₉₀ is the time point at the 90% of the drug was released in the media.

CONCLUSION

Mucoadhesive microspheres offer unique carrier system for many pharmaceuticals and can be tailored to adhere to any mucosal tissue, including those found in oral cavity and gastrointestinal tract. The mucoadhesive microspheres can be used not only for controlled release of the drugs to specific sites in body. Recent advances in medicine have envisaged the development of polymeric drug delivery systems for protein/peptide drugs and gene therapy. These challenges put forward by the medicinal advances can be successfully met by using increasingly accepted polymers, e.g. Chitosan, HPMC, polyacrylates, carbopol and its derivatives, polyphosphazenes, etc. Many studies have already been undertaken for exploring the prospects of mucoadhesive microspheres in local action in stomach. Although significant advances have been made in the field of mucoadhesive, there are still many challenges ahead in

this field of particular importance is the development of universally acceptable standard evaluation methods and development of newer site directed polymers. Efforts have been initiated on these lines in the form of novel techniques for evaluation of mucoadhesive strength of microspheres to specific cell types. Polymeric science needs to be explored to find newer mucoadhesive polymers with the added attributes of being biodegradable, biocompatible, mucoadhesive for specific cells or mucosa and which could also function as enzyme inhibitors for the successful delivery of proteins and peptides. A multidisciplinary approach will therefore be required to overcome these challenges and to employ mucoadhesive microspheres as a cutting edge technology for site of stomach controlled release drug delivery of new as well as existing drugs.

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